Magnesium Intake and Risk of Colorectal Cancer: A Meta-analysis of Prospective Cohort Studies

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Abstract

Background: Evidence from in vitro and in vivo studies indicates that magnesium may be involved in carcinogenesis. However, results from observational studies on dietary magnesium intake and colorectal cancer risk are inconsistent.

Methods and Results: A meta-analysis of cohort studies was conducted to examine the association between magnesium intake and colorectal cancer. Studies were included if they provided a relative risk (RR) and corresponding 95% confidence interval (CI) for colorectal cancer in relation to total or dietary magnesium intake. A database was developed based on 4 eligible studies including 255,826 individuals who were initially free of cancer with an average 14 years of follow-up. Pooled RR and 95% CI for colorectal cancer were calculated by using random-effect models. Compared with those in the lowest category of magnesium intake, individuals in the highest category had lower colorectal cancer; the pooled multivariate RRs were 0.81 (95% CI, 0.69-0.95) for total colorectal cancer, 0.81 (95%CI, 0.68-0.97) for colon cancer, and 0.84 (95% CI, 0.63-1.12) for rectal cancer.

Conclusions: These results indicate that magnesium intake may be a modifiable factor for colon cancer, although observational evidence only supports the beneficial effect of dietary magnesium on the development of colon cancer.

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Introduction

Magnesium is an essential mineral abundant in many unprocessed foods, such as whole grains, green leafy vegetables, legumes, and nuts.[1-3] Several nation-wide surveys indicate that the average magnesium intake in the US general population is suboptimal.[1,3-5] Emerging evidence indicates that high magnesium intake from diet or supplements may favorably affect metabolic syndrome, a cluster of metabolic abnormalities including insulin resistance, hypertension, and dyslipidemia. The metabolic syndrome is prevalent worldwide and is associated with certain forms of cancer including colorectal cancer. As an essential element for numerous biochemical reactions in the human body, magnesium plays an important role in nucleic acid metabolism, protein synthesis, and energy production. Previous animal studies and cell cultures have shown the role of magnesium in carcinogenesis via its effects on cell proliferation, differentiation, apoptosis, and angiogenesis[6] as well as innate immunity and inflammation.[7,8] With regard to colon cancer development, magnesium intake has been observed to maintain genomic stability,[9] inhibit c-*myc* oncogene expression in the colon cancer cells,[10] and reduce toxic effects of bile acids on colonic epithelial cells.[10] Magnesium supplementation in animals prevented development of experimentally induced colon cancer.[11]

The hypothetical relation between magnesium intake and cancer risk was first suggested by the results from earlier ecologic studies showing a negative correlation between water magnesium content and cancer mortality.[12,13] Due to confounding effects, ecologic correlations based on grouped data at the population level may not reflect the corresponding association at the individual level. Prospective cohort design is considered optimal for the study of long-term dietary intake in the primary prevention of chronic diseases and helps to postulate and test hypotheses. However, prospective data on the association between magnesium intake and colorectal cancer incidence are very sparse and their results have been inconsistent. Recently, the Swedish Mammary

Screening cohort study (SMSC) reported an inverse association with rectal cancer risk[14] and the Iowa Women's Health Study (IWHS) reported an inverse association with colon cancer risk.[14,15] In contrast, two recent large cohort studies did not replicate the observations. In the Women's Health Study, there was no significant association between magnesium intake and colorectal cancer incidence.[16] The Netherlands Cohort Study observed significant inverse trends in colorectal cancer across increasing quintiles of magnesium intake only among overweight individuals.[17]

Thus, we conducted a meta-analysis to reconcile the discrepant results from these previous prospective cohort studies to synthesize the available evidence and to explore potential between-study heterogeneity.

Methods

Data sources and study selection

All relevant observational studies were identified by searching the MEDLINE and EMBASE (up to May 2008). Search terms included "magnesium", "micronutrients", "cancer", "colorectal cancer", "colon cancer", "rectal cancer", and "carcinogenesis". The search was restricted to prospective cohort studies published in English-language journals. We also used information from bibliographies of the retrieved articles and recent reviews.

Two of our investigators (YS and HS) independently reviewed each published paper and extracted relevant information. Discrepancies were resolved by group discussion. In general, papers were included if 1) they reported relative risks (RRs) and their corresponding 95 percent confidence intervals (CIs) of cancer risk relating to each category of magnesium intake; and 2) they provided the median intake in each category, which permitted standardizing categorization of magnesium intake.

Of the 4 eligible published studies,[14-17] one study that included data from both women and men was counted as 2 separate cohorts in the meta-analysis.[17] The final dataset for our meta-analyses included 5 cohorts from 4 independent studies comprising 255,826 participants initially free of cancer. With an averaged 14 years of follow-up, a total of 4,504 incident cases of colorectal cancer, 3,224 colon cancer and 1,291 rectal cancer were identified.

Data extraction

The data we collected included the first author's name, year of publication, country of origin, duration of follow-up, range or mean of participants' age, sample size, proportion of women, number of events, category amount of magnesium intake, methods for measurement of magnesium intake, adjusted covariates, and RRs and 95% CIs of cancer risk for each category of magnesium intake. The natural logarithms (log) of the RRs and the 95% CIs were used to calculate the corresponding standard errors (SE).

Data synthesis

To test the hypothesis that magnesium intake reduces risk of colorectal cancer, we pooled the RRs and 95 percent CIs of total colorectal cancer in the highest category of magnesium intake versus the lowest category. We also combined RRs if the individual study reported RRs for colon and rectal cancer, separately. The pooled RR was obtained by averaging the log RRs weighted by the inverses of their variances.[18] We used DerSimonian and Laird's random-effects model to incorporate the between-study variability.[19] Formal tests of between-study heterogeneity were based on the Cochran's Q statistic, which follows a χ^2 distribution with a degree of freedom of k-1 (k = the number of individual studies included in the meta-analysis). Because the Cochran's Q statistic has a low statistical power to detect the impact of heterogeneity on meta-analysis, we also applied I^2 statistics to calculate the percentage of total variation due to the study heterogeneity across the k studies.[20,21] An $I^2 < 30\%$ is indicative of mild heterogeneity, 30-50% means moderate heterogeneity, and > 50% indicative of notable heterogeneity.[20,21]

We assessed publication bias primarily using a Begg's modified funnel plot, in which the RR was plotted on a logarithmic scale against its corresponding standard error for each study.[22] In the absence of publication bias, one would expect studies of all sizes to be scattered equally above and below the line showing the pooled estimate of log RR. Publication bias was also assessed by two formal tests: the Begg' adjusted rank correlation test and the Egger regression asymmetry test.[23] All analyses were performed using the STATA statistical software (Version 7.0, STATA Corp, College Station, TX).

Results

Table 1 lists the 4 eligible cohorts and selected characteristics. Two studies were from the United States[15,16] and 2 from Europe.[14,17] The number of participants ranged from 35,196 in the Women's Health Study by Lin et al[16] to 120,852 in the Netherlands Cohort Study by Van den Brandt et al.[17] Of these four large cohorts, only one study included male participants.[17] The follow-up period ranged from 11 to 17 years. In all cohorts, data on magnesium intake at baseline were collected by using a single, self-administered semi-quantitative food frequency questionnaire. Total dietary magnesium intake was classified into quintiles based on its distribution in each cohort. All studies reported multivariate adjusted RRs and 95 percent CIs. In total, there were 4,504 cases of colorectal cancer, 3,224 colon cancer and 1,291 rectal cancer.

Figure 1 shows the estimated RR and 95 percent CI for each individual study comparing the highest quintile to the lowest quintile of dietary magnesium intake. When the data from these independent five prospective cohorts were pooled together using a random-effects meta-analysis model, the pooled estimate of RRs comparing the highest category of dietary magnesium intake with the lowest category of intake were 0.81 (95% CI: 0.69-0.95) for total colorectal cancer

(study heterogeneity: P = 0.45 for Q test and I^2=0 [0,79]), 0.81 (95% CI: 0.68-0.97) for colon cancer (study heterogeneity: P= 0.82 for Q test and I^2=0 [0,79]), and 0.84 (95% CI: 0.63-1.12) for rectal cancer (study heterogeneity: P= 0.40 for Q test and I^2=1 [0,80]). Additionally, Begg's funnel plot (figure not shown) did not indicate the presence of publication bias. Though these tests are usually underpowered when the study number is small, Begg's adjusted rank correlation and Egger's regression asymmetry tests also indicated no evidence of substantial publication bias (P = 0.22-0.46 for Begg's test; P = 0.24-0.60 for Egger's test).

Discussion

In this meta-analysis of 4 prospective cohort studies, we found a consistently inverse association between magnesium intake and colorectal cancer, particularly for risk of colon cancer. These results indicate that there may be a significant beneficial effect of magnesium intake form diet on the carcinogenesis of colon cancer. Due to the nature of observational data and the inherent limit of single FFQ in assessing individual nutrients, future replications in large, well-defined, population-based studies are warranted.

Our findings from prospective observational data in humans seem biologically plausible, although the precise mechanisms underlying the relation of magnesium metabolism and carcinogenesis are unclear. As magnesium is an essential element for numerous biochemical reactions, it is thought to play an important role in nucleic acid metabolism, protein synthesis, and energy production via its involvement in cell proliferation, differentiation, apoptosis, and angiogenesis.[6] Magnesium is also involved in maintaining genomic stability,[9] inhibiting c-*myc* oncogene expression in colon cancer cells,[10] and potentially reducing toxic effects of bile acids on colonic epithelial cells.[10] Animal studies have shown that magnesium supplementation led to fewer experimentally induced colon tumors in rats.[11] However, such results should be interpreted cautiously because different cell types and experimental conditions were used. In addition, a body of evidence supports the anti-inflammatory effect of magnesium intake. Recently, a systematic review summarized data on C-reactive protein (CRP), an inflammatory marker, and colorectal cancer including 1,159 cases and 37,986 controls and found that CRP levels was positively related to risk of colorectal cancer.[24] Thus, anti-inflammatory effect of magnesium intake may partially explain the observed beneficial effect on colorectal cancer. Nevertheless, further *in vitro* and *in vivo* investigation will be needed to clarify the mechanisms underlying a biological role of magnesium in carcinogenic process.

Our meta-analysis was based on published cohort studies; the prospective study design minimizes selection and recall biases compared to retrospective case-control studies. In particular, all four included studies had large sample sizes and long-term follow-up periods. Thus, meta-analysis of these studies provides relatively high statistical power for estimating a prospective relation between baseline levels of dietary magnesium intake and incident colorectal cancer. In general, a meta-analysis of prospective cohort studies is a potentially powerful approach to reliably quantify the optimal amount and long-term benefits of dietary nutrient intake in primary prevention of chronic disease. The best approach to examine a cause-effect relation is to perform a double-blinded and placebo-controlled randomized trial, but it is impractical to conduct such a trial for primary prevention of cancer.

Our study bears several limitations that merit consideration. First, analyses are based on observational studies, and the inherent limitations of such studies may affect our findings. The possibility of residual confounding or bias including measurement errors cannot be excluded. Second, the amount of dietary magnesium intake in each quintile, especially in the lowest quintile (the reference group), varied across individual studies. These differences might lead to difficulties in estimating the true relative risks. However, the differences were not substantial and would not affect the hypothesis-testing nature of our pooled estimates using the comparison between the extreme quintiles from each study. Third, our results were likely to be affected by misclassification of dietary assessment because all included studies provided the data on dietary magnesium intake from a single FFQ measurement at baseline. Nevertheless, such bias was likely to be nondifferential and could have attenuated the final results. Fourth, we considered publication bias since our analyses were based on published studies. However, we found little evidence of publication bias involved in our results by visual examination and statistical tests. In addition, two of the four studies reported null findings. Finally, due to limited information and sample sizes, our meta-analysis lacked power to perform subgroup-analysis for detecting potential effect modifiers on the relation between magnesium intake and colorectal cancer.

In conclusion, our meta-analysis of four prospective cohort studies indicated an inverse association between magnesium intake and colon cancer, indicating a possible role of dietary magnesium for cancer prevention. Further investigation in large cohort studies with sufficient cancer cases or adenoma cases is necessary to provide solid evidence to support the hypothesis. The study adds additional evidence to support prevailing dietary recommendation that health foods rich in magnesium such as green leaf vegetables, whole grain products, legumes, and nuts should be recommended for primary prevention of cancer and other chronic diseases.

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