Iron Intake and the Risk of Colorectal Cancer[1,2]

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Abstract

Prospectively gathered data from the National Health and Nutrition Examination Survey I and the National Health Evaluation Follow-Up Study were analyzed to evaluate the risk of colorectal cancer due to consumption of iron. Morbidity and mortality data due to colorectal cancer were available on 14,407 persons first interviewed in 1971 and followed through 1986. A total of 194 possible colorectal cancers occurred in this group over the 15-year period. Subsite analysis showed that the risk of colon cancer due to iron intake was elevated throughout the colon for both men and women, with the highest adjusted risks for the interquartile range seen in the proximal colon for females (relative risk, 1.51; 95% confidence interval, 1.41–1.60). The risk of rectal cancer was not significantly elevated for men or women. Elevated serum iron was also associated with increased risk; however, this effect was strongest in the distal (rather than proximal) colon and was significant only among females (adjusted relative risk, 1.73; 95% confidence interval, 1.03–2.92). The mean transferrin saturation was higher among cases than controls (30.7 *versus* 28.7%), but total iron-binding capacity did not seem to predict the occurrence of colorectal cancer. Proportional hazards models confirmed that the effects of iron and serum iron were not confounded by age, gender, energy consumption, fat intake, or other known risk factors for colorectal cancer. These data suggest that iron may confer an increased risk for colorectal cancer, and that the localizaton of risk may be attributable to the mode of epithelial exposure. It seems that luminal exposure to iron increases risk proximally, whereas humoral exposure increases risk distally. These differences may be due to such factors as oxidation state, binding proteins and the presence of other cofactors such as bile acids, products of bacterial metabolism.

Introduction

Iron is a necessary nutrient that has been associated with increased cancer risk in humans. *In vitro* and *in vivo* data suggest that iron may be capable of mutagenic effects mediated through free-radical generation or tumor promotion through nutritional mechanisms (1–3). As a transition metal, iron is possessed of loosely bound electrons that are capable of participating in lipid peroxidation reactions. Such reactions are thought to lead to DNA damage and, in some cases, neoplasia (4–7).

An earlier interval analysis based upon NHANES[4] I (8) suggested that increased iron stores were associated with increased colorectal cancer risk, but this finding was based on a total of only 39 cases. The magnitude of risk was not specified, and there were too few cases to conduct a site- and gender-specific analysis. We sought to extend these observations by analyses of additional cases and years of follow-up data collected through 1987.

Materials and Methods

NHANES I aimed to determine the baseline health and nutritional status of the noninstitutionalized U.S. population. A total of 14,407 individuals, 25–74 years of age, were assessed between 1972 and 1974. Follow-up was obtained from 1982–1984, at which time 93% of the original cohort was traced, and again in 1986, when subjects older than 55 at intake were traced. The 1987 NHEFS was conducted for all members of the original cohort known not to be deceased as of 1986 (n = 11,750). Ultimately, 11,018 subjects (93.8%) were traced, and 9,998 subjects were interviewed (9). Measurements included a 24-h dietary intake and a food frequency questionnaire. Iron and other nutrient intakes were calculated by conversion of reported intakes using nutrient information from the U.S. Department of Agriculture Handbook No. 8. Supplemental iron was not considered. Biochemical measurements, including serum iron and total iron-binding capacity, were measured spectrophotometrically with the use of a modification of the automated Technicon AAII method (10). Detailed information on the design and conduct of the NHEFS has been published elsewhere (11–13).

A total of 196 possible colorectal cancers were identified in the cohort of 14,407. Two cases were excluded because they were subsequently identified as anal cancers. The diagnoses

Received 10/19/95; revised 4/4/96; accepted 4/4/96.
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[1] Supported in part by grants from the NIH (P30 DK34987, T32 DK07364, and RR00046).
[2] Although the research described in this article has been supported by the United States Environmental Protection Agency, it has not been subjected to Agency review and therefore does not necessarily reflect the views of the Agency and no official endorsement should be inferred. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.
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[4] The abbreviations used are: NHANES, National Health and Nutrition Examination Survey; NHEFS, NHANES Epidemiologic Follow-Up Study; CI, confidence interval; RR, relative risk.

were confirmed by examination of hospital and nursing home records, including pathology reports. When a subject was found to be deceased, a death certificate was obtained from the appropriate state vital statistics office (14). To eliminate confounding by occult disease or the inclusion of individuals not at risk for colon cancer, statistical analysis was limited to individuals not censored within the first 3 years of follow-up, and to individuals more than or equal to 31 years old, the age of the youngest case at intake. Nutritive intake was adjusted for caloric content by the regression method of Willett *et al.* (15). The crude risk was calculated by comparing cancer incidence in the second, third, and fourth quartiles of exposure to cancer incidence in the first quartile. This was done to demonstrate the presence and magnitude of the effect in the raw data. Ninety-five percent CIs were calculated according to the method described in Kleinbaum *et al.* (16). Cutoffs for quartiles were taken from univariate analyses of the initial data set. The significance of trends was calculated using the Mantel-Haenszel test (17). The means were compared by two-tailed *t* test (18).

The adjusted RR was calculated for the interquartile range of exposure, using proportional hazards models adjusting for age and gender (19). The location was coded by the rules of the International Classification of Diseases, Ninth Revision (20). The following codes were included in the analysis as colon cancers: 153.0, 153.1, 153.2, 153.4, 153.6, 153.7, 153.8, and 153.9; whereas 154.0 and 154.1 were classified as rectal cancers. The location of cancers was classified as: (*a*) either rectal or colon; and (*b*) either proximal or distal. Proximal cancers were considered to be those up to and including the splenic flexure. Distal colon cancers were distal to the splenic flexure (including the rectum). This was defined as such because it is presently understood that proximal colon cancers may have a different biology than distal colon or rectal cancers. It is not clear whether the risk changes gradually as one moves distally (suggesting the difference is due to an exposure gradient) or the difference starts abruptly at the rectosigmoid junction (suggesting that biological susceptibility is the reason for these differences). To simply split cancers into colon and rectal cancers is to assume the latter model, and possibly miss effects that may be present if the first model holds. Rather than assume one model, we have elected to show the effects based upon either assumption. Of note, a subset of colon cancers that did not have their sites specified (International Classification of Diseases codes 153.8 and 153.9; $n = 39$) could not be included in the analysis of proximal *versus* distal cancers. Risk was calculated for iron intake, serum iron, total iron-binding capacity, and transferrin saturation. Transferrin saturation was obtained by dividing serum iron by the total iron-binding capacity. The independence of the main effects was assayed by the inclusion of these variables in proportional hazards models with known risk factors for colorectal cancer (including age, body-mass index, fat and energy consumption, aspirin intake, vegetable consumption, physical activity, and education). Potential interactions were assayed by evaluating the RR due to iron at different levels of these same factors.

Results

The data set of 14,407 included all persons ages 25–74 who completed a medical examination at the time of the original NHANES I sample (1971–1975). After eliminating persons less than 31 years old and those censored within the first 3 years of follow-up, the final data set used as a basis for regression and stratified analyses was comprised of 11,317 individuals. A total of 156 individuals who developed colorectal cancer were included. There were 118 colon cancers and 38 rectal cancers. Within this data set, iron intake was available for 8876 persons (including 136 cases), and serum iron was available for 8345 persons (including 126 cases). Whites and women comprised 81.8% and 60.1% of the total sample, respectively. The initial and final data sets were similar in composition, as shown in Table 1. In the final data set, cases were significantly older than unaffected subjects: 62.2 years compared to 53.3 years, respectively ($P < 0.0001$). Cases also had significantly higher serum iron (107.7 *versus* 100.4 mcg/dl; $P = 0.03$) and transferrin saturation (30.7 *versus* 28.7%; $P = 0.05$) by two-tailed *t* test. Breakdown of a comparison by gender is presented in Table 2.

Table 1 Demographic and clinical comparisons of the initial and final data sets, NHANES I and NHEFS, 1982–1987

	Initial data set	Final data set
White	83.5%	84.1%
Black	15.3%	14.8%
Female	59.7%	59.1%
Age	50.0%	52.8%
College education	20.6%	20.7%
Colon cancers	$n = 140$	$n = 118$
Rectal cancers	$n = 54$	$n = 38$

Table 2 Mean iron indices of cases compared with unaffected subjects NHANES I and NHEFS, 1982–1987

	Females		Males	
	Controls	Cases	Controls	Cases
Iron intake (mg) (SE)	9.6 (.07)	9.4 (.58)	13.5 (.11)	14.4 (.87)
Serum iron (mcg/dl) (SE)	96.7 (.51)	104.5 (4.9)	106.1 (.64)	111.0 (4.8)
TIBC (mcg/dl) (SE)	365 (.86)	372 (6.5)	348 (.87)	343 (6.51)
Transferrin Sat. (%) (SE)	27.1 (0.2)	28.5 (1.3)	31.0 (0.2)	33.0 (1.6)

The crude risk of cancer due to iron intake by site and gender for the entire study population is shown in Table 3. Risk was highest for women in the proximal colon (RR, 7.76; 95% CI, 1.36–44.3) and was also elevated in the colon in general. A similar (but less pronounced) pattern is seen in males. The crude risk attributable to serum iron is shown in Table 4. Unlike iron intake, the risk attributable to serum iron increases as one progresses distally, with the peak risk seen in the rectum, again in women (RR, 9.77; 95% CI, 1.81–52.8). Risk is not significantly elevated for males distally. Significant effects were not seen for either total iron-binding capacity or transferrin saturation.

Proportional hazards models were run to adjust for possible confounders and interactions. After adjustment for age and gender, iron intake is associated with increased risk in the proximal colon (RR, 1.44; 95% CI, 1.23–1.69), but not in the distal colon (RR, 1.03; 95% CI, 0.80–1.32). Serum iron predicts rectal cancer (RR, 1.57; 95% CI, 1.08–2.30) and, to a lesser extent, colon cancer (RR, 1.24; 95% CI, 0.96–1.59). When these analyses were stratified by gender, the risk for rectal cancer was again higher for women for serum iron (RR, 1.73; 95% CI, 1.03–2.92) and for iron intake in the proximal colon (RR, 1.51, 95% CI, 1.41–1.60). Models including variables for age, sex, fat, calories, body mass index, physical activity, vegetable and meat intake, and recent aspirin consumption did not show these variables to be confounders, insofar as they did not lead to appreciable changes in risk due to iron.

Table 3 Crude risk due to iron intake by location and gender (RR, 95% CI), NHANES I and NHEFS, 1982–1987

	Proximal	Cases	Distal	Cases	Colon	Cases	Rectum	Cases
All								
1st Q		5		11		10		8
2nd Q	2.62 (0.95–7.32)	14	1.45 (0.69–3.08)	17	2.24 (1.10–4.59)	24	1.29 (0.63–3.15)	11
3rd Q	2.26 (0.82–6.23)	12	1.12 (0.50–2.49)	13	2.63 (1.32–5.25)	28	1.18 (0.47–2.98)	10
4th Q	3.15 (1.41–7.04)	21	1.47 (0.73–2.97)	16	3.35 (1.74–6.46)	36	1.01 (0.42–2.42)	9
Trend	$P = 0.007$		$P = 0.61$		$P < 0.001$		$P = 0.98$	
Males								
1st Q		4		5		6		3
2nd Q	1.97 (0.57–6.80)	6	2.10 (0.71–6.24)	8	1.75 (0.62–11.0)	8	2.63 (0.70–9.95)	6
3rd Q	1.39 (0.35–5.51)	4	1.67 (0.52–5.37)	6	2.30 (0.87–6.13)	10	2.31 (0.58–9.26)	5
4th Q	3.08 (1.06–8.97)	12	2.06 (0.72–5.88)	10	3.73 (1.62–8.59)	22	1.72 (0.42–7.17)	5
Trend	$P = 0.06$		$P = 0.27$		$P = 0.001$		$P = 0.58$	
Females								
1st Q		1		6		4		5
2nd Q	5.89 (0.95–36.6)	8	1.11 (0.40–3.10)	9	2.94 (1.04–8.31)	16	0.74 (0.22–2.54)	5
3rd Q	5.78 (0.93–36.1)	8	0.85 (0.29–4.76)	7	3.24 (1.17–8.97)	18	0.73 (0.21–2.51)	5
4th Q	7.76 (1.36–44.3)	9	0.87 (0.28–2.68)	6	3.01 (1.05–8.64)	14	0.70 (0.21–2.86)	5
Trend	$P = 0.05$		$P = 0.67$		$P = 0.08$		$P = 0.22$	

Table 4 Crude risk due to serum iron by location and gender (RR, 95% CI), NHANES I and NHEFS, 1982–1987

	Proximal	Cases	Distal	Cases	Colon	Cases	Rectum	Cases
All								
1st Q		13		8		23		3
2nd Q	0.82 (0.37–1.80)	11	1.93 (0.84–4.43)	16	0.84 (0.47–1.58)	20	3.86 (1.20–12.5)	12
3rd Q	1.23 (09.60–2.55)	16	2.24 (1.00–5.04)	18	1.05 (0.59–1.85)	24	4.32 (1.37–13.6)	13
4th Q	0.63 (0.24–1.65)	6	2.04 (0.85–4.89)	12	1.36 (0.77–2.41)	23	3.63 (1.05–12.5)	8
Trend	$P = 0.70$		$P = 0.10$		$P = 0.24$		$P = 0.06$	
Males								
1st Q		6		4		8		7
2nd Q	0.76 (0.25–2.37)	6	1.52 (0.46–4.98)	8	1.05 (0.42–2.59)	11	2.28 (0.48–10.8)	6
3rd Q	1.06 (0.38–2.96)	9	1.59 (0.50–5.07)	9	1.32 (0.57–3.09)	15	1.76 (0.35–8.87)	5
4th Q	0.44 (0.11–1.67)	3	1.20 (0.37–4.56)	6	1.08 (0.43–2.72)	10	1.73 (0.32–9.2)	4
Trend	$P = 0.40$		$P = 0.73$		$P = 0.73$		$P = 0.73$	
Females								
1st Q		7		4		15		1
2nd Q	0.79 (0.25–2.47)	5	2.19 (0.68–7.05)	8	0.66 (0.29–1.51)	9	6.58 (1.05–41.1)	6
3rd Q	1.23 (0.43–3.49)	7	2.75 (0.89–8.49)	9	0.74 (0.33–1.68)	9	9.77 (1.81–52.8)	8
4th Q	0.79 (0.21–3.03)	3	2.74 (0.82–9.20)	6	1.58 (0.76–3.29)	13	7.31 (1.13–47.2)	4
Trend	$P = 0.99$		$P = 0.09$		$P = 0.32$		$P = 0.04$	

Discussion

Stevens *et al.* (10) first suggested an association between iron stores and cancer risk in 1988, based upon NHANES I data. This report was based on a total of 242 cancers, including 22 colon and rectal cancers (21). An in-depth analysis of individual cancer types was not possible, given the small numbers involved. A subsequent report was based on a total of 39 colorectal cancers (8). We have undertaken a detailed analysis of risk factors for colon and rectal cancer, expecting that the additional data gained since the last report would bring more statistical power to the analysis.

Meat intake has generally been associated with increased risk of colorectal cancer (15, 22–32), but the specific mechanisms of carcinogenesis have been debated. Risk has been attributed to fat intake, but fat itself is not mutagenic and is better characterized as a tumor promoter. It has been postulated that mutagens are produced through the effects of bacterial enzymes on fat or bile acids (33, 34), or by the production of polycyclic aromatic hydrocarbons in the course of protein pyrolysis (35). On the other hand, iron is also consumed when meat is ingested and may induce damage and/or increased proliferation through lipid peroxidation (4, 5, 36). An effect may result merely from iron's status as a nutrient necessary for proliferation. In this regard, it has been argued that the anemia often seen with malignancy is an adaptation intended to slow tumor growth (37). Several studies have shown augmentation of tumor growth in rodent models with iron supplementation (2, 3, 37–39). Siegers *et al.* (40) have shown this effect to be dose dependent. In one study (38), supplementation with phytate (a chelator of iron found in high-fiber diets) abolished this effect, thus creating a theoretical basis for the protective effect of dietary fiber. Conversely, iron deficiency seems to inhibit the growth of tumor cells (1). Recently, Fukuchi *et al.* (41) have shown that iron deprivation increases p53 expression in two cell lines, suggesting that the carcinogenic effects of iron may be mediated by alteration of normal mechanisms for the maintenance of genomic stability. In this regard, the iron chelator has been shown to be a potent inhibitor of DNA-synthesis and cell proliferation (42, 43).

There is also evidence that iron may cause cancer in humans. Individuals with hereditary hemochromatosis are at increased risk for hepatocellular carcinoma (44, 45). Bradbear

et al. (46) note a nonsignificant excess of colorectal cancers in genetic hemochromatosis patients. Colorectal adenomas and gastric cancers have been associated with increased serum ferritin (47, 48).

The data we present supports the hypothesis that iron intake increases the risk of proximal cancers. This effect seems to be more pronounced in women. A variety of influences are thought to determine the location of cancers. McMichael and Potter (49) first noted an increased propensity for proximal cancer in women and attributed this to the effect of estrogen on the delivery of bile acids to the colon. Other factors that have been associated with proximal cancers include genotype and advanced age (50). Cancers due to hereditary mismatch repair defects are thought to favor the right side of the colon (51). These cancers would typically occur in younger individuals. However, there was no difference between the ages of cases reporting proximal cancers and those reporting distal cancers.

There are numerous physiological differences between the right and left colon that may explain this site-specific variation in risk. The left colon is more densely colonized with bacteria, and the proportion of anaerobic bacteria increases as one moves distally. The number and species of bacteria probably influence the production and metabolism of potential carcinogens.

Serum iron effects, on the other hand, are significant only in the distal bowel and rectum. This exposure differs from that of ingested iron in that it is relatively constant, controlled by endogenous binding proteins, not exposed to the actions or debris of bacterial metabolism, and not subjected to the high reducing potential of the colon's luminal milieu. In this data set, there is a weak correlation ($r = 0.04$; $P = 0.0001$) between serum iron and iron intake. This is because serum levels are also influenced by gastrointestinal losses, extraintestinal bleeding, efficiency of absorption, and an equilibrium with extravascular stores.

This study has the advantages of prospective design and large sample size, including a representative cross-section of the U.S. population. On the other hand, the measurement of dietary intake was relatively crude, and it may be argued that the effects attributed to iron were due to some other constituent of meat. However, meat intake was not a risk factor or a confounder, and the adjustment for fat intake did not alter the risk due to iron. In summary, these data suggest that iron may be an important determinant of colorectal cancer risk. This effect may be modified by several genetic, hormonal, and physiological factors, which in turn may impact the location of disease.

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