BRIEF COMMUNICATIONS

Heme Iron, Zinc, Alcohol Consumption, and Colon Cancer: Iowa Women's Health Study

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We examined associations among colon cancer incidence and dietary intake of heme iron, a possible prooxidant, zinc, a possible antioxidant, and alcohol, a disruptor of iron homeostasis. During 15 years of follow-up, 34 708 postmenopausal women, aged 55–69 years at baseline who completed a food-frequency questionnaire for the Iowa Women's Health Study, were followed for incident colon cancer. After adjusting for each micronutrient, the relative risks for proximal colon cancer increased more than twofold across categories of heme iron intake (P_{trend} = .01) and the corresponding relative risks decreased more than 50% across categories for zinc intake (P_{trend} = .01). The positive association with heme iron and the inverse association with zinc intake were stronger among women who consumed alcohol than among those who did not. Zinc intake was also associated with a decreased risk of distal colon cancer (P_{trend} = .03), regardless of alcohol or heme iron consumption. Our results suggest that intake of dietary heme iron is associated with an increased risk of proximal colon cancer, especially among women who drink, but that intake of dietary zinc is associated with a decreased risk of both proximal and distal colon cancer. [J Natl Cancer Inst 2004;96:403–7]

Although iron, a prooxidant, is thought to be carcinogenic *(1–3)*, epidemiologic evidence regarding its association with colon cancer is equivocal *(4–11)*. Several factors associated with epidemiologic study design may explain the inconsistent results. First, free iron, not iron bound to ferritin or transferrin, is carcinogenic *(12–14)*. To date, most epidemiologic markers of iron have reflected bound iron. It is generally believed that free iron exists only when transferrin is saturated in individuals who have an excess of iron *(15,16)*. However, free iron was found among individuals in the absence of transferrin saturation, suggesting that an alternative mechanism exists for the generation of free iron *in vivo (17,18)*. A trigger that disturbs iron homeostasis may transiently generate free iron. One such trigger may be alcohol consumption, which is known to disrupt iron homeostasis *(19–22)*.

Second, many epidemiologic studies consider only total dietary iron. In westernized countries, the majority of total dietary iron is the non-heme form, which has a low bioavailability, whereas the majority of stored body iron arises from the heme form *(23)*. The main food sources of non-heme iron are plant-based or iron-fortified commercial foods *(24)*. Therefore, outcomes associated with combining non-heme and heme iron into total dietary iron, as in most epidemiologic studies, may mostly reflect other nutrients contained in plant foods.

Third, if there are antioxidants that counter the possible prooxidant effect of iron, failure to adjust for that effect may obscure true associations. Although antioxidant vitamins have been considered important, many epidemiologic studies [for example, *see (25)*] have not considered a possible antioxidant role of zinc. Because the main food sources of zinc are similar to those of heme iron *(26)*, mixed effects of prooxidant iron and antioxidant zinc may negate associations between cancer and consumption of iron- and zinc-rich foods, such as meats.

In this study, we hypothesized that heme iron, a possible prooxidant, is positively associated with colon cancer incidence, whereas zinc, a possible antioxidant, is inversely associated. Furthermore, we hypothesized that alcohol consumption strengthens the positive association between heme iron and colon cancer.

Our study subjects were drawn from the Iowa Women's Health Study *(27)*, which was designed to examine risk factors and cancer incidence in 41 836 postmenopausal women, aged 55–69 years in January 1986, who were followed through December 2000. We excluded women who had a history of cancer other than skin cancer at baseline, were peri- or premenopausal, had a caloric intake of more than 5000 or less than 600 calories per day, or had 30 or more missing responses on the food-frequency questionnaire, leaving 34 708 women for this study. Women provided written informed consent, and this study was approved by the Institutional Review Boards of the Universities of Minnesota and Iowa.

The baseline questionnaire included questions on known risk factors for cancer and a 127-item food-frequency questionnaire similar to that used in the Nurses' Health Study *(28)*. Nutrient intake was computed by multiplying the frequency response by the nutrient content of the specified portion sizes. Heme iron content was calculated by applying a factor of 0.4 to the total iron content of all meat items. Nutrient supplements were excluded from consideration in intake calculations. Body measurement data were provided by study participants.

Incident colon cancers were identified by linkage with the Health Registry of Iowa. During the 15 years of follow-up, there were 438 proximal colon cancers and 303 distal colon cancers. Person-years were computed as the time from January 1986 to the first of a) colon cancer diagnosis, b) death (for residents of Iowa), c) midpoint of the interval between the date of last contact and the date of death (for residents outside Iowa), d) December 31, 2000 (end of

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See "Notes" following "References."

DOI: 10.1093/jnci/djh047

Journal of the National Cancer Institute, Vol. 96, No. 5,

follow-up), e) emigration from Iowa (if date known), or f) midpoint of interval between the date of last contact and either the date of next follow-up or December 31, 2000 (if date of move was unknown). We treated a colon cancer diagnosis as a censoring event.

Participants were assigned to categories according to quartiles of dietary heme iron or zinc intake. The highest quartile for each nutrient was additionally split at its median. We analyzed heme iron and zinc intakes separately and adjusting for each other. We used proportional hazards regression, adjusting for January 1986 values of age; total caloric intake; body mass index; physical activity score (low, medium, or high); cigarette smoking pack-years and current smoking status; alcohol consumption; history of diabetes; hormone replacement therapy (current, former, or never); and intake of multivitamins, saturated fat, soluble fiber, insoluble fiber, calcium, vitamin E, and folate from food and multivitamin supplements. Information regarding family history of colon cancer and aspirin intake was collected during the follow-up study performed in 1992 and was therefore often missing. Additional adjustment for these variables did not substantially change the final results (data not shown). Data were also analyzed after stratification by alcohol consumption. In tests for trend, median values of categories 1–5 were used.

Relative to women with lower dietary heme iron intake, women with higher dietary heme iron intake were younger and had a higher mean body mass index, were more likely to smoke, engage in less physical activity, consume less alcohol, not use postmenopausal hormones, and report a history of diabetes. These women also had higher caloric intake and consumed more saturated fat, but less calcium, vitamin E, folate, and multivitamin supplements. Baseline characteristics according to dietary zinc intake differed from those for heme iron in some factors. Women with higher dietary zinc intake were less likely to smoke, engaged in more physical activity, and consumed more folate and calcium than women with lower dietary zinc intake.

Neither heme iron nor zinc was statistically significantly associated with the risk of proximal colon cancer (Table 1). However, when heme iron and zinc were mutually adjusted, both the positive association of heme iron and the inverse association of zinc intake were statistically significantly associated with proximal colon cancer (Table 1). Table 2 shows the statistical validity of the regression analysis with these highly correlated variables (Pearson correlation coefficient = 0.8): heme iron showed a positive trend for colon cancer incidence within each category of zinc, whereas zinc showed an inverse trend for colon

Table 1. Relative risks (RRs) and 95% confidence intervals (CIs) of incident colon cancer according to intake of dietary heme iron and zinc among postmenopausal women enrolled in the Iowa Women's Health Study, 1986–2000

	Dietary categories					
	1	2	3	4	5	P_{trend}
Proximal colon cancer						
Heme iron, mg/day	≤0.76	0.77–1.15	1.16–1.64	1.65–2.04	≥2.05	
No. of case subjects	103	116	116	49	54	
Incidence density*	95	99	95	81	91	
Adjusted RR (95% CI)†‡	1.00 (referent)	1.13 (0.86 to 1.47)	1.16 (0.87 to 1.54)	1.04 (0.72 to 1.50)	1.30 (0.87 to 1.94)	.33
Multivariable RR (95% CI)†§	1.00 (referent)	1.14 (0.86 to 1.51)	1.16 (0.86 to 1.57)	1.07 (0.86 to 1.57)	1.41 (0.90 to 2.21)	.24
Adjusted RR (95% CI)‡‖	1.00 (referent)	1.19 (0.89 to 1.59)	1.35 (0.96 to 1.91)	1.35 (0.86 to 2.10)	2.25 (1.35 to 3.73)	<.01
Multivariable RR (95% CI)§‖	1.00 (referent)	1.16 (0.86 to 1.58)	1.28 (0.88 to 1.86)	1.30 (0.79 to 2.12)	2.18 (1.24 to 3.86)	.01
Zinc, mg/day	≤8.5	8.6–11.4	11.5–14.8	14.9–17.5	≥17.6	
No. of case subjects	116	116	115	54	37	
Incidence density*	107	98	95	91	61	
Adjusted RR (95% CI)†‡	1.00 (referent)	0.91 (0.69 to 1.20)	0.88 (0.64 to 1.19)	0.83 (0.55 to 1.25)	0.56 (0.33 to 0.93)	.05
Multivariable RR (95% CI)†§	1.00 (referent)	0.99 (0.74 to 1.32)	0.93 (0.67 to 1.30)	0.96 (0.62 to 1.49)	0.66 (0.38 to 1.16)	.23
Adjusted RR (95% CI)‡‖	1.00 (referent)	0.81 (0.59 to 1.10)	0.70 (0.48 to 1.04)	0.57 (0.34 to 0.95)	0.31 (0.16 to 0.60)	<.01
Multivariable RR (95% CI)§‖	1.00 (referent)	0.89 (0.64 to 1.23)	0.77 (0.50 to 1.18)	0.68 (0.38 to 1.19)	0.38 (0.17 to 0.74)	.01
Distal colon cancer						
Heme iron, mg/day	≤0.76	0.77–1.15	1.16–1.64	1.65–2.04	≥2.05	
No. of case subjects	75	73	86	34	35	
Incidence density*	69	62	71	56	59	
Adjusted RR (95% CI)†‡	1.00 (referent)	0.93 (0.67 to 1.29)	1.09 (0.78 to 1.51)	0.88 (0.57 to 1.36)	0.96 (0.59 to 1.56)	.87
Multivariable RR (95% CI)†§	1.00 (referent)	0.89 (0.64 to 1.25)	0.99 (0.70 to 1.39)	0.67 (0.42 to 1.07)	0.65 (0.38 to 1.11)	.09
Adjusted RR (95% CI)‡‖	1.00 (referent)	1.06 (0.75 to 1.51)	1.45 (0.96 to 2.19)	1.27 (0.74 to 2.18)	1.37 (0.74 to 2.55)	.27
Multivariable RR (95% CI)§‖	1.00 (referent)	0.98 (0.69 to 1.41)	1.26 (0.82 to 1.94)	0.94 (0.52 to 1.68)	0.90 (0.45 to 1.81)	.77
Zinc, mg/day	≤8.5	8.6–11.4	11.5–14.8	14.9–17.5	≥17.6	
No. of case subjects	84	77	74	32	36	
Incidence density*	78	65	61	54	59	
Adjusted RR (95% CI)†‡	1.00 (referent)	0.81 (0.59 to 1.13)	0.74 (0.51 to 1.07)	0.63 (0.39 to 1.04)	0.67 (0.38 to 1.19)	.11
Multivariable RR (95% CI)†§	1.00 (referent)	0.85 (0.61 to 1.18)	0.72 (0.49 to 1.06)	0.55 (0.32 to 0.93)	0.55 (0.30 to 1.02)	.03
Adjusted RR (95% CI)‡‖	1.00 (referent)	0.71 (0.49 to 1.03)	0.58 (0.36 to 0.93)	0.49 (0.26 to 0.90)	0.51 (0.24 to 1.06)	.06
Multivariable RR (95% CI)§‖	1.00 (referent)	0.79 (0.53 to 1.16)	0.65 (0.39 to 1.07)	0.53 (0.27 to 1.04)	0.58 (0.26 to 1.30)	.15

*Incidence density is expressed per 100 000 person-years.

†Heme iron and zinc were analyzed in separate models.

‡Relative risks were adjusted for age and caloric intake.

§Adjusted for age, total caloric intake, body mass index, physical activity, cigarette smoking, alcohol consumption, postmenopausal hormone use, diabetes, multivitamin use, and intake of saturated fat, calcium, vitamin E, folate, soluble fiber, and insoluble fiber.

‖Heme iron and zinc were simultaneously included in one model.

Table 2. Unadjusted risk of incident proximal colon cancer [number of case subjects/total number of subjects (percent incidence)] according to category of dietary heme iron and zinc intake, among postmenopausal women enrolled in the Iowa Women's Health Study, 1986–2000*

	Zinc intake					
Heme iron intake	Quartile 1 (%)	Quartile 2 (%)	Quartile 3 (%)	Quartile 4, lower half (%)	Quartile 4, upper half (%)	Total (%)
Quartile 1	75/5554 (1.4)	23/1870 (1.2)	3/542 (0.6)	2/90 (2.2)	0/94 (0)	103/8150 (1.3)
Quartile 2	38/2351 (1.6)	53/4046 (1.3)	19/1803 (1.1)	4/334 (1.2)	2/179 (1.1)	116/8713 (1.3)
Quartile 3	3/191 (1.6)	40/2694 (1.5)	60/4352 (1.4)	11/1282 (0.9)	2/500 (0.4)	116/9019 (1.3)
Quartile 4, lower half	0/1 (0)	1/153 (0)	28/1986 (1.4)	17/1535 (1.1)	4/770 (0.5)	49/4445 (1.1)
Quartile 4, upper half	0/1 (0)	0/15 (0)	5/299 (1.7)	20/1131 (1.8)	29/2935 (1.0)	54/4381 (1.2)
Total	116/8098 (1.4)	116/8778 (1.3)	115/8982 (1.3)	54/4372 (1.2)	37/4478 (0.8)	

*Cells with sufficient numbers of subjects are outlined in bold.

cancer incidence within each category of heme iron. Total zinc intake (from both food and multivitamin supplements) and zinc intake from multivitamin supplements only were not associated with proximal colon cancer (data not shown).

Both the positive association of heme iron intake and the inverse association of zinc intake were statistically significantly stronger among baseline alcohol drinkers than among nondrinkers (Table 3). The strength of the associations of heme iron and zinc intake with proximal colon cancer became stronger with increasing levels of alcohol consumption.

Both heme iron and zinc intake showed an inverse association with the risk of distal colon cancer when not mutually adjusted (Table 1). When mutually adjusted, only the inverse trend for zinc intake was statistically significant (Table 1). The association of zinc intake from both food and multivitamin supplements with distal colon cancer was weaker than that of zinc intake from food only (data not shown). The association of zinc intake with distal colon cancer did not differ by level of alcohol consumption (data not shown).

Among postmenopausal women, we found an increased risk of proximal colon cancer associated with intake of heme iron, especially among women who drink, but a decreased risk of proximal and distal colon cancers associated with intake of zinc. Our results support our prior biologically based hypotheses, with the exception that we did not anticipate a difference between proximal and distal colon cancers. However, there is some evidence that carcinogenesis in the proximal and distal colon proceeds via distinct pathogenic mechanisms *(29)*.

Recently, zinc has been shown to retard oxidative processes; zinc ions may replace redox active molecules and may

Table 3. Relative risks (RRs) and 95% confidence intervals (CIs) of incident proximal colon cancer according to intake of dietary heme iron and zinc stratified by alcohol consumption among postmenopausal women enrolled in the Iowa Women's Health Study, 1986–2000*

	Dietary categories					
	1	2	3	4	5	P_{trend}
Nondrinkers						
Heme iron, mg/day	≤0.76	0.77–1.15	1.16–1.64	1.65–2.04	≥2.05	
No. of case subjects	63	60	59	24	29	
Multivariable RR (95% CI)†	1.00 (referent)	1.04 (0.69 to 1.56)	1.18 (0.72 to 1.96)	1.01 (0.51 to 2.01)	1.55 (0.71 to 3.37)	.31
Zinc, mg/day	≤8.5	8.6–11.4	11.5–14.8	14.9–17.5	≥17.6	
No. of case subjects	68	59	55	30	23	
Multivariable RR (95% CI)†	1.00 (referent)	0.91 (0.58 to 1.41)	0.81 (0.45 to 1.44)	0.92 (0.43 to 1.97)	0.63 (0.24 to 1.64)	.38
Drinkers of alcohol (overall)						
Heme iron, mg/day	≤0.76	0.77–1.15	1.16–1.64	1.65–2.04	≥2.05	
No. of case subjects	39	56	57	25	25	
Multivariable RR (95% CI)†	1.00 (referent)	1.36 (0.86 to 2.17)	1.44 (0.82 to 2.52)	1.69 (0.83 to 3.43)	3.23 (1.40 to 7.47)	<.01
Zinc, mg/day	≤8.5	8.6–11.4	11.5–14.8	14.9–17.5	≥17.6	
No. of case subjects	47	57	60	24	14	
Multivariable RR (95% CI)†	1.00 (referent)	0.88 (0.54 to 1.43)	0.73 (0.39 to 1.38)	0.50 (0.21 to 1.16)	0.22 (0.07 to 0.67)	<.01
Drinkers (1–9 g of alcohol per day)						
Heme iron, mg/day	≤0.76	0.77–1.15	1.16–1.64	1.65–2.04	≥2.05	
No. of case subjects	30	37	45	18	17	
Multivariable RR (95% CI)†	1.00 (referent)	1.09 (0.64 to 1.88)	1.23 (0.65 to 2.33)	1.35 (0.60 to 3.04)	2.48 (0.94 to 6.58)	.07
Zinc, mg/day	≤8.5	8.6–11.4	11.5–14.8	14.9–17.5	≥17.6	
No. of case subjects	30	43	46	18	10	
Multivariable RR (95% CI)†	1.00 (referent)	1.03 (0.58 to 1.85)	0.86 (0.41 to 1.81)	0.54 (0.20 to 1.44)	0.22 (0.06 to 0.82)	.03
Drinkers (≥10 g of alcohol per day)						
Heme iron, mg/day	≤0.76	0.77–1.15	1.16–1.64	1.65–2.04	≥2.05	
No. of case subjects	9	19	12	7	8	
Multivariable RR (95% CI)†	1.00 (referent)	2.35 (0.96 to 5.76)	2.31 (0.73 to 7.36)	3.38 (0.79 to 14.56)	7.20 (1.33 to 38.91)	.03
Zinc, mg/day	≤8.5	8.6–11.4	11.5–14.8	14.9–17.5	≥17.6	
No. of case subjects	17	14	14	6	4	
Multivariable RR (95% CI)†	1.00 (referent)	0.60 (0.24 to 1.47)	0.45 (0.13 to 1.57)	0.40 (0.07 to 2.19)	0.22 (0.03 to 1.91)	.13

*Heme iron and zinc intakes were simultaneously included in the model.

†Adjusted for age, total caloric intake, body mass index, physical activity, cigarette smoking, alcohol consumption, postmenopausal hormone use, diabetes, multivitamin use, and intake of saturated fat, calcium, vitamin E, folate, soluble fiber, and insoluble fiber.

induce the synthesis of metallothionein, a sulfhydryl-rich protein that protects against free radicals *(25)*. Zinc finger proteins are expressed infrequently in normal colonic mucosa but are expressed in more than 80% of colon cancers, suggesting that dysregulation of zinc finger proteins may be implicated in colon carcinogenesis *(30)*. At a molecular level, metals such as iron can substitute for zinc and may be responsible for metal-induced DNA damage and carcinogenesis *(31,32)*, suggesting a close interrelationship between the two nutrients.

Despite the correlation coefficient of 0.8 between dietary zinc and heme iron, suggesting that intake may be associated with similar food types, there were some women who consumed more heme iron than zinc or vice versa. Besides meat, fish, and poultry, other important food sources of zinc are beans, nuts, whole grains, fortified breakfast cereals, and dairy products. Therefore, because our database did not separate zinc into animal and plant sources, we inferred that relatively high zinc intake was likely accounted for by intake of a variety of non-meat products. This suggests that other nutrients besides zinc, contained in these food items, might explain the inverse association between zinc intakes and colon cancer. However, these food items, with the exception of dairy products, were not themselves inversely associated with the risk of colon cancer. Dairy products are a main source of calcium, which was inversely associated with colon cancer.

Multicollinearity might be of concern in the analysis of dietary zinc and heme iron. In most studies, multicollinear variables show the same direction of association with disease endpoints, and simultaneous adjustment of the highly correlated variables makes the standard errors of coefficients unstable. However, in this analysis, the associations for zinc and heme iron intake with proximal colon cancer were in opposite directions, even after close stratification. Indeed, adjustment for zinc strengthened the association of heme iron with proximal colon cancer.

Our study has several limitations. Questions on the food-frequency questionnaire used in the Iowa Women's Health Study, previously evaluated for reproducibility and validity in 44 study participants *(33)*, did not separate heme iron intake from total dietary iron intake and did not specifically evaluate zinc intake. Although the lack of specific questions may have resulted in some women being misclassified, generally non-differential misclassification of exposure variables leads to a null association rather than a spurious association. In addition, although the model is highly specific biologically, we cannot rule out the possibility that some of the findings within small subgroups occurred by chance. Moreover, because our study was limited to postmenopausal women, the results may not be generalizable to other groups. Finally, women who consumed more dietary zinc tended to have healthier behavioral and dietary patterns, despite the high correlation between dietary heme iron and zinc intake. Therefore, we cannot exclude uncontrolled confounding.

In summary, our results suggest that high dietary heme iron intake may increase the risk of proximal colon cancer, especially among postmenopausal women who drink. However, high dietary zinc intake may decrease the risk of colon cancer (proximal and distal). Our results may explain, at least in part, inconsistent findings with respect to the role of meat consumption in colon cancer.

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NOTES

The Iowa Women's Health Study was funded by Public Health Service grant RO1 CA39742 (to A. R. Folsom) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

Manuscript received July 18, 2003; revised December 18, 2003; accepted December 29, 2003.