Plasma Ferritin, Iron Intake, and the Risk of Colorectal Polyps

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High iron exposure has been associated with colorectal neoplasia in several studies. The authors investigated plasma ferritin, an indicator of iron stores, and iron intake as risk factors for adenomatous polyps, intermediate markers for colorectal cancer. During 1991-1993, they collected fasting blood samples from and administered questionnaires to men and women 50-75 years old who visited free sigmoidoscopy clinics at a health maintenance organization. Data from 965 subjects (467 cases, 498 controls) were analyzed. Compared with those who had low-normal plasma ferritin concentrations (73-141 μg/liter), those with elevated concentrations (>289 μg/liter) had a multivariate-adjusted odds ratio of 1.5 (95% confidence interval (CI) 1.0-2.3) after excluding subjects with possible non-iron-related elevations in ferritin. Compared with subjects consuming an adequate amount of iron (11.6-13.6 mg/day), multivariate-adjusted odds ratios were 1.6 (95% CI 1.1-2.4) for <11.6 mg/day and 1.4 (95% CI 0.9-2.0) for >27.3 mg/day. These results provide further support for a weak positive association between iron exposure and colorectal polyps. Am J Epidemiol 1996;144:34-41.

Colonic polyps; colorectal neoplasms; ferritin; iron

Using data from the First National Health and Nutrition Examination Survey (NHANES I), Stevens and coworkers (1) found that high body iron stores may be a risk factor for cancers common in Western populations, including colorectal cancer. If iron causes cancer, the two most likely mechanisms are that readily available body iron 1) spurs the growth of transformed cells and/or 2) acts as a prooxidant, increasing carcinogenic DNA changes or increasing general oxidative stress. Support for the high iron stores hypothesis comes from animal experiments (2-6) and a few epidemiologic studies (1, 7-10). Studies of people with the excessive iron accumulation of hereditary hemochromatosis (11-15) have consistently found a high risk of liver cancer but equivocal results for other cancers.

Iron deficiency may also increase the risk of some cancers. Although little work has been done in this area, this effect has been suggested by animal experiments (16, 17) and by descriptive observations in humans. In the first half of this century, iron-deficient Scandinavian women with Plummer-Vinson syndrome (18-20) frequently presented with upper alimentary cancers; and it has been proposed that iron deficiency contributes to the development of gastric cancer in South America (21). Iron deficiency and iron overload both appear to impair immune function (22, 23).

Few studies have examined blood measures of iron exposure in relation to colorectal polyps (8-10), which are widely held to be intermediate markers of colorectal cancer (24). No study has examined total iron intake (including supplemental iron) as a risk factor for colorectal polyps. We hypothesized that total iron intake and plasma ferritin, a blood measure that reflects body iron stores over a wide range (25-27), might exhibit a U-shaped relation to the prevalence of colorectal polyps.

MATERIALS AND METHODS

Study population

Subjects were eligible for the study if they underwent screening by flexible sigmoidoscopy at either of two Southern California Kaiser Permanente medical
centers from January 1, 1991, through August 25, 1993. Eligible men and women were 50–75 years old; were free of invasive cancer, inflammatory bowel disease, and familial polyposis; were fluent in English; had no previous bowel surgery; were residents of Los Angeles County; and had no physical or mental disability precluding an interview. In addition, subjects who had symptoms suggestive of any organic intestinal disease were excluded. Cases were subjects diagnosed for the first time with one or more histologically confirmed adenomatous polyps. Controls had no polyps of any type discovered at sigmoidoscopy, had no history of polyps, and were individually matched to cases by sex, age (±5 years), date of sigmoidoscopy (±3 months), and Kaiser center. The study was approved by the Human Subjects Protection Committee of the University of California, Los Angeles, and by the Kaiser Permanente Institutional Review Board. This was a case-control study of polyps with regard to the rectosigmoid region only inasmuch as carcinomas arising from polyps may arise from polyps in the rectosigmoid region (28).

Additional details of subject recruitment and data collection have been provided elsewhere (29). Briefly, polyps data were obtained from Kaiser pathology reports. Data on a variety of nondietary risk factors were obtained during a script-standardized, in-person interview, administered on average 5 months after sigmoidoscopy.

Assays of plasma ferritin and other biochemical indicators

A fasting blood sample was drawn in the morning, on average 6 months after sigmoidoscopy, into a tube coated with ethylenediaminetetraacetic acid. The plasma was placed in a cryogenic tube and stored at −70°C until the day of assay. Plasma ferritin samples were assayed in batches over time by one medical technologist, who was blinded as to case-control status. All assays were performed using Allegro ferritin radioimmunoassay kits (Nichols Institute, San Juan Capistrano, California) and Beckman Gamma 5500 or Gamma 4000 gamma counters (Beckman Instruments, Fullerton, California).

A plasma pool and two commercial control samples (Bio-Rad Lyphochek, Levels 1 and 3; Bio-Rad Laboratories, Hercules, California) were used to monitor accuracy and between-run variation in plasma ferritin results. At mean plasma ferritin levels of 59.8, 99.1, and 487.8 μg/liter, the between-run coefficients of variation during the study were 3.5, 4.2, and 5.4 percent, respectively. The within-run coefficient of variation, using multiple aliquots of a plasma pool (mean level = 72.7 μg/liter), was 4.3 percent.

Other nutritional indicators measured were several plasma carotenoids, whole blood ascorbate, plasma folate, and red cell folate. Samples for all assays were treated with stabilizing agents, if needed, and stored at −70°C. Plasma carotenoid samples were assayed later by high performance liquid chromatography. Whole blood ascorbate samples were assayed using a spectrophotometric, bis-2,4-diphenylhydrazine method. Both whole blood and plasma folate samples were assayed using Quantaphase and Quantaphase II radioassay kits (Bio-Rad Laboratories). Hematocrits were measured using freshly drawn whole blood samples on a Coulter counter.

Iron intake

Diets were assessed by means of a modified version of a 126-food semiquantitative food frequency questionnaire (30) that was mailed and that contained questions about diet in the year before sigmoidoscopy. The questionnaires were reviewed for completeness during the in-person interview and analyzed using the Nutrition Data System (31) for nutrients from foods and a supplement database developed for the questionnaire. Eighty percent of multivitamin users who provided complete information about their supplement used one that contained iron. Therefore, for the 15 percent of all subjects unable to describe the specific multivitamin supplement used, it was assumed that they used one containing the US Recommended Dietary Allowance for iron.

Statistical analysis

Plasma ferritin values were obtained for 980 subjects, of whom 15 were dropped from the dataset because they lacked food frequency questionnaires. The final data set contained 402 matched pairs as well as unmatched controls (n = 96) and cases (n = 65). The latter generally occurred when one subject in a pair did not provide a blood sample or the sample was not assayed, but a few occurred for other reasons (e.g., nonfluent in English).

Plasma ferritin values were divided into quartiles and total iron intakes (food plus supplements) into quintiles, using their distributions across all subjects. The second to lowest quartile of ferritin values and the second to lowest quintile of iron intake were designated the reference categories. The reference levels were chosen a priori to be biologically meaningful. For example, the reference quartile for plasma ferritin was the quantile most unlikely to contain subjects with either iron overload or iron deficiency, while the ref-
ference quintile for iron intake contained the lowest estimated iron intakes not expected to produce iron deficiency over time. (Using quartiles of iron intake mingled subjects with adequate and inadequate intakes in the lowest quartile.) Prevalence odds ratios were computed in a Mantel-Haenszel analysis. We used these results to determine whether logistic regression models should be fit to categorical or continuous forms of the iron variables (32).

A conditional logistic regression model (n = 402 pairs) was fit to a plasma ferritin or iron intake variable, with and without potential confounding variables. The matching was then broken, and unconditional logistic regression models were fit, stratifying on the matching variables, the same potential confounders, and using the same 804 subjects. The conditional and unconditional analyses yielded similar results, which was expected inasmuch as they both controlled for the matching variables (33). Next, unconditional models with all 965 subjects (including the unmatched) were examined. These models also gave similar results. Results reported in this paper are from unconditional models that included all subjects for whom we had information.

RESULTS

This was an ethnically diverse population of men and women around retirement age and living in relatively urban neighborhoods in Los Angeles County. There were 167 female cases, 167 female controls, 300 male cases, and 331 male controls, of whom 54 percent were white, 17 percent black, 19 percent Latino, 9 percent Asian/Pacific Islander, and 1 percent "other." Ethnicity, education, and income did not vary appreciably between cases and controls (not shown).

In table 1, medians and ranges of plasma ferritin and other relevant variables are shown. The median plasma ferritin concentration was higher in cases than in controls, although this was not statistically significant in either sex (Wilcoxon signed rank test). Plasma ferritin concentrations covered a wide range in both sexes, including values suggestive of nonexistent body iron stores (<12 μg/liter) as well as the high values typically seen either in iron overload diseases (>400 μg/liter) or in common pathologic conditions (>200 μg/liter) (34). Few control women (3.9 percent) had plasma ferritin levels >500 μg/liter, whereas 13.1 percent of male controls had levels >500 μg/liter. Although it is usual for men to average higher ferritin values than women (34), the ferritin distribution for men displayed a shift toward unusually high values.

The initial analysis of plasma ferritin revealed no evidence of a relation with polyps risk (table 2). Ferritin levels may be increased by pathologic conditions not accompanied by excess body iron (35, 36). Therefore, we repeated the analysis after excluding subjects likely to have such conditions: those with very high ferritin levels (>500 μg/liter) or with low or missing hematocrits (females, <35 percent; males, <41 percent). We chose low hematocrit as a criterion because anemias in older people are usually associated with non-iron-related elevations in ferritin levels (35, 36). After the exclusions, the odds ratio for the highest category increased slightly (table 3). A weak U-shaped relation emerged; this was consistent across sex (not shown) and unaltered by adjustment for various potential confounding variables (table 3). Adjusting for whole blood ascorbate and red cell folate did not materially alter ferritin odds ratios (not shown).

Categorized by the site and size of the largest adenoma, 30 percent of cases had rectal polyps (vs. left colon polyps), and 19 percent of all cases had polyps more than 1 cm in diameter. The U-shaped relation between plasma ferritin and polyps was of greatest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n = 167)</td>
<td>Controls (n = 300)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Plasma ferritin (μg/liter)</td>
<td>105</td>
<td>3-582</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>40.6</td>
<td>28.9-48.1</td>
</tr>
<tr>
<td>Calories (kcal)</td>
<td>1,676</td>
<td>550-5,302</td>
</tr>
<tr>
<td>Total iron intake (mg)</td>
<td>19.7</td>
<td>3.4-143.9</td>
</tr>
<tr>
<td>Supplemental iron use (%)</td>
<td>45.5</td>
<td>35.3</td>
</tr>
<tr>
<td>Iron users with low hematocrit (%)</td>
<td>5.3</td>
<td>1.7</td>
</tr>
</tbody>
</table>

* All data = median (range), except where indicated.
† Mean (range).
‡ (Number of subjects using iron supplements who had low hematocrits) x 100/(number of subjects who used iron supplements). Low hematocrits were defined as <35% for women and <41% for men.
The association between iron intake and polyps also displayed a weak U-shaped pattern. The lowest quintile of energy-adjusted total iron intake and the two highest quintiles were associated with increased risk (table 4). This weak U-shaped relation persisted after adjustment for smoking, calories, red meat, total fruit and vegetables, saturated fat, and ethanol (table 4), as well as when adjusted for whole blood ascorbate and plasma beta-carotene concentrations (not shown). A clear difference in the iron intake-polyp association for rectal versus left colon polyps was not found (table 4), nor did there appear to be a difference across polyp size (not shown). The iron intake results were not substantially altered when we excluded subjects with low hematoctrits (who might have been taking iron supplements), those with blood in stool, or those referred for symptoms.

The two highest quintiles of iron intake contained a higher proportion of all cases and controls referred for specific minor symptoms (29), including the 10.7 percent of all cases and 6.4 percent of controls referred because of possible bleeding (e.g., visible or occult blood in stool). Excluding subjects with possible bleeding or with any minor symptoms did not alter ferritin odds ratios.

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TABLE 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association of quintiles of total iron intake with colorectal polyps, Los Angeles, California, 1991–1994*

<table>
<thead>
<tr>
<th>Iron Intake (mg/day)</th>
<th>&lt;11.6</th>
<th>11.6–13.6</th>
<th>13.7–17.2</th>
<th>17.3–27.3</th>
<th>&gt;27.3†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
</tr>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted (n = 965)</td>
<td>1.7</td>
<td>1.1–2.5</td>
<td>1.0</td>
<td>0.7–1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Further adjusted (n = 965)</td>
<td>1.6</td>
<td>1.1–2.4</td>
<td>1.0</td>
<td>0.7–1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Further adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women (n = 334)</td>
<td>0.9</td>
<td>0.4–1.9</td>
<td>1.0</td>
<td>0.6–1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Men (n = 631)</td>
<td>2.1</td>
<td>1.3–3.5</td>
<td>1.0</td>
<td>0.9–2.4</td>
<td>1.9</td>
</tr>
<tr>
<td>By site</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rectum§ (n = 638)</td>
<td>1.4</td>
<td>0.7–2.6</td>
<td>1.0</td>
<td>0.6–2.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Left colon (n = 824)</td>
<td>1.8</td>
<td>1.1–2.7</td>
<td>1.0</td>
<td>0.7–1.6</td>
<td>1.4</td>
</tr>
</tbody>
</table>

* Unconditional logistic regression models fitted to quintiles of energy-adjusted residuals of iron intake, including iron from supplements. All models stratified on matching variables (see table 2). Cases: n = 487. Controls: n = 498.

† Ranges (in mg/day) estimated by entering the study population median caloric intake (1,901 kcal) into the equation: total iron = a° + a'(kcal) + e.

‡ Further adjusted using the same potential confounding variables in table 3.
§ Stratified on matching variables only. Rectal cases: n = 138. Left colon cases: n = 326. Controls: n = 498. Site data missing for n = 3.

TABLE 5. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association of categories of total iron intake with colorectal polyps after excluding subjects whose placement in total iron intake quintile was dependent on iron supplement use, Los Angeles, California, 1991–1994*

<table>
<thead>
<tr>
<th>Iron Intake (mg/day)</th>
<th>&lt;11.6</th>
<th>11.6–13.6</th>
<th>13.7–17.2</th>
<th>17.3–27.4</th>
<th>&gt;27.3†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
<td>95% CI</td>
<td>OR</td>
</tr>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted (n = 645)</td>
<td>1.5</td>
<td>0.9–2.4</td>
<td>1.0</td>
<td>0.5–1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Further adjusted (n = 645)</td>
<td>1.2</td>
<td>0.7–1.9</td>
<td>1.0</td>
<td>0.5–1.1</td>
<td>0.6</td>
</tr>
<tr>
<td>Further adjusted</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women (n = 206)</td>
<td>0.7</td>
<td>0.3–1.8</td>
<td>1.0</td>
<td>0.4–1.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Men (n = 439)</td>
<td>1.5</td>
<td>0.9–2.8</td>
<td>1.0</td>
<td>0.4–1.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Unconditional logistic regression models fitted to categories of energy-adjusted residuals of iron intake (categories defined by quintiles using all subjects). Subjects were excluded if total (supplemented) iron intake placed them in a higher quintile than did food iron intake alone. All models stratified on matching variables (see table 2).

† Ranges (in mg/day) estimated by entering the study population median caloric intake (1,901 kcal) into the equation: total iron = a° + a'(kcal) + e.

‡ Further adjusted using the same potential confounding variables in table 3.

Intestinal lumen, increasing polyps risk even if never absorbed. Therefore, we included iron intake and plasma ferritin in the same model; odds ratios for both variables were unchanged, and confidence intervals widened only slightly (not shown). Plasma ferritin was only weakly associated with some of the factors known to influence iron absorption: intakes of total or food iron, red meat, or alcohol (Pearson r = 0.10–0.20). It was not associated with other dietary variables examined (e.g., heme intake).

Slowly progressing polyps may predominate in subjects screened for the first time. Hypothetically, a lack or excess of iron could increase polyp incidence or, alternatively, could slow the progression of colorectal polyps to cancer. Therefore, we restricted the cases in one analysis to those with a previously negative sigmoidoscopy (within the past 10 years). For plasma ferritin quartiles (83 cases, 420 controls), the odds ratios (95 percent confidence intervals) from the first (lowest) to the fourth quartiles were 0.9 (0.5–1.8), 1.0 (referent), 1.3 (0.7–2.5), and 1.2 (0.5–2.5). (See the "further adjusted" model in table 3 for comparison.) For iron intake quintiles (100 cases, 420 controls), the odds ratios from the first (lowest) to the fifth quintiles were 1.2 (0.5–2.6), 1.0, 1.2 (0.6–2.4), 2.1 (1.1–4.3), and 1.4 (0.7–3.0). (Compare with the "further adjusted" model for all subjects in table 4.) To summarize, the weak association of low iron (plasma ferritin or intake) with polyps was largely eliminated, and the association of high iron and polyps was not.

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DISCUSSION

We did not find a strong relation, U-shaped or otherwise, between iron variables and adenomatous polyps. A weak association between high plasma ferritin concentrations, high iron intake, and increased polyps risk was present. In all previous reports, blood indicators of iron status have been positively associated with colorectal neoplasia (1, 8–10), although sample sizes were small and results were not statistically significant in some studies (1, 9). Serum ferritin has been measured in only one of these studies: Nelson and coworkers (8) observed a strong positive ferritin-polyps association, especially for polyps of the rectum and right colon. The association in our data was also strongest for rectal polyps (we did not have data on right colon polyps).

In this study, the ferritin-polyps association became statistically significant only after excluding subjects whose ferritin levels may have reflected inflammation or aging rather than iron stores. Examining NHANES I data, Yip and Dallman (38) reported evidence of inflammation (elevated erythrocyte sedimentation rate) in 24 percent of women and 30 percent of men 60–74 years old, which were two to four times the percentages in younger age groups. Thus, there could be an appreciable bias toward no association in any evaluation of a ferritin-polyps relation in studies not excluding subjects whose elevated ferritin levels reflected factors other than high iron stores. Because serum ferritin is considered the best blood measure of body iron stores over a broad range (25–27), its use here was reasonable; but additional measures of iron status and of inflammation would have been useful.

The association between iron intake and polyps appears to support the ferritin-polyps association. However, iron intake odds ratios were dependent on iron supplement use; there was no association between iron ingested from food only and polyps risk. Previous studies also found that increased iron from food was not associated with increased polyp risk (39, 40). Unfortunately, these studies did not have data on supplemental iron. Something associated with supplement use may have been responsible for the present association. However, adjusting for lifestyle-associated factors (e.g., smoking) and excluding subjects who might have had gastrointestinal bleeding did not alter our results. It may be that iron promotes carcinogenesis only when ingested separately from food or in large single doses. Phytates and other factors present in food interact with iron, perhaps eliminating carcinogenic activity (4, 41, 42).

The association in our data between high plasma ferritin levels and polyps was not as strong as previously reported (8). In discussing our preliminary results (43), Nelson and coworkers (8) suggested that having controls with adenomas in the right colon, not detected by sigmoidoscopy, may have masked a strong ferritin association. Our odds ratios may have been attenuated by false-negative controls, but not greatly. Only about 15 percent of individuals with no family history of colorectal cancer have polyps exclusively in the right colon (44, 45).

The association observed between low plasma ferritin levels and polyps was very weak and not statistically significant. It is still possible that undetected chronic bleeding was responsible for the association (46). However, bleeding does not explain the statistically significant association of low iron intake with polyp prevalence.

Using the lowest category of each iron variable as the reference category would not have altered our conclusions. One finds that high plasma ferritin values are still associated with polyps risk, but the association no longer achieves statistical significance. That this is not a chance observation is nevertheless suggested by the findings of previous studies (1, 8–10). Moreover, the second lowest category consistently displays an odds ratio less than 1.0. When the analysis is restricted to subjects known to have had a previous negative sigmoidoscopy, this apparent inverted risk disappears, and risk appears to increase with increasing iron exposure (from ferritin or iron intake).

The present study population was large and consisted of older people who had a sigmoidoscopy free of charge, usually as part of the routine health screening encouraged at Kaiser (29). This is in contrast to most studies of colorectal polyps, in which both cases and controls generally have had gastrointestinal symptoms or other diagnostic evidence of abnormality. The high recruitment rate of the study minimizes the chance that results were distorted by selection bias. Unlike previous studies, iron exposures from food, from supplements, and in body stores were estimated concurrently. Also, comprehensive data were collected and considered during data analysis, including several different nutritional assays of blood.

However, a potential weakness of the study is that blood was collected an average of 6 months after sigmoidoscopy. Although it is possible that subjects changed lifestyle habits and their plasma ferritin levels after polyp diagnosis, results were unchanged when we adjusted for the time elapsed from examination to blood collection. Because this was a prevalence study with largely asymptomatic subjects, polyps inclined to progress quickly to cancer may have been underrepresented relative to slowly developing polyps. Individuals with cancer were excluded from the study. If so, iron exposure levels that were lower than normal...
(referent) levels may have been associated with polyps in this study because a lack of iron prevented adenomas from progressing quickly to cancer (47).

In conclusion, this study found a weak positive association between plasma ferritin, iron intake, and colorectal polyps. A possible interpretation is that excess iron increases polyp incidence. If this interpretation proves correct, there are important policy implications. Iron deficiency continues to be a serious problem in some population groups. However, iron fortification of foods and iron supplement use are widespread; and serum ferritin concentrations have displayed an unexplained increase in NHANES data over time, especially in men (48). The ferritin values reported here are higher than those reported in past population studies (49–51), which seems to support the NHANES findings. It remains to be determined whether the serum ferritin increase reflects secular increases in body iron stores or dietary iron, and whether either of the latter constitutes a serious health threat.

ACKNOWLEDGMENTS

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