Lee et al. (1) recently reported a positive association of heme iron intake and an inverse association of zinc intake with the risk of colon cancer among women who consumed alcohol. To examine these associations further, we analyzed data from the population-based Swedish Mammography Cohort of 61,433 women who were aged 40–75 years and without cancer at baseline in 1987–1990 (2). Intake of heme iron and zinc was assessed at baseline and in 1997 using self-administered food frequency questionnaires. The data met the proportional hazards assumptions, and we computed rate ratios (RRs) using Cox proportional hazards models stratified on age in months and calendar time. To reduce within-person variation and to best represent long-term variation and to best represent long-term calendar time. To reduce within-person variation and to best represent long-term calendar time. To reduce within-person variation and to best represent long-term calendar time. To reduce within-person variation and to best represent long-term calendar time.

During a mean of 14.8 years of follow-up, from March 1987 through June 2004, 547 women were diagnosed as having colon cancer. After controlling for potential confounders, we observed a statistically significant positive association between heme iron intake and colon cancer risk (Table 1) among women who consumed at least 20 g/week of alcohol (multivariable RR comparing top and bottom quintiles of heme iron intake = 2.29, 95% confidence interval [CI] = 1.25 to 4.21). The comparable RR among women who consumed less than 20 g/week of alcohol was 1.05 (95% CI = 0.74 to 1.48). A test for interaction between heme iron and alcohol in relation to colon cancer risk was statistically significant (P = .01). High consumption of red meat, the main source of heme iron, was also associated with an increased risk of colon cancer among women with an alcohol consumption of at least 20 g/week; the multivariable RR adjusted for the same variables as in Table 1 except for heme iron was 2.85 (95% CI = 1.30 to 6.26) for women in the highest quintile compared with those in the lowest quintile of red meat consumption. When we included heme iron and red meat simultaneously in a multivariable model (Spearman correlation coefficient = 0.6), the RR comparing extreme quintiles was 1.78 (95% CI = 0.87 to 3.65) for heme iron intake and 1.93 (95% CI = 0.76 to 4.90) for red meat consumption. There were too few cases among women who consumed at least 20 g/week of alcohol to examine subsites in the colon. We found no statistically significant linear association between zinc intake and colon cancer risk (Table 1).

Our findings for heme iron and colon cancer are consistent with those from Lee et al. (1). In that study, the RR of proximal colon cancer, comparing extreme categories of heme iron intake, was 2.48 (95% CI = 0.94 to 6.58) among women who consumed 1 to 9 g/day of alcohol and 7.20 (95% CI = 1.33 to 38.91) among women who consumed at least 20 g/day of alcohol. Lee et al. (1) did not control for red meat consumption.

### Table 1. RR of colon cancer by intake of heme iron and zinc (using cumulative updating) among all women and among women who consume alcohol (≥20 g/week)

<table>
<thead>
<tr>
<th>Group and parameter</th>
<th>Quintile of intake</th>
<th>All women</th>
<th>Women consuming alcohol, ≥20 g/wk</th>
<th>All women</th>
<th>Women consuming alcohol, ≥20 g/wk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1*</td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td>Q5</td>
</tr>
<tr>
<td>Heme iron, mg/day‡</td>
<td>&lt;0.67</td>
<td>0.67–1.04</td>
<td>1.04–1.52</td>
<td>1.53–2.05</td>
<td>≥2.06</td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)§</td>
<td>1.00</td>
<td>0.93 (0.71 to 1.22)</td>
<td>0.94 (0.72 to 1.22)</td>
<td>1.06 (0.82 to 1.39)</td>
<td>1.26 (0.97 to 1.64)</td>
</tr>
<tr>
<td>Multivariable RR (95% CI)§</td>
<td>1.00</td>
<td>0.94 (0.71 to 1.24)</td>
<td>0.97 (0.73 to 1.28)</td>
<td>1.11 (0.83 to 1.47)</td>
<td>1.31 (0.98 to 1.75)</td>
</tr>
<tr>
<td>Women consuming alcohol, ≥20 g/wk¶</td>
<td>20</td>
<td>34</td>
<td>37</td>
<td>35</td>
<td>45</td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)§</td>
<td>1.00</td>
<td>1.30 (0.74 to 2.29)</td>
<td>1.25 (0.71 to 2.19)</td>
<td>1.44 (0.82 to 2.53)</td>
<td>2.06 (1.20 to 3.53)</td>
</tr>
<tr>
<td>Multivariable RR (95% CI)§</td>
<td>1.00</td>
<td>1.38 (0.77 to 2.48)</td>
<td>1.37 (0.76 to 2.48)</td>
<td>1.55 (0.85 to 2.82)</td>
<td>2.29 (1.25 to 4.21)</td>
</tr>
<tr>
<td>Zinc, mg/day¶</td>
<td>&lt;9.0</td>
<td>9.0–9.6</td>
<td>9.7–10.3</td>
<td>10.4–11.0</td>
<td>≥11.1</td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)§</td>
<td>1.00</td>
<td>0.75 (0.57 to 0.98)</td>
<td>0.83 (0.65 to 1.07)</td>
<td>0.85 (0.65 to 1.11)</td>
<td>0.84 (0.64 to 1.09)</td>
</tr>
<tr>
<td>Multivariable RR (95% CI)§</td>
<td>1.00</td>
<td>0.75 (0.57 to 0.99)</td>
<td>0.85 (0.64 to 1.12)</td>
<td>0.89 (0.65 to 1.21)</td>
<td>0.90 (0.65 to 1.25)</td>
</tr>
<tr>
<td>Women consuming alcohol, ≥20 g/wk¶</td>
<td>37</td>
<td>30</td>
<td>45</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)§</td>
<td>1.00</td>
<td>0.72 (0.44 to 1.19)</td>
<td>0.94 (0.60 to 1.48)</td>
<td>0.92 (0.56 to 1.52)</td>
<td>0.90 (0.54 to 1.49)</td>
</tr>
<tr>
<td>Multivariable RR (95% CI)§</td>
<td>1.00</td>
<td>0.65 (0.39 to 1.13)</td>
<td>0.85 (0.50 to 1.44)</td>
<td>0.78 (0.43 to 1.43)</td>
<td>0.79 (0.41 to 1.51)</td>
</tr>
</tbody>
</table>

*Referent group.
†P values for trend based on Wald statistics using the median value of each quintile treated as a continuous variable.
‡The major food sources of heme iron were red meat, poultry, and processed meats (including blood pudding).
§RR adjusted for age (in months), body mass index (quartiles), educational level (less than high school, high school, and university), total energy (continuous), and quintiles of energy-adjusted intakes of saturated fat, folate, calcium, and dietary fiber. Heme iron and zinc were simultaneously included in one model.
¶Approximately 38% of all women. The 75th percentile of alcohol consumption in this subgroup was 47.7 g/week.
†The major food sources of zinc were red meat, poultry, dairy products, and whole grains.
In summary, in this large population-based cohort study, both heme iron and red meat intake, when mutually adjusted, showed a positive association with the risk of colon cancer among women who consumed alcohol. These findings suggest that heme iron may only partly explain the apparent increased risk of colon cancer associated with a high red meat consumption and that other factors in red meat may be implicated in colon carcinogenesis.

Susanna C. Larsson
Hans-Olov Adami
Edward Giovannucci
Alicia Wolk

REFERENCES


NOTES

Affiliations of authors: Division of Nutritional Epidemiology, The National Institute of Environmental Medicine (SCL, AW), and Department of Medical Epidemiology and Biostatistics (HOA), Karolinska Institutet, Stockholm, Sweden; Departments of Epidemiology and Nutrition, Harvard School of Public Health, and Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital/Harvard Medical School, Boston, MA (EG).

Correspondence to: Susanna C. Larsson, Division of Nutritional Epidemiology, The National Institute of Environmental Medicine, Karolinska Institutet, P.O. Box 210, SE-171 77 Stockholm, Sweden (e-mail: susanna.larsson@imm.ki.se).

Support was provided by research grants from the Swedish Cancer Foundation, the Swedish Research Council/Longitudinal Studies, and the Swedish Foundation for International Cooperation in Research and Higher Education (STINT).

DOI: 10.1093/jnci/dji032

RESPONSE

Our recent publication (1) linking heme iron positively and dietary zinc inversely with colon cancer among alcohol drinkers was based on biologically driven hypotheses. Our analysis involved the study of interactions, which, in the absence of a biologic basis, are difficult to replicate due to low statistical power. Therefore, we read with interest the letter from Larsson et al. reporting that they closely replicated our findings.

We note, however, that some of their findings are not consistent with ours. In their study, red meat consumption was positively associated with colon cancer, even after adjusting for heme iron, suggesting that heme iron only partly explained the positive association of red meat consumption with colon cancer. In our data, there was no association between red meat consumption and colon cancer after adjusting for heme iron intake. The difference in results between their study and ours may be explained, at least in part, by the possibly imprecise estimates of heme iron intake. In our study, heme iron intake was calculated by assuming that heme iron was 40% of the total iron contained in all meats, as proposed by Monsen (2). Although Larsson et al. did not clearly state how they calculated heme iron, we presume they used a similar strategy. This crude method might be problematic because mean heme iron content in animal foods (e.g., meat, viscera, and blood; fish or other marine animals) varies between 17.4% and 80.8% of the total iron content (3). The consequence of this problem might differ depending on the dietary pattern in a specific population. We note that the correlation coefficient between heme iron and red meat intake was only 0.6 in the Swedish Mammography Cohort compared with almost 0.9 in the Iowa Women’s Health Study. To our knowledge, there is no available nutrient database that specifies heme and non-heme iron. The National Cancer Institute is developing a heme-iron database that takes into account cooking methods of meat, which can change the bioavailability of dietary iron (R. Sinha, NCI, personal communication).

The different findings for dietary zinc are also important to note. In our study (1), zinc intake had a clear inverse association with both proximal and distal colon cancers. Larsson et al. also found that dietary zinc had an inverse association, albeit a weak and not statistically significant association. Important food sources of zinc include seafood such as oysters and crabs. If these foods are more commonly consumed in Sweden than in Iowa, then the relatively weak association of zinc intake with colon cancer in the Swedish study might be related to a low validity of zinc intake, which was calculated based on a food frequency questionnaire with 67 food items.

Both studies are important because of the potential etiologic insight they provide. The interaction analyses involve a small proportion of study subjects, and thus the findings might have limited public health significance. Nevertheless, the findings may have general applicability for two reasons. First, in our study, alcohol consumption was chosen as one trigger that can release free iron from the bound form by disturbing iron homeostasis. Theoretically, other triggers such as chronic inflammation might also disturb iron homeostasis. Indeed, in vitro, superoxide or nitric oxide, both of which are produced by stimulated polymorphonuclear leukocytes and macrophages during inflammation, can release iron from ferritin (4,5). Second, oxidative stress is implicated as a common mechanism in the pathogenesis of various diseases (6). We found similar results for diabetes (7) and other chronic diseases (unpublished Iowa Women’s Health Study results concerning upper digestive tract cancer, breast cancer, and cardiovascular mortality).

Duk-Hee Lee
David R. Jacobs, Jr.
Kristin E. Anderson

REFERENCES

NOTES

Affiliations of authors: Department of Preventive Medicine, College of Medicine, Kyungpook National University, Daegu, Korea (DHL); Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, MN (DRJ, KEA); Department of Nutrition, University of Oslo, Oslo, Norway (DRJ).

Correspondence to: Kristin E. Anderson, PhD, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 1300 South 2nd St., Suite 300, Minneapolis, MN 55454 (e-mail: anderson_k@epi.umn.edu).

DOI: 10.1093/jnci/dji033