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Body Iron Stores and Risk of Colonic Neoplasia

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Background: **Body iron stores and dietary iron intake have both been shown to be positively associated with subsequent risk of colon cancer. This finding comes from a cohort study involving 14000 men, but the positive association occurred in only 12 cases.** ***Purpose:*** **We performed a case–control study of 264 men and 98 women to test for an association between serum ferritin levels and the presence of adenoma of the colon that would be independent of other known risk factors.** ***Methods:*** **Serum ferritin levels were determined in this study from sera, frozen at –80 °C for 5-8 years, that had been originally obtained between 1984-1987 at the Walter Reed Army Medical Center from adult male and postmenopausal female patients undergoing routine colonoscopic examination and previously enrolled in a case–control study that assessed the potential dietary and environmental risk factors for colonic neoplasia. The presence of fecal occult blood in the stool or the suggestion of colonic polyps seen on barium enema defined eligibility for the study. Patients with known preexisting colonic disease were excluded. Eligible patients had their blood drawn and serum prepared. Following colonoscopy and histologic review, the patients were classified into three groups: normal (without neoplastic disease), 159 subjects; adenoma, 145 subjects; and colon cancer, 29 subjects. Body iron stores were determined by measuring serum ferritin levels by a competitive-binding radiometric immunoassay. Ferritin levels categorized into quintiles for adenoma were defined. Crude and adjusted odds ratios (OR_{adj}) with 95% confidence intervals (CIs) for cancer and adenoma related to ferritin were calculated, controlling for known or suspected risk factors including sex, age, race, body mass index, family history, tobacco use, and alcohol consumption.** ***Results:*** **Statistically significant associations of adenoma risk were seen in the third ([OR_{adj}] = 3.8; 95% CI = 1.5-9.5) and fourth (OR_{adj} = 5.1; 95% CI = 2.0-12.7) quintiles of ferritin relative to the first quintile, for smoking history (OR_{adj} = 2.4; 95% CI = 1.3-4.3), for male sex (OR_{adj} = 1.9; 95% CI = 1.0-3.7), and for family history of polyps or cancer (OR_{adj} = 1.8; 95% CI = 1.0-3.4). From a second set of analyses that excluded 36 patients with serum ferritin of greater than or equal to 399 ng/mL, the greatest effect of ferritin on adenoma risk by anatomic subsite was seen in the right colon.** ***Conclusion:*** **The apparent dose–response for serum ferritin level and adenoma risk suggest that exposure to iron may be related to adenoma formation. [J Natl Cancer Inst 86:455–460, 1994]**

It has been suggested that the protective effect of dietary fiber observed in epidemiologic studies of human colorectal cancer may not be caused by alterations in fecal bulk, water content, transit time, or pH (*1*), but rather by the chelation of dietary iron by the phytate content of high-fiber foods (*2*). The western diet, which has a high intake of red meat and is low in fiber and high in fat, is rich in bioavailable iron and also provides copious lipid substrate for oxidation reactions catalyzed by iron (*3,4*). Products of these reactions have been shown to be genotoxic as manifested through both DNA strand breaks and mutagenicity (*4,5*). These reactions have also been found to be sensitive to iron availability in vivo for iron delivered either parenterally or enterally (*6,7*). Iron has been positively associated with both the initiating and the promoting phases of carcinogenesis (*8,9*), and excess iron can overcome the body's natural iron-withholding defenses against early cancers (*10,11*).

Body iron stores and dietary iron intake were both shown to be positively associated with subsequent risk of colon cancer in males in the National Health and Nutrition Examination Survey #1 (NHANES-I) (*12*). The NHANES-I cohort was large, more than 14000 individuals, although the association of iron stores specific to colon cancer was based on only 12 cases. To investigate this matter further, we performed a case–control study of 264 men and 98 women (data missing on five individuals) to test for an association between serum ferritin levels and the presence of adenoma of the colon that would be independent of other known risk factors.

Subjects and Methods

During the years 1984 to 1987, all adult men and postmenopausal women undergoing colonoscopy at Walter Reed Army Medical Center (WRAMC) were screened after referral for, but

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See "Notes" section following "References."

prior to, colonoscopy for eligibility to participate in a case–control study that assessed potential dietary and environmental risk factors for colonic neoplasia. Only subjects in good general health were recruited. Indications for colonoscopy that led to referral and permitted inclusion in the study were occult blood in the stool or the suggestion of colonic polyps seen on barium enema. Other indications for colonoscopy, such as a history of colonic adenomas or colorectal cancer, familial polyposis, or inflammatory bowel disease, resulted in the exclusion of these individuals. In addition, patients with malabsorption, alcoholism, hepatic or renal disease, or recent weight loss in excess of 15 pounds were excluded. A dietary and environmental risk factor questionnaire was administered before colonoscopy. This questionnaire quantified, among other factors, current and past use of alcoholic beverages and tobacco. Body mass index (BMI)—weight in kilograms over height/meters squared—was calculated from self-reported heights and weights. Because the initial focus of the study was dietary exposure to vitamin A, carotenoids, and cruciferous vegetables, the focus of the dietary questionnaire was on foods containing these micronutrients. For this reason, dietary iron data were not collected and are not available for this population.

Written informed consent was obtained from each subject for phlebotomy and a health history and habits interview prior to colonoscopy. This original study and the subsequent measurement of ferritin levels in stored sera were done with the approval of the internal review boards of WRAMC and the University of Illinois.

Blood was drawn from each patient after an overnight fast into a foil-wrapped 30-mL polypropylene syringe (Sarstedt-Monovette, Newton, N.C.). It was allowed to clot at room temperature for 30-180 minutes prior to centrifugation (1500*g*) in the dark for 5 minutes at 3000 rpm. Following this procedure, serum was removed and recentrifuged at 3000 rpm for 10 minutes. Supernatant serum was then mixed and aliquoted into several air-tight 1.5-mL-polypropylene storage tubes (Belart Products, Pequannock, N.J.) and frozen at –40 °C. Batches of tubes were shipped overnight in dry ice and then frozen at –80 °C for 5-8 years at the University of Illinois. Selected sera were periodically tested for stability of individual carotenoid levels over the 8-year period. Carotenoids are extremely sensitive to oxidative degradation upon improper storage. Individual values remained stable over the entire storage period. All sera were thawed at the same time, and serum ferritin levels were measured in the clinical laboratories of the University of Illinois Hospital by a competitive-binding radiometric immunoassay (Baxter Travenol Diagnostics, Cambridge, Mass.). A precipitating antiserum was used to separate antibody-bound tracer from unbound tracer. Nonradioactive ferritin from patient samples, ferritin standards, and controls competed with a constant amount of ^{125}I-labeled ferritin tracer for binding sites on the ferritin antibody, which was held at a limiting concentration. The amount of tracer that will bind to the antibody is inversely proportional to the amount of nonradioactive ferritin present in the assay tube. The precipitating antiserum reagent containing a second antibody in a polymer solution was used to separate the antibody-bound tracer from unbound tracer by immunoprecipitation. The assay tubes were centrifuged, and the supernatant was decanted. The antibody-bound tracer that was located in the precipitate was counted in a gamma counter. A standard curve was constructed, and the ferritin concentration of the subject was read from the standard curve (*13*).

Colonoscopy was performed jointly by a staff gastroenterologist and and a gastroenterology fellow. Subjects were classified as having colonic adenomas or adenocarcinoma or as controls on the basis of the results of colonoscopy with biopsy or excision of all polyps. Histologic assessment was initially performed by members of the Anatomic Pathology Service at WRAMC. Subsequent blinded review of histologic material from 204 subjects by a single pathologist resulted in reclassification of only one patient from the adenoma group to the control group. Histologic material from 80 subjects, including all subjects whose original diagnoses included carcinoma in situ, high-grade dysplasia, severe dysplasia, or carcinoma arising in a pedunculated adenoma, was later submitted for reinterpretation to one of the authors (L. H. Sobin) who had no knowledge of the original diagnosis. This procedure resulted in reassignment of one additional subject. Adenomas were classified anatomically as being in the right colon, left colon, or rectum by the endoscopist.

Subjects were designated as controls only if colonoscopy was complete to the cecum and if histologic assessment of adequate tissue obtained from each discovered, suspected polyp was negative for neoplasia. Subjects with hyperplastic polyps were classified as controls if they did not also have neoplastic polyps.

Overall frequencies of both case groups were compared with those of controls for serum ferritin and for other potential risk factors (age, race, sex, BMI, current alcoholic beverage intake, cigarette smoking history, and family history of colonic neoplasia). To assess the effect of ferritin after we controlled for identified independent risk factors, stratified and multivariate analyses were conducted. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed using single-factor adjustment with the Mantel–Haenszel method and 95% CI estimates (*14*). Adjustment for several factors was simultaneously accomplished using a logistic regression model with adjusted ORs and 95% CIs estimated from appropriate β coefficients and standard errors (*15,16*). An overall analysis used ferritin categorized into levels by quintiles. A second restricted analysis (excluding individuals with serum ferritin >399 ng/mL for reasons outlined in the "Discussion" section) used ferritin categorized by quartiles.

Results

Of the original 367 subjects, sera were available for 333 who were classified by adequate colonoscopy and histologic assessment. Of that group, 145 individuals were classified as having adenoma, 29 were classified as having colon cancer, and 159 were classified as neoplasia-free controls. Of the adenomas, 52 were found in the right colon, 117 in the left colon, and 22 in the rectum.

The serum ferritin levels in the entire population varied from 8 to 928 ng/mL. The mean ferritin level (± SD) for the entire population was 171 ng/mL (±166 ng/mL); for control subjects, it was 170 ng/mL (±183 ng/mL); for adenoma subjects, it was 182 ng/mL (±153 ng/mL); and for cancer subjects, it was 125 ng/mL (±161 ng/mL).

The results of the multivariate analysis of the adenoma and control population are presented in Table 1. Statistically significant associations of adenoma risk were seen in the third (adjusted odds ratio [OR_{adj}] = 3.8; 95% CI = 1.5-9.5) and fourth (OR_{adj} = 5.1; 95% CI = 2.0-12.7) quintiles of ferritin relative to the first quintile, for smoking history (OR_{adj} = 2.4; 95% CI = 1.3-4.3), for male sex (OR_{adj} = 1.9; 95% CI = 1.0-3.7), and for family history of polyps or colorectal cancer (OR_{adj} = 1.8; 95% CI =1.0-3.4).

Thirty-six individuals had serum ferritin levels of 399 ng/mL or more. After these 36 individuals were excluded from analysis, there remained 131 adenoma subjects, 26 cancer subjects, and 140 control subjects. A second set of analyses was performed with this exclusion: The results of these analyses are shown in Figs. 1 and 2 and Table 2. In Fig. 1, crude (unadjusted) and single factor adjustment analyses demonstrate ORs for colon cancer consistently near or less than 1.0, whereas those for adenoma were always greater than 2.0, in this case using high and low ferritin, divided by the median value of ferritin in this group (83 ng/mL). Fig. 2 shows graphically the multivariate analysis of adenoma risk by quartiles of ferritin. Significant increases in risk were seen in the third and fourth quartiles with significance for trend ($P<.001$). Table 2 demonstrates the relative contribution of ferritin to adenoma risk by anatomic subsite, showing the greatest effect of ferritin in the right colon. The other findings of the unrestricted population shown in Table 1 regarding age, sex,

Table 1. All subjects: adjusted ORs and 95% CIs for ferritin levels and other risk factors for colonic adenomas*

Variable (range)	No. of case subjects	No. of control subjects	OR	95% CI
Ferritin: quintiles				
1st (8-41 ng/mL)	14	32	1.0	
2nd (42-75 ng/mL)	15	32	1.2	0.4-3.4
3rd (76-129 ng/mL)	36	31	3.8	1.5-9.5
4th (130-256 ng/mL)	54	33	5.1	2.0-12.7
5th (257-998 ng/mL)	26	31	2.1	0.8-5.3
Age, y: tertiles				
1st (26-54)	36	50	1.0	
2nd (55-64)	55	60	1.4	0.7-2.7
3rd (65-87)	53	48	1.7	0.9-3.4
Sex				
Male	115	102	1.9	1.0-3.7
Female	28	55		
BMI, kg/m^2				
<22	10	23	0.5	0.2-1.3
22-27	78	72	1.0	
>27	56	63	0.8	0.5-1.4
Race				
White	118	126	1.1	0.5-2.2
Nonwhite	25	32		
Ever smoked				
Yes	110	97	2.4	1.3-4.3
No	31	57		
Family history of polyps or cancer				
Yes	38	33	1.8	1.0-3.4
No	99	123		
Current alcohol drinking†				
Yes	91	101	0.6	0.3-1.1
No	46	49		

*Each OR estimate is adjusted for those other risk factors shown in the table. Subject numbers represent distribution of each variable before logistic regression, missing values excluded.

†A significant association (P = .002) of adenoma risk and beer consumption as well as tobacco use has been previously reported in this population (*18*).

race, current alcohol drinking, family history of polyps or colorectal cancer, and smoking history were essentially duplicated in this restricted multivariate analysis.

Discussion

We have demonstrated an association between serum ferritin levels and the presence of adenoma in the colon that is independent of other known risk factors. Male sex, family history of polyps and cancer, and a positive smoking history were also shown to be significant independent risk factors for adenoma.

It is believed that most, if not all, cancers of the colon are preceded by adenomatous change and that the presence of adenomas is the best known predictor of subsequent cancer risk (*17*). Yet adenomas themselves rarely cause symptoms. Therefore, assessment of nutritional parameters such as iron stores at the time of polyp diagnosis rather than after the development of cancer will better reflect nutritional factors truly associated with neoplastic risk. In cancer patients, however, the disease itself, through blood loss, for example, can affect nutritional parameters and therefore precludes accurate assessment. Indeed, the pattern of risk observed for adenoma was not seen in cancer cases (Fig. 1), apparently for this reason.

The finding that smoking is an independent risk factor for adenoma has been previously reported (*18*), as has male gender (*19*). That gender should occur independently of iron stores limits the potential mechanisms to consider. Data concerning parity in women and prior hormone usage are not available in this study, although these data would be of value to examine in future studies, since estrogen exposure and, possibly, parity have been shown to be associated with diminished colon cancer risk and may also relate to adenoma risk (*20*).

BMI was not found to be an independent risk factor for adenoma or cancer in this population, although both excess caloric intake and increased BMI have both been associated with increased risk of colorectal cancer and adenoma in previous reports (*21*). In our study, we calculated the BMI herein from self-reported heights and weights, which may have led to significant errors, but not systematically so between groups.

One of our concerns was that there be no systematic introduction of bias in the selection of the control group. We favored a colonoscopy-normal control group because, in a study of risk factors for colonic adenomas, there would be a strong bias toward negative results if a control population was used who were not subjected to colonoscopy and found to be free of neoplasia. There is a high prevalence (>30%) of asymptomatic adenomas in the general population of this age range (>50 years) (*22*). In comparing the two groups (adenoma and control), we found that the mean size of resected adenomas in the polyp group was less than 1 cm, a size at which bleeding is unlikely to be detected. Alternative sources of bleeding were seldom identified in either group. In that respect, the adenoma and control groups were similar, in that the fecal occult blood tests in both groups detected bleeding that was probably unrelated to neoplasia (*23*). Careful review of the historical data from subjects referred because of abnormal results obtained from barium enema testing showed that control subjects and case subjects were examined for similar complaints also unrelated to the ultimate finding of polyps, such as bleeding or symptoms of irritable bowel syndrome. One individual had a symptom, diarrhea, that resolved after resection of a sigmoid villous adenoma. This was the only case in which the polyp appeared to explain the symptom that led to the barium enema. These considerations suggest that the colonoscopy-normal

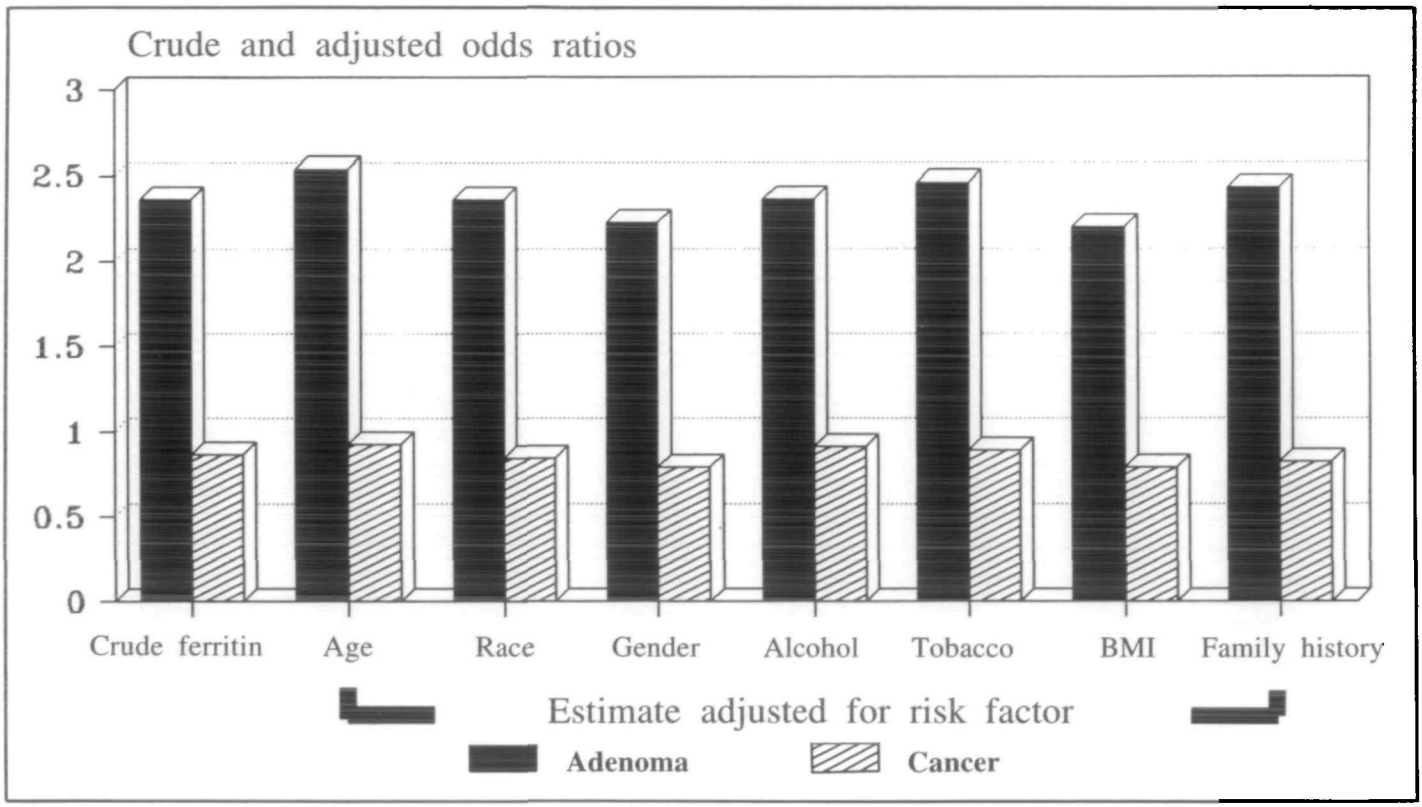

Fig. 1. ORs for ferritin (high [>83 ng/mL] versus low) and either cancer or adenoma, using single-factor adjustment for selected risk factors, excluding individuals with ferritin levels greater than 399 ng/mL. Median ferritin level = 83 ng/mL for patients with ferritin levels less than 400 ng/mL.

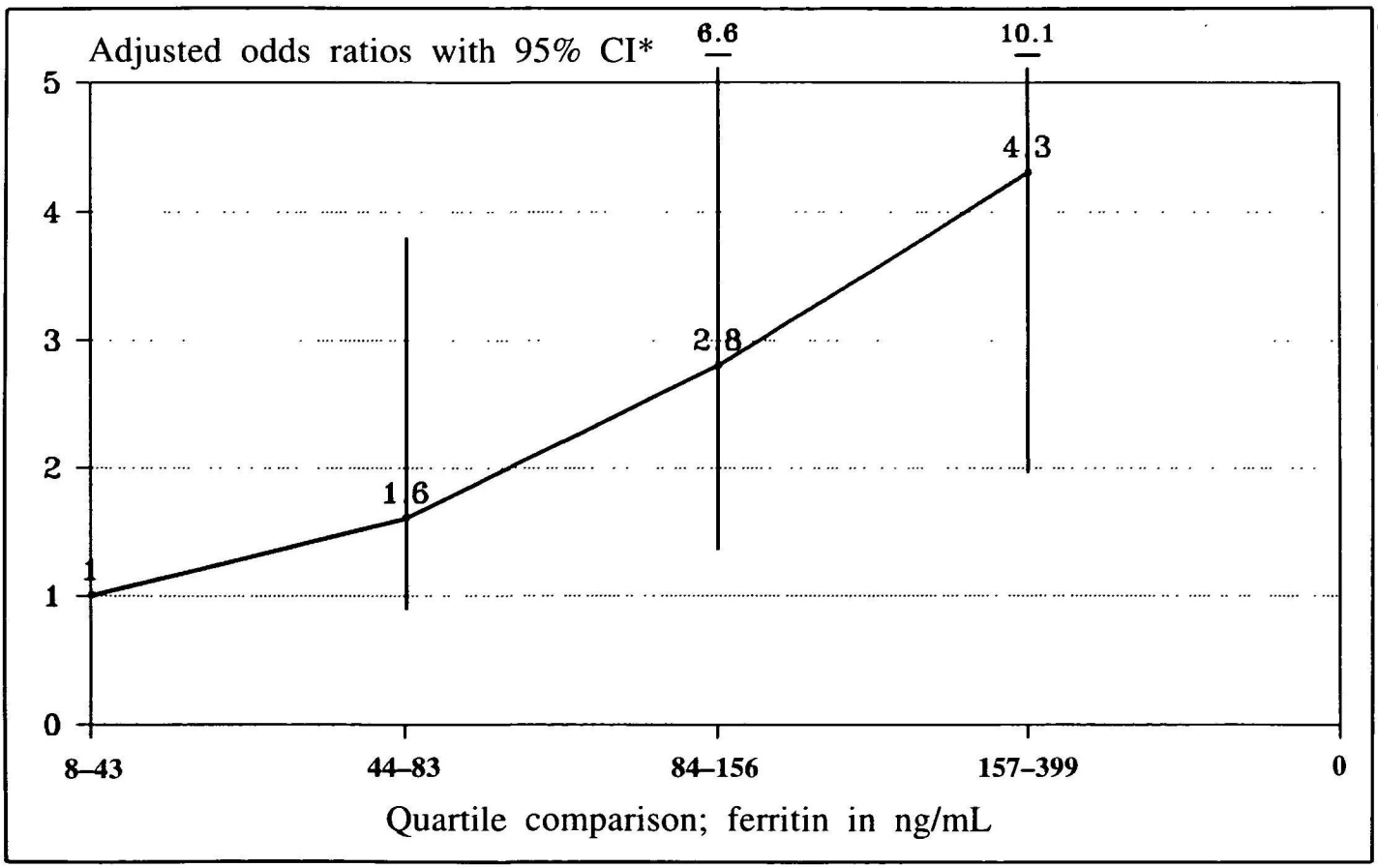

Fig. 2. ORs for ferritin and adenoma risk by quartile, excluding individuals with ferritin levels greater than 399 ng/mL. $P<.001$ for trend. *Adjusted for age, gender, alcohol consumption, cigarette smoking, family history of polyps or cancer, and race.

Table 2. Quartile analysis of effect of ferritin on adenoma risk by location of adenoma in colon: subjects with ferritin less than 400 ng/mL

Ferritin*: quartiles (range)	OR		
	Right colon	Left colon	Rectum
1st (0-43 ng/mL)			
2nd (44-83 ng/mL)	3.0	1.3	5.0
3rd (84-156 ng/mL)	4.7	1.9	7.0
4th (157-400 ng/mL)	6.0	2.9	7.0
Collapsed OR comparing high versus low ferritin (> or <83 ng/mL)	2.7	2.1	2.3

*For subjects with ferritin levels <400 ng/mL, the median ferritin level = 83 ng/mL.

group was not systematically different from the adenoma group regarding alternative diagnoses.

Measurement of serum ferritin levels is generally thought to be the best means to evaluate body iron stores (*24-27*). The level of serum ferritin does not directly reflect dietary iron intake, because many other factors affect iron stores including age, gender, sources of blood loss such as hookworm or colon cancer, genetic abnormalities of iron absorption, and other dietary factors such as ethanol, ascorbate, tannins, and phytate (*9*). Nevertheless, the level of serum ferritin is usually a measure of endogenous iron exposure. Therefore, the apparent dose–response for serum ferritin level and adenoma risk (Table 1 and Fig. 2) suggests that exposure to iron may be related to adenoma formation.

The relationship of the OR of ferritin for adenoma in the fifth quintile (OR = 2.2) and the fourth relative to the first (OR = 5.3; Table 1) implies either that ferritin levels greater than roughly 300 ng/mL (and thus iron exposure at this level) are less supportive of adenoma formation than ferritin levels just below this or that ferritin levels, when elevated above 300 or 400 ng/mL, may not truly reflect iron stores. Elevations in serum ferritin levels may occur independently of iron stores, specifically in acute inflammatory conditions or in individuals with liver disease. In these conditions, the ferritin is usually found to be in excess of 400 ng/mL serum (*26*), although transferrin saturation would be low. Also, in a population of this size, it is likely that at least one individual would have homozygous hereditary hemochromatosis, a disease that is characterized by dysfunction of the liver, heart, and pancreas. Hepatocellular cancer risk is increased in patients with hereditary hemochromatosis but not colon cancer risk (*27*). Serum ferritin levels in excess of 400 ng/mL have been used to define iron overload (*28-30*) and to screen for individuals with homozygous hereditary hemochromatosis in diabetes clinics (*31*). We therefore chose to repeat the analyses, excluding subjects whose ferritin levels were greater than 399 ng/mL; we hypothesized that iron exposure might then be more accurately assessed in relation to adenoma risk. Estimated ORs were not greatly altered from those seen in Table 1 by this restriction (Fig. 2), and a consistent dose–response relationship emerged.

Two studies (*12,32*) have related iron to colorectal cancer in humans. Body iron stores were analyzed by total iron-binding capacity and transferrin saturation in the NHANES-I cohort. In 242 men who developed cancer, body iron stores were higher than in 3113 men who remained free of cancer. Women did not show an increased cancer risk. Lung, bladder, esophagus, and colon were the organs most at risk. In a quartile comparison of colon cancer only, an apparent increase in risk was seen with increasing iron stores, although the effect was not statistically significant ($P = .1$ for trend) because of the small number of cases (n = 12). Dietary iron was also greater in members of the cohort who developed colon cancer only (*12*). In a case–control study of rectal cancer, dietary iron intake was also positively associated with risk in men only (*33*). Supplemental iron use was not measured in that study, which would make the data on female subjects more difficult to interpret because many women ingest iron supplements (*32*).

Several animal studies (*34-37*) have investigated either the role of iron and/or phytate in the development of colorectal cancer. These studies support the hypothesis that increased exposure to iron, parenteral or dietary, augments colorectal cancer induction and that the phytate component of dietary fiber reverses this effect.

There have been three case–control studies (*38-40*) of adenomatous polyps of the colon that included iron data. The first two studies (*38,39*) showed a decreasing risk of polyps with increasing iron ingestion, significantly ($P = .01$) so in the study from Norway (*38*). Neither of these studies reported supplemental iron use nor were body iron stores reported. The third study (*40*) found no significant association of serum ferritin levels to adenoma risk (*40*), although ascertainment of disease status was by sigmoidoscopy only, a procedure which would miss polyps in the proximal colon. If one assumes that all the right-sided polyps and one third of the left-sided polyps would be missed by fiberoptic sigmoidoscopy, our results demonstrate that 48% of the polyps in our adenoma patient population would have been missed on sigmoidoscopy. This would have resulted in substantial misclassification in the control group and a bias toward negative results, a bias further demonstrated in Table 2.

Iron exposure as a risk factor for colorectal cancer is conceptually attractive because it is closely related nutritionally and metabolically to other known risk factors (*9*). It would be of interest to re-examine more established risk factors of colorectal cancer when iron is considered in the analyses.

Lastly, these data along with a report of ferritin and cardiac disease risk (*29*) imply that there may be danger in the supplementation of iron in many foods or in unnecessary pharmacologic supplements of iron when only a very small percentage of the population truly has iron-deficiency anemia (*41*).

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