Magnesium intake and colorectal tumor risk: a case-control study and meta-analysis

Petra A Wark, Rosa Lau, Teresa Norat, and Ellen Kampman

ABSTRACT
Background: Dietary magnesium might be related to colorectal tumor risk through the pivotal roles of magnesium in cellular metabolism, insulin resistance, and systemic inflammation.
Objective: We evaluated the hypothesis of whether higher dietary magnesium intake is associated with reduced colorectal tumor risk.
Design: A case-control study on colorectal adenomas (768 cases; 709 polyp-free control subjects) and a meta-analysis of colorectal adenomas (3 case-control studies) and carcinomas (6 prospective cohort studies) were conducted. Dietary magnesium was estimated from food-frequency questionnaires in the case-control study and most studies in the meta-analyses. Data analysis comprised multiple logistic regression analysis (case-control study) and fixed- and random-effects meta-analyses.
Results: The case-control study showed a nonsignificant inverse association between dietary magnesium intake and risk of colorectal adenomas (OR for every 100-mg/d increase: 0.81; 95% CI: 0.62, 1.06). However, inverse associations were observed only in subjects with BMI (in kg/m²) ≥25, in subjects aged ≥55 y, and for advanced adenomas. Associations did not vary by the calcium-to-magnesium intake ratio. In the meta-analysis, every 100-mg/d increase in magnesium intake was associated with 13% lower risk of colorectal adenomas (OR for every 100-mg/d increase: 0.81; 95% CI: 0.62, 1.00) and 12% lower risk of colorectal cancer (RR: 0.88; 95% CI: 0.81, 0.97).
Conclusions: Our findings support the hypothesis that higher intakes of dietary magnesium are associated with lower risk of colorectal tumors. The consumption of magnesium-rich foods may be a new avenue to explore further in the search for cancer-prevention strategies.

INTRODUCTION
Magnesium is an essential mineral, which is most notably present in foods rich in dietary fiber, nonstarchy vegetables, fruit, nuts, and dairy products. A high consumption of these foods is thought to reduce risk of colorectal cancer (1). Magnesium is required for many physiologic processes that affect colorectal carcinogenesis, including DNA synthesis and repair, glucose metabolism, the regulation of cell proliferation and apoptosis, and defense against oxidative stress (2, 3). Furthermore, magnesium may affect insulin sensitivity and inflammatory responses (4–6), which also influence colorectal carcinogenesis (7).

Indeed, magnesium hydroxide reduced the incidence of chemically induced colorectal cancer in rats (8, 9). Its protective effect, however, might be limited to early stages in tumor development, with some evidence pointing toward the promotion of tumor growth in later stages (3). Observational studies also suggested possible beneficial effects. The rate of colorectal cancer for people in the highest fifth of dietary magnesium intake was 41% lower than the rate of colorectal cancer for people in the lowest fifth of intake in the Swedish Mammography Cohort (10). Most subsequent prospective cohort studies also reported inverse associations (11–14), but they tended to be weaker, were not always significant, or were visible only in analyses stratified by site, sex, or BMI. Dietary magnesium was not associated with colorectal cancer risk in a prospective study from Germany (15). Most (16–20), but not all (21, 22), case-control studies observed lower risks of colorectal cancer in subjects with high magnesium intakes, which was also seen in 3 case-control studies in colorectal adenomas (23–25). In one of these studies (25), magnesium intake was most markedly associated with reduced risk of colorectal adenomas in people whose calcium intakes, compared with magnesium intakes, were relatively small. Calcium competes with magnesium for intestinal absorption and transport.

We aimed to shed additional light on the role of magnesium intake in colorectal carcinogenesis by studying advanced, nonadvanced, multiple, and single adenomas separately in a case-control study in which we also evaluated whether the hypothesized inverse association between dietary magnesium and adenoma risk was stronger in people with low calcium-to-magnesium intake ratios. In addition, we conducted meta-analyses of the association of magnesium intake with risks of colorectal adenomas and carcinomas. Where possible, we stratified analyses by tumor location. In addition, we explored whether the associations depended on sex and BMI.
SUBJECTS AND METHODS

Case-control study

Study population

Trained staff from 10 outpatient clinics in the Netherlands recruited cases and control subjects among all eligible people who underwent endoscopy of the large bowel between June 1997 and October 2002. The trained staff either handed eligible people the information package at the time of endoscopy or mailed the package ≤3 mo thereafter. Cases had to ever have had a histologically confirmed colorectal adenoma, whereas control subjects were never diagnosed with any type of polyp.

Potential participants had to be between 18 and 75 y old, be white, be able to speak Dutch, be free of hereditary colorectal cancer syndromes and chronic inflammatory bowel diseases, and lack histories of colorectal cancer and (partial) bowel resection. The overall response rate was 54% and ranged from 35% to 91% in the various outpatient clinics. A total of 1526 people gave written informed consent, completed food-frequency and general questionnaires, and agreed to provide a blood sample. Forty-nine people were excluded because their dietary data either were incomplete or resulted in implausible energy intakes.

Medical records of the remaining 768 cases and 709 control subjects were reviewed to obtain information on the indication for endoscopy, polyp history, colonoscopy completeness, and adenoma location, size, and number. Ninety-two percent of cases and 85% of control subjects underwent full endoscopy (ie, full colonoscopy or sigmoidoscopy combined with an X-ray). The case-control study was approved by the Medical Review Boards of participating hospitals and Wageningen University. All participants provided written informed consent.

Exposure assessment

The 178-item food-frequency questionnaire referred to the year before study inclusion or symptom onset (26, 27). Data from the Dutch Food Composition Table (28) were used for conversion to daily energy and nutrient intakes. The questionnaire was suitable for ranking individuals according to most food groups and nutrients, with their 6- and 12-mo reproducibility of the assessment being moderate to high (26, 27).

The general questionnaire inquired about demographic, socioeconomic, and lifestyle factors and medical history. It included a question on drugs used at least monthly, which was used to identify takers of magnesium-containing drugs (ie, magnesium hydroxide, carbonate, oxide, peroxide, and sulfate).

Statistical analyses

Intakes of all nutrients except alcohol were adjusted for total energy intake by obtaining the residuals of linear regression analyses of log-transformed nutrients on log-transformed total energy intake and subsequently adding the log of the nutrient intake of interest at the mean caloric intake (29). The resulting values were exponentiated and subdivided into quantiles according to the distribution in control subjects.

Logistic regression was used to evaluate associations of energy-adjusted magnesium intake and use of magnesium-containing drugs with colorectal adenoma risk. ORs for different strata were obtained by inclusion of crossproduct terms with quantiles of magnesium intake into regression models. Corresponding likelihood ratio tests provided additional evidence for or against effect modification. All models on dietary magnesium included age and total energy intake as continuous variables and sex. The following factors were evaluated as potential confounders: BMI; smoking; alcohol consumption; physical activity; education level; family history of colorectal cancer; gastrointestinal complaints; use of nonsteroidal antiinflammatory drugs and multivitamins; consumption of fruit, vegetables, and red meat; and dietary intakes of calcium, folate, zinc, fiber, riboflavin, and vitamins B-6 and B-12. Only dietary folate and vitamin B-6 altered the OR for dietary magnesium by >10% and were included in the final regression models. To test for a linear trend, the median intake in control subjects within a given exposure category was assigned to the corresponding category and subsequently evaluated as a single ordinal term. Analyses of magnesium-containing drugs were adjusted for age, sex, and bowel complaints.

We examined whether the associations depended on the histopathology, number, or location of adenomas by using multinominal logistic regression analyses. Participants with advanced adenomas had either a (tubulo) villous adenoma according to the pathology report or an adenoma ≥1 cm according to the endoscopy report. Multiple-adenoma patients were defined as patients diagnosed with one or more adenomas at full colonoscopy. Cases with a single adenoma who underwent a full colonoscopy were classified as subjects with distal (between the rectum and the splenic flexure) and subjects with proximal lesions. In sensitivity analyses, we restricted the analyses to people who underwent their first endoscopy; excluded users of the drug furosemide (which may increase the renal loss of magnesium) (30), multivitamin users, and subjects who indicated having made dietary changes because of experiencing bowel complaints; and repeated the analyses by using quintiles instead of tertiles. In additional sensitivity analyses, we explored whether the associations depended on heavy alcohol consumption (≥40 g/d for men and ≥20 g/d for women) or having diabetes because these increase renal excretion of magnesium (30), on high physical activity because of possible losses via sweat (31), and on older age or the presence of bowel complaints because of possible magnesium malabsorption (30).

Meta-analysis

Study identification and selection

We performed a systematic search for publications on magnesium intake from the diet or supplements and risk of colorectal adenomas and carcinomas in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) without any language restriction from 1966 to 31 July 2011 by using the search strategy implemented for the World Cancer Research Fund/American Institute for Cancer Research report (1). Medical subject headings and text words covered a broad range of factors on foods and foods components, physical activity, and anthropometric measures. We also hand-searched reference lists from retrieved articles, reviews, and meta-analyses. The complete protocol and full search strategy used is available at http://www.dietandcancerreport.org/cu/ (32). See Supplemental Text 1 under “Supplemental data” in the online issue for a description of the search terminology. The reporting on the systematic review and meta-analysis followed the preferred reporting items for systematic reviews and meta-analyses statement (33).
The flowchart shown in Figure 1 illustrates the study-selection process. An overview of the 20 original publications from which data were extracted is available online (see Supplemental Tables 1–3 under “Supplemental data” in the online issue) and is summarized in the Results. Publications that presented RR estimates and their variances or sufficient data to obtain these effect measures were eligible for inclusion in the meta-analysis. If multiple publications presented findings on the same study population, only the most recent information was used. The meta-analysis eventually comprised 9 studies, which were inclusive of our case-control study.

Statistical analyses

We first conducted a meta-analysis of the dose-response relation of magnesium from diet or supplements with risk of colorectal adenomas and carcinomas. Category-specific risk estimates were transformed into estimates of the RR by the use of an estimation of generalized least-squares for trends with assumption of a linear relation (34). Mean or median exposure values per category level were used directly in the trend estimation when provided; otherwise, the mean exposure level for each category was computed (35). We also performed a meta-analysis in which we compared the highest to lowest categories of intake (36). Fixed- and random-effects models were fitted in both types of meta-analyses for which the most adjusted risk estimate from each study was used. Heterogeneity between studies was quantified with the $I^2$ statistic as a measure of the proportion of total variation in estimates because of heterogeneity. We excluded one study at a time in the sensitivity analyses and prepared funnel plots to assess for small study effects that may have been caused by publication bias. The Stata/SE statistical software package was used for all data analyses (version 9.2; Stata Corp).

RESULTS

Case-control study

The study population according to case-control status is described in Table 1. Cases were, on average, older and more likely to be men, have a higher BMI, and have ever smoked and drank more alcohol than control subjects. Cases had higher energy intakes; had higher absolute intakes of fat, folate, and vitamin B-12; and tended to consume more red meat and vegetables than did control subjects. Fewer cases than control subjects underwent endoscopy because of lower gastrointestinal complaints and used magnesium-containing drugs.

Lifestyle and medical characteristics of control subjects according to energy-adjusted dietary magnesium intake are described in Table 2. Control subjects in the highest one-third of energy-adjusted intake of dietary magnesium were, on average, older than control subjects with lower intakes. The top one-third...
The calcium-to-magnesium ratio (tween dietary magnesium and adenoma risk did not depend on 0.65 (0.46, 0.92) for distal adenomas]. The association be-
compared with lowest tertile: 0.47 (0.28, 0.79) for proximal and
did not depend on their location [OR (95% CI) for highest
use of multivitamin supplements [n (%)]

**Medical history [n (%)]**
- Positive family history of colorectal cancer 173 (23.5) 136 (20.1) 0.12
- Regular use of NSAIDs\(^3\)
- Ever smokers [n (%)] 204 (26.6) 207 (29.2) 0.26
- Bowel complaints or defecation problems as indication of endoscopy 366 (47.7) 544 (76.7) <0.001
- Users of drugs containing magnesium\(^6\) 9 (1.17) 26 (3.67) 0.0016

**Dietary factors\(^7\)**
- Total energy intake (kJ/d) 8703 ± 2484 8434 ± 2498 0.038
- Protein (g/d) 79.0 ± 22.5 76.9 ± 21.6 0.065
- Carbohydrates (g/d) 226.5 ± 69.9 229.0 ± 71.0 0.50
- Fat (g/d) 79.3 (62.6, 95.9)\(^7\) 75.1 (58.4, 97.2) 0.034
- Fruit (g/d) 127.2 (73.7, 249.7) 124.7 (72.5, 243.9) 0.35
- Vegetables (g/d) 113.2 (89.6, 142.7) 109.2 (83.3, 139.1) 0.025
- Red meat (g/d) 60.3 (33.4, 82.0) 53.5 (30.2, 79.0) 0.017
- Alcohol (g/d) 9.6 (1.0, 24) 4.2 (0.33, 15) <0.001
- Dietary calcium (mg/d) 1055 (817.2, 1299) 1040 (795.9, 1323) 0.91
- Dietary magnesium (mg/d) 337.7 (288.4, 395.0) 332.7 (277.5, 391.5) 0.15
- Dietary fiber (g/d) 23.4 (19.2, 28.1) 22.6 (18.8, 27.2) 0.076
- Dietary folate (\(\mu g/d\)) 192.8 (161.6, 231.2) 184.1 (155.6, 219.7) 0.0010
- Dietary riboflavin (mg/d) 1.53 (1.25, 1.92) 1.54 (1.21, 1.90) 0.43
- Dietary vitamin B-6 (mg/d) 1.59 (1.34, 1.90) 1.55 (1.30, 1.86) 0.057
- Dietary vitamin B-12 (mg/d) 4.43 (3.40, 5.72) 4.18 (3.16, 5.52) 0.0059

**TABLE 1**

**Characteristics of the study population in our case-control study**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adenoma cases ((n = 768))</th>
<th>Endoscopy control subjects ((n = 709))</th>
<th>(P^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics and lifestyle factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age [y]</td>
<td>59.1 ± 10.1(^2)</td>
<td>51.5 ± 13.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men [n (%)]</td>
<td>411 (53.5)</td>
<td>272 (38.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>26.1 ± 3.8</td>
<td>25.5 ± 4.1</td>
<td>0.0019</td>
</tr>
<tr>
<td>Low educational level [n (%)](^4)</td>
<td>249 (35.7)</td>
<td>215 (33.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Ever smokers [n (%)]</td>
<td>511 (67.0)</td>
<td>389 (55.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High physical activity [n (% in top quintile)](^5)</td>
<td>132 (18.4)</td>
<td>137 (20.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Use of multivitamin supplements [n (%)]</td>
<td>134 (17.5)</td>
<td>127 (17.9)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Medical history [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive family history of colorectal cancer</td>
<td>173 (23.5)</td>
<td>136 (20.1)</td>
<td>0.12</td>
</tr>
<tr>
<td>Regular use of NSAIDs(^3)</td>
<td>204 (26.6)</td>
<td>207 (29.2)</td>
<td>0.26</td>
</tr>
<tr>
<td>Bowel complaints or defecation problems as indication of endoscopy</td>
<td>366 (47.7)</td>
<td>544 (76.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Users of drugs containing magnesium(^6)</td>
<td>9 (1.17)</td>
<td>26 (3.67)</td>
<td>0.0016</td>
</tr>
</tbody>
</table>

\(1\) Unadjusted \(P\) values were based on chi-square, \(t\), or Mann-Whitney \(U\) test statistics as appropriate.
\(2\) Mean ± SD (all such values).
\(3\) Primary school or lower vocational training only.
\(4\) On the basis of a continuous activity score.
\(5\) NSAIDs, nonsteroidal antiinflammatory drugs. Use ≥12 times/y.
\(6\) Magnesium hydroxide, magnesium carbonate, magnesium oxide, magnesium peroxide, or magnesium sulfate.
\(7\) Assessed values (not energy-adjusted or log-transformed).
\(8\) Median; 25th, 75th percentiles in parentheses (all such values).

intake band contained more control subjects with a family his-
tory of colorectal cancer than other intake bands. The majority
of control subjects underwent (full) endoscopy for the first time.
Only a few control subjects reported the use of furosemide,
taking magnesium-containing drugs, or having diabetes, the lat-
er of which was more common in the top one-third intake band.
A larger proportion of control subjects in the bottom one-third
intake band underwent endoscopy because of bowel complaints.

The higher the dietary magnesium intake was, the lower was
the risk of colorectal adenomas (Table 3). This particularly
applied to risk of advanced and multiple adenomas (Table 3) but
did not depend on their location [OR (95% CI) for highest
compared with lowest tertile: 0.47 (0.28, 0.79) for proximal and
0.65 (0.46, 0.92) for distal adenomas]. The association be-
tween dietary magnesium and adenoma risk did not depend on
the calcium-to-magnesium ratio (\(P\)-interaction = 0.86) or sex
(\(P\)-interaction = 0.43) but depended on BMI and age (Table 3).
Inverse associations between dietary magnesium intake and
adenoma risk were detected only in overweight subjects and in
subjects aged ≥55 y. A comparable pattern was observed in
analyses according to adenoma subtype (results not shown).
Sensitivity analyses supported our findings; the exclusion of
subjects who underwent a repeated endoscopy (OR for highest
compared with lowest tertile of dietary magnesium intake: 0.68,
95% CI: 0.47, 1.00), takers of magnesium-containing drugs
(OR: 0.73; 95% CI: 0.53, 1.00), furosemide users (OR: 0.68;
95% CI: 0.49, 0.93), multivitamin users (OR: 0.70; 95% CI:
0.49, 0.98), and subjects who indicated having changed their
diet (OR: 0.61; 95% CI: 0.40, 0.93) did not affect the conclu-
sions. Besides, an inverse, albeit not significant, association was
also shown when quintiles of dietary magnesium intake were
studied (OR for highest compared with lowest quintile: 0.72,
95% CI: 0.47, 1.10; \(P\)-linear trend = 0.07). These associations
did not depend on heavy alcohol consumption, diabetes, high
physical activity, or having bowel complaints (\(P\)-interaction ≥
0.33). The data supported a linear dose-response relation (see
Supplemental Figure 1 under “Supplemental data” in the online
issue).
### TABLE 2
Distribution of lifestyle and medical factors according to tertiles of energy-adjusted magnesium intake in endoscopy control subjects in our case-control study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Energy-adjusted intake of dietary magnesium in endoscopy control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;315.9 mg/d (n = 236)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>49.7 ± 14.8 (n = 236)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1 ± 3.98 (n = 236)</td>
</tr>
<tr>
<td>Low educational level [n (%)]</td>
<td>77 (35.5) (n = 236)</td>
</tr>
<tr>
<td>Ever smokers [n (%)]</td>
<td>146 (62.1) (n = 236)</td>
</tr>
<tr>
<td>High physical activity [n in top quintile]</td>
<td>49 (22.1) (n = 236)</td>
</tr>
<tr>
<td>Alcohol consumption (g/d)</td>
<td>104 (45.6) (n = 236)</td>
</tr>
<tr>
<td>Made dietary changes because of bowel complaints</td>
<td>104 (45.6) (n = 236)</td>
</tr>
<tr>
<td>Takers of drugs containing magnesium</td>
<td>104 (45.6) (n = 236)</td>
</tr>
</tbody>
</table>

1 Unadjusted \( P \) values were based on ANOVA, Kruskal-Wallis, or chi-square test statistics as appropriate.
2 Mean ± SD (all such values).
3 Primary school or lower vocational training only.
4 On the basis of a continuous activity score.
5 Median; 25th, 75th percentiles in parentheses (all such values).
6 A total of ≥40 g/d for men and ≥20 g/d for women.
7 NSAIDs, nonsteroidal antiinflammatory drugs. Use ≥12 times/y.
8 Full colonoscopy or sigmoidoscopy combined with X-ray.
9 All changes are likely to have affected dietary magnesium intake.
10 Magnesium hydroxide, magnesium carbonate, magnesium oxide, magnesium peroxide, or magnesium sulfate.
11 This drug may increase renal loss of magnesium (30).

Cases were less likely to have used magnesium-containing drugs than were control subjects (OR: 0.52; 95% CI: 0.23, 1.20), but the point estimate was imprecise and not significant.

### Meta-analysis

**Magnesium and colorectal adenomas**

The literature search revealed 3 case-control studies on magnesium and risk of colorectal adenomas (23–25) but no prospective studies (see Supplemental Table 1 under “Supplemental data” in the online issue). The only study that made use of population control subjects did not provide cell counts or CIs and could not be included in the meta-analysis (OR for highest compared with lowest quartile: 0.43; \( P \)-linear trend = 0.030) (24).

The meta-analysis, which, thus, was based on 2 published studies along with our case-control study and included a total of 1703 cases and 2253 control subjects, showed that the higher the intake of magnesium, the lower the risk of colorectal adenomas (OR for every 100-mg/d increase in dietary magnesium intake: 0.87; 95% CI: 0.75, 1.00; [Figure 2]). A linear dose-response relation could be assumed (see Supplemental Figure 2 under “Supplemental data” in the online issue).

One of the included studies observed an inverse (but not significant) association with dietary magnesium, whereas a significant and stronger inverse association was seen when magnesium from supplements and magnesium from the diet were studied jointly (25). The use of combined rather than dietary estimates for this study in the meta-analysis increased the strength of the association (OR for every 100-mg/d increase in magnesium intake: 0.80; 95% CI: 0.71, 0.90). The highest compared with lowest comparison also showed that subjects with higher magnesium intakes had lower colorectal adenoma risks (OR: 0.76; 95% CI: 0.60, 0.96; see Supplemental Figure 1 under “Supplemental data” in the online issue).

**Magnesium and colorectal cancer**

Eleven publications on 7 case-control studies (16–22, 37–40) on magnesium intake and colorectal cancer were identified, and all of them were based on dietary estimates (see Supplemental Table 2 under “Supplemental data” in the online issue). A meta-analysis was not conducted because only 2 of the 11 publications reported sufficient data to undertake a meta-analysis (16, 22). Three (16–20) of the 7 (16–20) case-control studies showed inverse associations but only in the smallest of these three
studies (399 cases and 399 control subjects) (16) was signif-

cance reached. The study in 1993 cases and 2410 control

subjects showed no evidence for an association (39, 40) and

neither did the 3 studies with

300 cases and control subjects

each (21, 22, 38).

In addition, 6 prospective cohort studies were identified

(10–15), which included a total of 5834 cases. Follow-up time

ranged from 7.9 to longer than 17 y, and 3 of these studies in-

cluded only women (see Supplemental Table 3 under “Supple-

mental data” in the online issue). The highest compared with

lowest category of intake (RR: 0.84; 95% CI: 0.73, 0.97; see

Supplemental Figure 1 under “Supplemental data” in the online

issue) as well as the dose-response meta-analysis (Figure 2)

showed inverse associations of similar magnitude for colorectal,

colon, and rectum cancer risks. Between-study heterogeneity

was observed, but this appeared to be largely due to the Swedish

Mammography Cohort (10). Exclusion of the latter study only

slightly attenuated the pooled RR [RR for colorectal cancer

for every 100-mg/d increase in magnesium intake: 0.90; 95% CI:

0.83, 0.99; I^2 = 5.4%, P for heterogeneity = 0.38; compared

with RR of 0.88 (Figure 2) when all studies were included]. Dose-

response graphs suggested a linear relation (see Supplemental

Figure 2 under “Supplemental data” in the online issue).

Two studies presented analyses according to sex and obesity.

The Netherlands Cohort Study on Diet and Cancer reported com-

parable results for men and women and observed an inverse
dose-response relation for colon and proximal cancer in over-

weight individuals only (13). In contrast, the Japan Public Health

| TABLE 3 |

| Association between energy-adjusted intake of dietary magnesium (mg/d) and risk of colorectal adenomas in the case-control study^ |  |

<table>
<thead>
<tr>
<th>Comparisons, subgroups, and parameters</th>
<th>&lt;315.9 mg/d</th>
<th>315.9 to 358.85 mg/d</th>
<th>≥358.85 mg/d</th>
<th>P-linear trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>All^</td>
<td>270/236</td>
<td>267/236</td>
<td>231/237</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Referent</td>
<td>0.90 (0.68, 1.19)</td>
<td>0.73 (0.53, 1.00)</td>
<td>0.050</td>
</tr>
<tr>
<td>BMI (in kg/m^2) &lt;25</td>
<td>104/134</td>
<td>121/109</td>
<td>89/112</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Referent</td>
<td>1.39 (0.93, 2.09)</td>
<td>0.87 (0.56, 1.35)</td>
<td>0.58</td>
</tr>
<tr>
<td>BMI ≥25</td>
<td>161/100</td>
<td>143/127</td>
<td>140/124</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Referent</td>
<td>0.62 (0.42, 0.90)</td>
<td>0.64 (0.43, 0.95)</td>
<td>0.025</td>
</tr>
<tr>
<td>Age &lt;55 y</td>
<td>72/141</td>
<td>100/138</td>
<td>86/125</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Referent</td>
<td>1.16 (0.77, 1.74)</td>
<td>1.01 (0.65, 1.56)</td>
<td>0.98</td>
</tr>
<tr>
<td>Age ≥55 y</td>
<td>198/95</td>
<td>167/98</td>
<td>145/112</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Referent</td>
<td>0.72 (0.50, 1.05)</td>
<td>0.56 (0.37, 0.83)</td>
<td>0.004</td>
</tr>
<tr>
<td>Nonadvanced adenomas compared with control subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All^</td>
<td>89/236</td>
<td>92/236</td>
<td>92/237</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Referent</td>
<td>0.93 (0.64, 1.35)</td>
<td>0.92 (0.61, 1.39)</td>
<td>0.69</td>
</tr>
<tr>
<td>Advanced adenomas compared with control subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All^</td>
<td>163/236</td>
<td>157/236</td>
<td>125/237</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Referent</td>
<td>0.86 (0.62, 1.19)</td>
<td>0.60 (0.42, 0.87)</td>
<td>0.007</td>
</tr>
<tr>
<td>Single adenoma compared with control subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All^</td>
<td>104/208</td>
<td>111/195</td>
<td>106/199</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Referent</td>
<td>0.96 (0.67, 1.38)</td>
<td>0.85 (0.57, 1.27)</td>
<td>0.43</td>
</tr>
<tr>
<td>Multiple adenomas compared with control subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All^</td>
<td>144/208</td>
<td>132/195</td>
<td>103/199</td>
<td></td>
</tr>
<tr>
<td>OR (95% CI)</td>
<td>Referent</td>
<td>0.89 (0.63, 1.26)</td>
<td>0.69 (0.46, 1.03)</td>
<td>0.072</td>
</tr>
</tbody>
</table>

1 ORs (95% CIs) were adjusted for age, sex, total energy intake, dietary folate, and vitamin B-6.  
2 OR for every 100-mg/d increase in magnesium intake: 0.81 (95% CI: 0.62, 1.06).  
3 P-interaction = 0.011.  
4 P-interaction = 0.081.  
5 Despite not being significant, the odds of having advanced rather than nonadvanced colorectal adenomas in people in the highest tertile of dietary magnesium intake seemed to be lower than the odds of having advanced rather than nonadvanced colorectal adenomas in people in the lowest tertile of dietary magnesium intake (OR: 0.66; 95% CI: 0.42, 1.02; P-linear trend = 0.064).  
6 Applies to subjects who underwent a full endoscopy (700 cases and 602 control subjects). The difference between associations with multiple and single adenomas was not significant (OR for having multiple rather than single adenomas for the highest compared with the lowest tertile of dietary magnesium: 0.81; 95% CI: 0.52, 1.26; P-linear trend = 0.36).
Center-based Prospective Study only detected associations in men with BMI (in kg/m²) < 25 (14). The literature search did not identify any studies on magnesium-containing drugs.

**DISCUSSION**

In addition to conducting case-control analyses of colorectal adenomas, we provided a comprehensive overview of the epidemiologic evidence on magnesium and colorectal tumors available. Both our case-control study and the meta-analyses showed inverse associations between magnesium intake and risk of colorectal tumors. In the case-control study, associations with colorectal adenomas were restricted to overweight individuals and subjects aged ≥ 55 y and were more clearly visible for advanced and multiple adenomas. The associations did not depend on the calcium-to-magnesium intake ratio. Neither the case-control study nor the meta-analysis suggested differential associations according to tumor location.

The available data have limitations. Our case-control study included more cases than any other identified study on magnesium intake and colorectal adenomas, but overall, the available evidence was limited. Only 3 studies on adenomas and 6 studies on carcinomas have been published to our knowledge. In contrast to the cohort studies on which the meta-analysis of colorectal cancer was based, the meta-analysis of colorectal adenomas included only endoscopy-based case-control studies. Endoscopy-based populations may include a proportion of people with chronic diarrhea or intestinal and biliary fistulae in whom magnesium absorption is impaired (30, 41). Because the association between dietary magnesium intake and risk of colorectal adenomas was similar in subjects with and without bowel complaints, the presence of this subcategory does not compromise the validity in our

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**TABLE 2.** Dose-response meta-analysis of magnesium intake and risk of colorectal adenomas and cancer.

<table>
<thead>
<tr>
<th>Author, year (reference)</th>
<th>Country</th>
<th>Sex</th>
<th>Cases</th>
<th>N</th>
<th>RR per 100 mg/d (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. colorectal adenoma*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macquart-Moulin (Dietary Mg), 1987 (23) France</td>
<td>M+F</td>
<td>252</td>
<td>490</td>
<td></td>
<td>0.75 (0.55, 1.03)</td>
<td>21.26</td>
</tr>
<tr>
<td>Dai (Dietary Mg), 2007 (25) USA</td>
<td>M+F</td>
<td>683</td>
<td>1989</td>
<td></td>
<td>0.96 (0.78, 1.17)</td>
<td>49.66</td>
</tr>
<tr>
<td>Wark (Dietary Mg), 2012 Netherlands</td>
<td>M+F</td>
<td>768</td>
<td>1477</td>
<td></td>
<td>0.81 (0.62, 1.06)</td>
<td>29.08</td>
</tr>
<tr>
<td>I-V Subtotal (I-squared = 0.00, p = 0.380)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.87 (0.75, 1.00)</td>
<td>100.00</td>
</tr>
<tr>
<td>D+L Subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.87 (0.75, 1.00)</td>
<td></td>
</tr>
<tr>
<td>2. colorectal cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larsson (Dietary Mg), 2005 (10) Sweden</td>
<td>F</td>
<td>806</td>
<td>61,433</td>
<td></td>
<td>0.46 (0.28, 0.76)</td>
<td>3.16</td>
</tr>
<tr>
<td>Folsom (Total Mg), 2006 (11) USA</td>
<td>F</td>
<td>1112</td>
<td>35,196</td>
<td></td>
<td>0.87 (0.77, 1.00)</td>
<td>45.27</td>
</tr>
<tr>
<td>Lin (Total Mg), 2006 (12) USA</td>
<td>F</td>
<td>259</td>
<td>38,345</td>
<td></td>
<td>1.01 (0.81, 1.27)</td>
<td>15.52</td>
</tr>
<tr>
<td>van den Brandt (Dietary Mg), 2007 (13) Netherlands</td>
<td>M+F</td>
<td>2328</td>
<td>6453</td>
<td></td>
<td>0.92 (0.75, 1.12)</td>
<td>19.30</td>
</tr>
<tr>
<td>Ma (Dietary Mg), 2010 (14) Japan</td>
<td>M+F</td>
<td>1129</td>
<td>87,117</td>
<td></td>
<td>0.77 (0.59, 0.99)</td>
<td>11.54</td>
</tr>
<tr>
<td>Li (Dietary Mg), 2011 (15) Germany</td>
<td>M+F</td>
<td>201</td>
<td>24,323</td>
<td></td>
<td>1.14 (0.76, 1.68)</td>
<td>5.21</td>
</tr>
<tr>
<td>I-V Subtotal (I-squared = 54.7%, p = 0.050)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.88 (0.81, 0.97)</td>
<td>100.00</td>
</tr>
<tr>
<td>D+L Subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.87 (0.75, 1.01)</td>
<td></td>
</tr>
<tr>
<td>3. colon cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larsson (Dietary Mg), 2005 (10) Sweden</td>
<td>F</td>
<td>547</td>
<td>61,433</td>
<td></td>
<td>0.58 (0.31, 1.07)</td>
<td>2.85</td>
</tr>
<tr>
<td>Folsom (Total Mg), 2006 (11) USA</td>
<td>F</td>
<td>900</td>
<td>35,196</td>
<td></td>
<td>0.85 (0.74, 0.99)</td>
<td>49.57</td>
</tr>
<tr>
<td>Lin (Total Mg), 2006 (12) USA</td>
<td>F</td>
<td>199</td>
<td>38,345</td>
<td></td>
<td>1.06 (0.83, 1.37)</td>
<td>16.78</td>
</tr>
<tr>
<td>van den Brandt (Dietary Mg), 2007 (13) Netherlands</td>
<td>M+F</td>
<td>1578</td>
<td>6453</td>
<td></td>
<td>0.89 (0.71, 1.12)</td>
<td>20.84</td>
</tr>
<tr>
<td>Ma (Dietary Mg), 2010 (14) Japan</td>
<td>M+F</td>
<td>716</td>
<td>87,117</td>
<td></td>
<td>0.71 (0.51, 0.98)</td>
<td>9.96</td>
</tr>
<tr>
<td>I-V Subtotal (I-squared = 29.6%, p = 0.225)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.87 (0.76, 0.96)</td>
<td>100.00</td>
</tr>
<tr>
<td>D+L Subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.86 (0.75, 0.99)</td>
<td></td>
</tr>
<tr>
<td>4. rectal cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larsson (Dietary Mg), 2005 (10) Sweden</td>
<td>F</td>
<td>252</td>
<td>61,433</td>
<td></td>
<td>0.27 (0.11, 0.62)</td>
<td>3.96</td>
</tr>
<tr>
<td>Folsom (Total Mg), 2006 (11) USA</td>
<td>F</td>
<td>236</td>
<td>35,196</td>
<td></td>
<td>0.96 (0.73, 1.26)</td>
<td>38.37</td>
</tr>
<tr>
<td>Lin (Total Mg), 2006 (12) USA</td>
<td>F</td>
<td>53</td>
<td>38,345</td>
<td></td>
<td>0.77 (0.44, 1.38)</td>
<td>11.15</td>
</tr>
<tr>
<td>van den Brandt (Dietary Mg), 2007 (13) Netherlands</td>
<td>M+F</td>
<td>750</td>
<td>6453</td>
<td></td>
<td>0.99 (0.73, 1.35)</td>
<td>29.89</td>
</tr>
<tr>
<td>Ma (Dietary Mg), 2010 (14) Japan</td>
<td>M+F</td>
<td>413</td>
<td>87,117</td>
<td></td>
<td>0.85 (0.56, 1.29)</td>
<td>16.63</td>
</tr>
<tr>
<td>I-V Subtotal (I-squared = 54.4%, p = 0.067)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.88 (0.74, 1.04)</td>
<td>100.00</td>
</tr>
<tr>
<td>D+L Subtotal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.82 (0.62, 1.08)</td>
<td></td>
</tr>
</tbody>
</table>

**FIGURE 2.** Dose-response meta-analysis of magnesium intake and risk of colorectal adenomas and cancer. The center of the solid boxes represents the sizes of the RR for each study, with the area of these boxes representing the weight that each study contributes to the overall RR. Horizontal lines indicate the corresponding 95% CIs. The center of the diamonds indicates summary RRs, and the left and right extremes represent the corresponding CIs. *Case-control studies. D+L, DerSimonian and Laird (random-effects) model; I-V, prospective cohort studies I-V that represent the inverse-variance–weighted (fixed-effects) model.
In conclusion, we observed that magnesium intake was inversely associated with risk of colorectal adenomas and colorectal cancer. However, the number of studies on this topic is small. In particular, the observation that the association was limited to overweight individuals in the case-control study requires confirmation. Elucidation of pathways that involve dietary magnesium and insulin resistance in colorectal carcinogenesis is also warranted.
We thank the endoscopy staff and gastroenterologists of the following hospitals in the Netherlands: Sluisland Ziekenhuis (Doe tenhem), Ziekenhuis Gelderse Vallei (Ede), Radboud University Nijmegen Medical Centre (Nijmegen), Antonius Ziekenhuis (Nieuwegein), Meander Medisch Centrum (Amersfoort), Ziekenhuis Rijnstate (Arnhem), Ziekenhuis Rivierenland (Tiel), Slotervaart Ziekenhuis (Amsterdam), Jeroen Bosch Ziekenhuis (Den Bosch), and Canisius Wilhelmina Ziekenhuis (Nijmegen). We are also grateful to Marga Ocké from the National Institute of Public Health and the Environment, Bilthoven, Netherlands, for calculation of food and nutrient intakes and to Lorijn van Rooijen for contributing to the literature research. We also thank all of the Wageningen University staff who were involved in the recruitment, data collection, and data management of the case-control study, and to all staff who contributed to the World Cancer Research Fund meta-analysis project on colorectal adenomas and carcinomas at Wageningen University and Imperial College London.

The authors’ responsibilities were as follows—TN and EI: designed the research and had primary responsibility for the final content of the manuscript; PAW and RL: conducted the research and analyzed data; PAW: drafted the manuscript; and all authors: provided critical revisions for important intellectual content and read and approved the final manuscript. None of the authors had a conflict of interest.

REFERENCES


