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Short Communication

Magnesium intake and colorectal cancer risk in the Netherlands Cohort Study

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Energy-adjusted magnesium intake was nonsignificantly inversely related to risk of colorectal cancer (n = 2328) in the Netherlands Cohort Study on Diet and Cancer that started in 1986 (n = 58 279 men and 62 573 women). Statistically significant inverse trends in risk were observed in overweight subjects for colon and proximal colon cancer across increasing quintiles of magnesium uptake (P-trend, 0.05 and 0.02, respectively). Although an overall protective effect was not afforded, our results suggest an effect of magnesium in overweight subjects, possibly through decreasing insulin resistance.

Keywords: colorectal cancer; cohort studies; magnesium; BMI

MATERIALS AND METHODS

The NLCS started in 1986 and included 58 279 men and 62 573 women aged 55 – 69 years. At baseline, cohort members completed a mailed, self-administered questionnaire on dietary habits, anthropometry, and other risk factors for cancer (Van den Brandt et al, 1990a). Habitual consumption of food and beverages during the year preceding baseline was assessed using a 150-item semiquantitative food frequency questionnaire (Goldbohm et al, 1994). From this, nutrient intakes were calculated from the 150 food items using the computerized Dutch food composition table (Nevo-table, 1986). Nutrient intake was adjusted for energy intake by the residual method (Willett and Stampfer, 1986).

Data were processed and analysed using the case–cohort approach, enumerating the cases for the entire cohort, and estimating the person-years at risk from a subcohort of 5000 subjects, which was randomly sampled from the entire cohort immediately after the baseline measurement and followed up for vital status. Follow-up for cancer incidence is established by record linkage with the Netherlands Cancer Registry and PALGA, a nationwide pathology database (Van den Brandt et al, 1990b). After 13.3 years of follow-up, a total of 2679 incident colorectal cancer cases were reported. Cases and subcohort members were excluded if they reported cancer other than non-melanoma skin cancer, or had incomplete data for diet, anthropometry, or confounders. Finally, 4125 subcohort members and 2328 colorectal cancer cases were available for analysis.

Statistical analysis

Incidence rate ratios (RR) and 95% confidence intervals for colorectal cancer and subsites were estimated using Cox proportional hazards models (Cox, 1972), with Stata software (Cleves et al, 2002). Standard errors were estimated using the robust Huber–White sandwich estimator to account for additional variance introduced by sampling from the cohort (Schoenfeld, 1982). All RRs are adjusted for confounders that contributed significantly to the model or influenced the RR of magnesium more than 10% (age, sex, family history of colorectal cancer, body mass index (BMI), physical activity, energy-adjusted intakes of fat, fiber, calcium, folate, beta-carotene, vitamins E and B6, alcohol, and energy intake).

RESULTS

Mean (± s.d.) energy-adjusted magnesium intake was 332 (± 58) and 292 (± 48) mg day⁻¹ among subcohort men and women, respectively. Important sources of magnesium were wholewheat bread, dairy, pulses, coffee, tea, and peanuts/peanut butter. Magnesium supplements were used by only 0.2% of individuals. Baseline characteristics of the subcohort are presented in Supplementary Table. Magnesium intake was weakly inversely associated with colorectal and colon cancer risks in men and
women, but nonsignificantly (Table 1). Exclusion of the first 2 years of follow-up yielded similar results. Because men and women showed comparable results, we combined them in analyses stratified by BMI. Table 2 shows that the association with colorectal cancer and its subsites varied by BMI: for those with a BMI $\geq 25$ kg m$^{-2}$, this was inverse (except rectum), with P-trend reaching significance for colon, and especially proximal colon cancer. The RRs of proximal colon cancer for increasing quintiles of magnesium were 1.0, 0.69, 0.65, 0.48, and 0.54, respectively ($P$-trend $= 0.02$). For those with BMI $< 25$ kg m$^{-2}$, there was no

### Table 1  Relative rates (RRs) of colorectal cancer according to energy-adjusted magnesium intake, Netherlands Cohort Study 1986–1999

| Quintiles of energy-adjusted magnesium intake (mg day$^{-1}$) | Q1 | Q2 | Q3 | Q4 | Q5 | P-trend |
|-------------------------------------------------------------|----|----|----|----|----|--------|
| **Men**<br>Colorectal cancer<br>Cases                      | 275| 281| 297| 264| 263| 0.57   |
| Age-adjusted RR<sub>a</sub>                                 | 1.0| 1.00 (0.80–1.25) | 1.04 (0.83–1.29) | 0.95 (0.76–1.18) | 0.96 (0.77–1.20) | 0.57   |
| Multivariate RR<sub>b</sub>                                 | 1.0| 0.96 (0.75–1.22) | 0.96 (0.74–1.26) | 0.87 (0.64–1.17) | 0.91 (0.62–1.35) | 0.50   |
| **Colon cancer**<br>Cases                                   | 192| 180| 185| 167| 159| 0.13   |
| Age-adjusted RR<sub>a</sub>                                 | 1.0| 0.92 (0.71–1.18) | 0.92 (0.72–1.18) | 0.86 (0.67–1.10) | 0.83 (0.64–1.07) | 0.13   |
| Multivariate RR<sub>b</sub>                                 | 1.0| 0.89 (0.67–1.17) | 0.87 (0.64–1.19) | 0.82 (0.59–1.15) | 0.85 (0.54–1.33) | 0.41   |
| **Proximal colon cancer**<br>Cases                          | 77 | 81 | 86 | 73 | 64 | 0.27   |
| Age-adjusted RR<sub>a</sub>                                 | 1.0| 1.03 (0.73–1.45) | 1.07 (0.76–1.50) | 0.94 (0.66–1.33) | 0.83 (0.58–1.20) | 0.27   |
| Multivariate RR<sub>b</sub>                                 | 1.0| 0.95 (0.65–1.38) | 0.95 (0.63–1.43) | 0.81 (0.51–1.28) | 0.73 (0.39–1.36) | 0.28   |
| **Distal colon cancer**<br>Cases                            | 103| 90 | 95 | 90 | 85 | 0.30   |
| Age-adjusted RR<sub>a</sub>                                 | 1.0| 0.85 (0.62–1.17) | 0.88 (0.65–1.21) | 0.86 (0.63–1.18) | 0.82 (0.60–1.14) | 0.30   |
| Multivariate RR<sub>b</sub>                                 | 1.0| 0.84 (0.59–1.19) | 0.86 (0.58–1.27) | 0.87 (0.57–1.31) | 0.94 (0.53–1.64) | 0.85   |
| **Rectum cancer<sup>c</sup>**<br>Cases                       | 83 | 101| 112| 97 | 104| 0.27   |
| Age-adjusted RR<sub>a</sub>                                 | 1.0| 1.19 (0.86–1.65) | 1.29 (0.94–1.78) | 1.15 (0.83–1.59) | 1.25 (0.91–1.73) | 0.27   |
| Multivariate RR<sub>b</sub>                                 | 1.0| 1.12 (0.79–1.59) | 1.18 (0.80–1.73) | 0.99 (0.63–1.55) | 1.07 (0.61–1.89) | 0.94   |
| **Women**<br>Colorectal cancer<br>Cases                     | 217| 185| 172| 186| 188| 0.42   |
| Age-adjusted RR<sub>a</sub>                                 | 1.0| 0.84 (0.66–1.07) | 0.79 (0.62–1.01) | 0.88 (0.69–1.12) | 0.88 (0.69–1.12) | 0.42   |
| Multivariate RR<sub>b</sub>                                 | 1.0| 0.83 (0.63–1.08) | 0.78 (0.58–1.06) | 0.89 (0.63–1.24) | 0.89 (0.59–1.35) | 0.77   |
| **Colon cancer**<br>Cases                                   | 159| 136| 127| 135| 138| 0.45   |
| Age-adjusted RR<sub>a</sub>                                 | 1.0| 0.94 (0.64–1.10) | 0.80 (0.61–1.05) | 0.87 (0.66–1.14) | 0.88 (0.67–1.15) | 0.45   |
| Multivariate RR<sub>b</sub>                                 | 1.0| 0.83 (0.62–1.12) | 0.79 (0.57–1.11) | 0.89 (0.61–1.29) | 0.89 (0.56–1.40) | 0.77   |
| **Proximal colon cancer**<br>Cases                          | 95 | 70 | 64 | 70 | 84 | 0.70   |
| Age-adjusted RR<sub>a</sub>                                 | 1.0| 0.73 (0.52–1.03) | 0.68 (0.48–0.97) | 0.77 (0.54–1.08) | 0.92 (0.66–1.28) | 0.70   |
| Multivariate RR<sub>b</sub>                                 | 1.0| 0.71 (0.49–1.03) | 0.66 (0.44–1.01) | 0.75 (0.47–1.20) | 0.86 (0.49–1.52) | 0.69   |
| **Distal colon cancer**<br>Cases                            | 58 | 61 | 60 | 59 | 50 | 0.46   |
| Age-adjusted RR<sub>a</sub>                                 | 1.0| 1.02 (0.69–1.50) | 1.01 (0.69–1.49) | 1.02 (0.69–1.51) | 0.84 (0.56–1.26) | 0.46   |
| Multivariate RR<sub>b</sub>                                 | 1.0| 1.03 (0.67–1.59) | 1.03 (0.63–1.67) | 1.09 (0.64–1.88) | 0.93 (0.47–1.84) | 0.98   |
| **Rectum cancer<sup>c</sup>**<br>Cases                       | 58 | 49 | 45 | 51 | 50 | 0.67   |
| Age-adjusted RR<sub>a</sub>                                 | 1.0| 0.83 (0.55–1.25) | 0.78 (0.51–1.18) | 0.90 (0.60–1.35) | 0.87 (0.58–1.31) | 0.67   |
| Multivariate RR<sub>b</sub>                                 | 1.0| 0.81 (0.52–1.25) | 0.76 (0.46–1.25) | 0.89 (0.51–1.55) | 0.91 (0.46–1.79) | 0.90   |

*Data presented as RR (95% confidence interval). †The model included age, family history of colorectal cancer, BMI, physical activity, energy-adjusted intakes of fat, fibre, calcium, folate, beta-carotene, vitamin E, vitamin B6, alcohol, and energy intake. ‡Includes rectosigmoid.*
Table 2  Relative rates (RRs) of colorectal cancer according to magnesium intake and BMI in men and women combined, Netherlands Cohort Study 1986–1999

| Quintiles of energy-adjusted magnesium intake (mg day⁻¹) | Q1   | Q2   | Q3   | Q4   | Q5   | P-trend |
|---------------------------------------------------------|------|------|------|------|------|---------|
| Quintile cutoffs (mg day⁻¹)                             | <270 | 271–298 | 299–320 | 321–350 | >350 |         |
| Median (mg day⁻¹)                                       | 248  | 286  | 309  | 335  | 375  |         |
| Person-years in subcohort                               | 9707 | 9939 | 9956 | 9902 | 10077|         |
| Colorectal cancer                                        |      |      |      |      |      |         |
| Cases                                                    | 522  | 472  | 451  | 433  | 450  | 0.56    |
| Multivariate RRa                                         | 1.0  | 0.91 (0.76–1.09) | 0.89 (0.73–1.08) | 0.88 (0.70–1.10) | 0.93 (0.70–1.23) |         |
| BMI < 25 kg m⁻²                                          |      |      |      |      |      | 0.51    |
| Cases                                                    | 257  | 250  | 217  | 229  | 235  |         |
| Multivariate RRa                                         | 1.0  | 1.05 (0.82–1.35) | 0.99 (0.75–1.31) | 1.14 (0.83–1.57) | 1.11 (0.75–1.64) |         |
| BMI ≥ 25 kg m⁻²                                          |      |      |      |      |      | 0.14    |
| Cases                                                    | 265  | 222  | 234  | 204  | 215  |         |
| Multivariate RRa                                         | 1.0  | 0.77 (0.59–1.01) | 0.79 (0.59–1.05) | 0.67 (0.48–0.93) | 0.77 (0.50–1.18) |         |
| Colon cancer                                             |      |      |      |      |      |         |
| Cases                                                    | 365  | 327  | 298  | 290  | 298  | 0.48    |
| Multivariate RRa                                         | 1.0  | 0.89 (0.73–1.09) | 0.83 (0.67–1.05) | 0.85 (0.66–1.10) | 0.91 (0.66–1.25) |         |
| BMI < 25 kg m⁻²                                          |      |      |      |      |      | 0.34    |
| Cases                                                    | 172  | 170  | 141  | 153  | 160  |         |
| Multivariate RRa                                         | 1.0  | 1.09 (0.82–1.44) | 0.99 (0.72–1.37) | 1.20 (0.84–1.72) | 1.22 (0.79–1.91) |         |
| BMI ≥ 25 kg m⁻²                                          |      |      |      |      |      | 0.05    |
| Cases                                                    | 193  | 157  | 157  | 137  | 138  |         |
| Multivariate RRa                                         | 1.0  | 0.72 (0.53–0.96) | 0.69 (0.50–0.95) | 0.60 (0.42–0.87) | 0.67 (0.41–1.08) |         |
| Proximal colon cancer                                     |      |      |      |      |      |         |
| Cases                                                    | 169  | 167  | 145  | 134  | 149  | 0.18    |
| Multivariate RRa                                         | 1.0  | 0.91 (0.70–1.18) | 0.80 (0.59–1.07) | 0.75 (0.54–1.04) | 0.82 (0.54–1.25) |         |
| BMI < 25 kg m⁻²                                          |      |      |      |      |      | 0.64    |
| Cases                                                    | 78   | 87   | 64   | 71   | 80   |         |
| Multivariate RRa                                         | 1.0  | 1.19 (0.82–1.72) | 0.96 (0.62–1.47) | 1.13 (0.71–1.81) | 1.25 (0.70–2.22) |         |
| BMI ≥ 25 kg m⁻²                                          |      |      |      |      |      | 0.02    |
| Cases                                                    | 91   | 80   | 81   | 63   | 69   |         |
| Multivariate RRa                                         | 1.0  | 0.69 (0.47–1.01) | 0.65 (0.43–0.98) | 0.48 (0.30–0.78) | 0.54 (0.29–1.00) |         |
| Distal colon cancer                                       |      |      |      |      |      |         |
| Cases                                                    | 176  | 149  | 144  | 147  | 135  | 0.81    |
| Multivariate RRa                                         | 1.0  | 0.89 (0.68–1.17) | 0.90 (0.67–1.22) | 1.00 (0.72–1.39) | 0.99 (0.64–1.53) |         |
| BMI < 25 kg m⁻²                                          |      |      |      |      |      | 0.26    |
| Cases                                                    | 81   | 77   | 70   | 76   | 71   |         |
| Multivariate RRa                                         | 1.0  | 1.10 (0.75–1.60) | 1.11 (0.72–1.71) | 1.39 (0.87–2.24) | 1.29 (0.71–2.36) |         |
| BMI ≥ 25 kg m⁻²                                          |      |      |      |      |      | 0.49    |
| Cases                                                    | 95   | 72   | 74   | 71   | 64   |         |
| Multivariate RRa                                         | 1.0  | 0.72 (0.49–1.07) | 0.74 (0.48–1.13) | 0.74 (0.46–1.18) | 0.77 (0.40–1.49) |         |
| Rectum cancerb                                           |      |      |      |      |      |         |
| Cases                                                    | 157  | 145  | 153  | 143  | 152  | 0.98    |
| Multivariate RRa                                         | 1.0  | 0.95 (0.72–1.25) | 1.02 (0.75–1.38) | 0.95 (0.67–1.35) | 0.99 (0.64–1.52) |         |
| BMI < 25 kg m⁻²                                          |      |      |      |      |      | 0.95    |
| Cases                                                    | 85   | 80   | 76   | 76   | 75   |         |
| Multivariate RRa                                         | 1.0  | 0.98 (0.67–1.43) | 0.99 (0.65–1.52) | 1.05 (0.64–1.72) | 0.92 (0.50–1.71) |         |
| BMI ≥ 25 kg m⁻²                                          |      |      |      |      |      | 0.98    |
| Cases                                                    | 72   | 65   | 77   | 67   | 77   |         |
| Multivariate RRa                                         | 1.0  | 0.91 (0.60–1.39) | 1.07 (0.69–1.67) | 0.85 (0.50–1.44) | 1.06 (0.54–2.05) |         |

*The model included age, sex, family history of colorectal cancer, BMI, physical activity, energy-adjusted intakes of fat, fibre, calcium, folate, beta-carotene, vitamin E, vitamin B6, alcohol, and energy intake. bIncludes rectosigmoid.*
association with magnesium. Tests for interaction were nonsignificant. Results for men and women separately were essentially similar (data not shown).

DISCUSSION

An inverse association between magnesium intake and colorectal cancer risk in women was first reported in a Swedish cohort study (Larsson et al., 2005). In the Iowa Women’s Health Study, an inverse association was found only for colon cancer. We found weak inverse associations with risks of colorectal and colon cancer in men and women, which were generally nonsignificant. In both sexes, the inverse association was most evident for proximal colon cancer risk. When we stratified by BMI level, the inverse association was observed only in those with BMI \( \geq 25 \text{ kg m}^{-2} \). As overweight is related to decreased insulin sensitivity (Fung et al., 2003), this may suggest that magnesium is inversely associated with colorectal cancer risk through improved insulin sensitivity. Recently, magnesium intake was found to be associated with increased levels of adiponectin, which may improve insulin sensitivity (Qi et al., 2005); adiponectin was inversely associated with colorectal cancer risk among men (Wei et al., 2005).

Strengths of our study include large numbers of cases, scope for comparing the sexes, and the completeness of follow-up. We found weaker inverse associations between colorectal cancer and magnesium intake than in the Sweden (Larsson et al., 2005) and, to a lesser extent, Iowa studies (Folsom and Hong, 2006). It may be relevant that reported magnesium intake levels are lower in Sweden than in the Netherlands: median intakes in lowest and highest quintiles were 198 and 268 mg day\(^{-1}\) (Larsson et al., 2005), and 236 and 349 mg day\(^{-1}\) in Dutch women, respectively. Magnesium intake of up to 325 mg day\(^{-1}\) was recently found to be associated with insulin sensitivity, and intakes above this level might not provide further benefits; sex-specific data were not presented (Ma et al., 2006). We observed no further decrease in risk in our subsite-specific analyses (Table 2) in quintile 5 (> 350 mg day\(^{-1}\); median 375) compared to quintile 4 (321 – 350 mg day\(^{-1}\); median 313), which is in line with the threshold finding. The magnesium intake in Iowa women (Folsom and Hong, 2006) was comparable to our study, but Iowa women were generally heavier (Folsom and Hong, 2006) than Dutch women, which could explain the different findings given the modification by BMI.

In conclusion, our results provide no clear support for an overall protective effect of magnesium on colorectal cancer in men or women, but are compatible with an impact in the subgroup of overweight subjects, possibly through reduced insulin resistance. Further studies are needed to elucidate this relationship.

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