Correlation of iron and colon adenomas

Corrélation du statut martial et de la présence d’adénomes du côlon

N.P. Muthunayagama, J.E. Rohrer, S.E. Wright

Department of Internal Medicine, Amarillo Veterans Administration Health Care System, 6010, Amarillo Boulevard West, Amarillo, TX 79106, USA

Department of Internal Medicine, Texas Tech University Health Sciences Center, 1400, Wallace, Amarillo, TX 79106, USA

Department of Health Services Research, Texas Tech University Health Sciences Center, 1400, Wallace, Amarillo, TX 79106, USA

Available online 13 January 2009

Summary

Background and objective. — Better colon cancer screening guidelines are needed. This study was conducted to explore the relationship between serum transferrin saturation (as iron is a potential carcinogen) and presence of colon adenomas. This may aid to evolve better colon cancer screening guidelines.

Methods. — This study is a retrospective review of computer records. Patients who had colonoscopy and iron studies done between May 1996 and December 2003 were included in the study. The adjusted odds ratio, derived from multiple logistic regression analysis, was used to measure the association between transferrin saturation and colon adenomas.

Results. — Complete data were available for 124 subjects. The adjusted odds ratio, for predicting the presence of polyp in those patients with transferrin saturation above the median was 10.9 (CI 4.0—29.5, \( P < 0.001 \)). A one percent increase in transferrin saturation was associated with a 1.07 increase the odds of adenoma (CI 1.03—1.11, \( P < 0.001 \)).

Conclusions. — Iron levels are directly linked to presence of colon polyps, and might help in evolving better screening guidelines.

© 2008 Elsevier Masson SAS. All rights reserved.

Résumé

Rationnel et objectifs. — De nouveaux outils sont nécessaires pour améliorer l’efficience du dépistage du cancer du côlon. Cette étude a été réalisée pour explorer la relation entre la mesure de la saturation de la transferrine dans le sérum (le fer étant un cancérigène potentiel) et la présence d’adénomes coliques.

Funding was provided by the Amarillo Veterans Administration Health Care System (AVAHCS) and Texas Tech University Health Sciences Center (TTUHSC), and research was performed at AVAHCS, 6010, Amarillo Boulevard West, Amarillo, TX 79106, and TTUHSC, 1400, Wallace, Amarillo, TX 79106.

* Corresponding author.

E-mail addresses: [Stephen.Wright@med.va.gov](mailto:Stephen.Wright@med.va.gov), stephen.wright@ttuhsc.edu (S.E. Wright).

0399-8320/S - see front matter © 2008 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.gcb.2008.08.004
diagnosis or screening for higher-risk individuals [9]. For individuals getting colonoscopies too frequently and delayed patients with low risk of colon cancer, the cumulative disease increases the risk of developing cancer [6,7]. How-ever, these high-risk groups account for only one quarter of age [5], a personal history of ovarian, endometrial or adenoma, first degree relative with colorectal cancer, first degree relative diagnosed with adenoma before 60 years of age, since iron may accumulate with age [11,12].

Stratifying subjects for colon cancer screening should increase the benefit. This study was conducted to explore the relationship between serum transferrin saturation, as a surrogate for iron overload (as iron is a potential carcinogen), and presence of colon adenomas. Confirming this relationship would add subjects with iron overload to the high-risk category.

Material and methods

This study is a retrospective review of computer records done in AVAHCS, Texas. The AVAHCS research and development committee approved the study. The TTUHSC institutional review board granted exemption from human subjects review. All patients who had colonoscopy and iron studies done between May 1996 and December 2003 were included in the study. Exclusion criteria were as follows: presence of colon pathologies, such as colon cancer, angiodyplasia, inflammatory bowel disease (as they might be sources of significant blood loss) and chronic viral hepatitis and alcoholic liver disease (since they can masquerade as iron overload). Forty-five patients were excluded. Complete data were available for 124 patients.

The investigator reviewed the subject’s electronic records. The serum iron parameters and colonoscopic findings were recorded. The investigator recorded the findings in a manner so that subjects could not be identified. All patients had colonoscopy, which was complete up to the cecum.

In addition to the presence of adenomatous polyps, other data collected included:

- transferrin saturation (transferrin saturation [%] = serum iron × 100/total iron binding capacity [10]);
- hemoglobin levels;
- history of smoking;
- presence of other coexistent malignancies;
- family history of cancers;
- age, since iron may accumulate with age [11,12].

Transferrin saturation was evaluated in two ways: as a dichotomous variable divided at the mean and as a continuous variable.

The data were analyzed by means tests (student’s t, two-way tables (Chi-square) and multiple logistic regressions (adjusted odds ratios) using Epi Info™ 3.4.3.
**Results**

Descriptive statistics and univariate significance tests are shown in Table 1. Forty-five (36.3%) patients had polyps and 79 (63.7%) did not. Six of the 124 patients were female. The mean age was 70.1 years (standard deviation [S.D.] 10.4). The mean hemoglobin was 12.7 g/dL (S.D. 5.9). The median transferrin saturation was 17. Eighty-eight (71%) patients were smokers, 25 (20.2%) had a family history of cancer and 26 (21%) had other cancers.

Among those patients with adenomas, 37 (82.2%) had high (above the median) saturation and only eight (17.8%) had low (below the median) saturation ($P < 0.001$). Fifty-four patients (68.4%) had low saturation and no adenomas, whereas 25 patients (31.6%) did not have adenomas but had high saturation. The mean saturation among patients with polyps was 28.3% but only 16.5% among patients with no adenoma ($P < 0.001$). None of the covariates were significantly associated with the presence of adenomas in the univariate analyses.

Multiple logistic regression analyses are shown in Table 2. The adjusted odds ratio, for predicting the presence of polyps in those patients with transferrin saturation above the median was 10.9 (CI 4.0—29.5, $P < 0.001$). A one percent increase in transferrin saturation was associated with a 1.07 increase for the odds of adenoma (CI 1.03—1.11, $P < 0.001$). No statistically significant independent relationship was found between smoking, family history of cancer, hemoglobin levels, presence of other cancers and presence or absence of polyps.

**Discussion**

The results of this study demonstrate that transferrin saturation is a strong independent marker for presence of colon adenomas. Colon adenomas are precursors of colon cancer [13]. Male gender, positive smoking history and family history have been shown to be independent risk factors for adenoma [14]. Because of these risk factors and the high number of other cancers, the veteran population studied in this report may be at high risk for adenoma. Additional research in other populations would be required to determine the generality of these findings.

Iron has been implicated as a carcinogen in upper aero-digestive tract cancers [15], neural tumors [16], cutaneous tumors [17], hepatocellular carcinoma [18] and colon cancer [14,19–21]. Many theories have been proposed to explain iron as a carcinogen. They include:

- free radical production;
- reduction of the body's protective mechanism to combat oxidative stress;
- inhibition of the immune system;
- inhibition of essential nutrient function;
- facilitation of cancer growth;
- suppression of anti-tumor activity of macrophages;
- lowering the ratio of cellular differential 4 (CD4) and CD8 positive lymphocytes [22,23].

Studies in mice have shown that iron promotes carcinogenesis by reducing both macrophage and tumor cells-derived NO release and thus inhibiting tumor cell destruction [16].

<table>
<thead>
<tr>
<th>Variable [N (%)]</th>
<th>Overall</th>
<th>Adenoma [N = 45 (36%)]</th>
<th>No Adenoma [N = 79 (64%)]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transferrin saturation [mean (S.D.)]</td>
<td>21 (14)</td>
<td>28 (12)</td>
<td>16 (13)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Transferrin saturation above 50th percentile [N (%)]</td>
<td>62 (50)</td>
<td>37 (82)</td>
<td>25 (32)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking [N (%)]</td>
<td>88 (71)</td>
<td>32 (71)</td>
<td>56 (71)</td>
<td>1.00</td>
</tr>
<tr>
<td>Other cancer [N (%)]</td>
<td>98 (79)</td>
<td>33 (73)</td>
<td>65 (82)</td>
<td></td>
</tr>
<tr>
<td>Cancer history [N (%)]</td>
<td>52 (42)</td>
<td>12 (27)</td>
<td>40 (53)</td>
<td>0.24</td>
</tr>
<tr>
<td>Age [mean (S.D.)]</td>
<td>70 (10)</td>
<td>71 (10)</td>
<td>70 (11)</td>
<td>0.49</td>
</tr>
<tr>
<td>Hemoglobin [mean (S.D.)]</td>
<td>13 (6)</td>
<td>13 (2)</td>
<td>12 (7)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

S.D.: standard deviation; N: number.

$^a$ Epi Info™.

$^b$ Median = 17 (range 2–66).
This has led to the approach of using iron chelators in the treatment of cancer [22,24]. Iron chelators may delete iron or cause oxidative stress in the tumor due to redox perturbations in its environment. Desferoxamine has been shown to have anti-tumor activity in the treatment of neuroblastoma, leukemia, bladder carcinoma and hepatocellular carcinoma [22].

Iron in diet has been implicated as a carcinogen in the evolution of colorectal cancer. Red meat (containing heme) causes damage to colonic mucosa. This results in compensatory hyper proliferation of the epithelium, which increases the risk for colon cancer [19,25,26]. This raises concern about supplementation of iron in foods and unnecessary pharmacologic supplementation of iron even though a percentage of the population is iron deficient [27]. It has also been suggested that fiber diet decreases risk of colon cancer by chelating iron. In three studies [28–30], that looked at iron data and adenomatous polyp, a direct relationship was not seen. However, two of the studies did not report supplemental iron use and the third one used sigmoidoscopy to look for polyps. The third group did find a direct relationship in a later study using serum ferritin [30].

Body iron stores have been correlated with colon neoplasm [14,21,31–33].

Elevated serum iron was associated with increased cancer risk in the distal colon [33]. In the national health and nutrition examination survey-I cohort, 242 men who developed cancer had higher body iron levels than the 3113 men who remained free of cancer. 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. This effect was not however statistically significant (P = 0.1) because of the small number of cases (N = 12). In another study by Nelson et al., which studied 264 men and 98 women with colon adenomas, a statistically significant relationship was demonstrated between serum ferritin and colon adenomas [14], as in an additional study [30]. However, serum ferritin is an acute phase reactant. Its elevation in colon neoplasm could be similar to the elevation of CRP. It may not relate to body iron stores in inflammation.

In our study, we used transferrin saturation, which has been reported to better distinguish iron overload than serum ferritin [34]. In addition, the sensitivity of transferrin saturation was superior to serum ferritin in a screening study for hemochromatosis [35]. We have demonstrated a direct relationship between the presence of colon adenomas and serum transferrin saturation. Furthermore, only two of the subjects had above 60% at 66%. Thus, even at transferrin saturation below levels used to screen for iron overload [35] a direct correlation exists for transferrin saturation and polyps. Our study supports the studies [14,30] using serum ferritin as a marker of body iron stores and direct association with polyps. In addition, it expands on the above-mentioned studies, which showed that individuals with higher body iron stores are at greater risk for colorectal adenomas than those with normal or low body iron stores by using transferrin saturation as the indicator of body iron stores. Our study is an advance since transferrin saturation is less likely to have false positive results for iron overload than serum ferritin. It should improve survival by screening for colon adenomas associated with high normal rather than for cancer which required more than 60% transferrin saturation.

Other variables that were used in the study did not show any significant relationship to presence or absence of a polyp. This might be due to the small number of patients.

This study, being a retrospective study, has many caveats. The major one being the absence of definite time interval between the collection of blood for iron studies and colonoscopy. A prospective study, solely designed for this purpose, with a blood sample collected at the same date of colonoscopy and a detailed questionnaire including details such as oral iron supplements and other variables, which we think might predict the presence of adenomatous polyp, will help in answering this question.

We believe that serum transferrin saturation, if used in conjunction with other parameters including age and genotyping for hemochromatosis [36], which is associated with increased colon cancer, could aid in evolving a scoring system that might help in predicting the presence of colon polyps. This could assist in channeling our resources (screening colonoscopy) better.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>Confidence interval</th>
<th>P value</th>
<th>Odds Ratio</th>
<th>Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transferrin saturation</td>
<td>1.07</td>
<td>1.03–1.11</td>
<td>&lt;0.01</td>
<td>10.90</td>
<td>4.02–29.53</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Transferrin saturation above 50th percentile</td>
<td>1.07</td>
<td>0.43–2.69</td>
<td>0.33</td>
<td>0.92</td>
<td>0.35–2.44</td>
<td>0.87</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.66</td>
<td>0.60–4.62</td>
<td>0.37</td>
<td>2.20</td>
<td>0.73–6.65</td>
<td>0.16</td>
</tr>
<tr>
<td>Other cancer</td>
<td>1.60</td>
<td>0.58–4.44</td>
<td>0.59</td>
<td>1.38</td>
<td>0.47–4.83</td>
<td>0.56</td>
</tr>
<tr>
<td>Cancer history</td>
<td>1.01</td>
<td>0.97–1.06</td>
<td>0.91</td>
<td>1.01</td>
<td>0.97–1.06</td>
<td>0.59</td>
</tr>
<tr>
<td>Age</td>
<td>1.01</td>
<td>0.84–1.22</td>
<td>0.99</td>
<td>0.98</td>
<td>0.80–1.20</td>
<td>0.86</td>
</tr>
</tbody>
</table>

The first three columns report the logistic regression results using transferrin saturation as an independent variable. The last three columns are the same model but the high vs low transferrin saturation is included in the model instead of a continuous variable.

*Epi InfoTM; N = 124.*
In summary, we conclude that body iron levels are directly linked to presence of colon polyps and could aid in selecting subjects for colonoscopy.

Conflicts of interest

None.

Acknowledgements

We thank Bruce Boland, AVAHCS, for compiling lists of data and Crystal Tabor, Kyndness Garza, Amy Boyer and Jeremiah Bresnahan for editorial contributions.

References


