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.

© 2020 Elsevier Masson SAS. Tous droits réservés. - Document téléchargé le 16/05/2020 Il est interdit et illégal de diffuser ce document.
Méthodes. — Ce travail est une étude rétrospective des dossiers informatiques. Les patients ayant eu une coloscopie et un bilan martial entre mai 1996 et décembre 2003 ont été inclus dans l’étude. L’odds ratio ajusté, après analyse de régression multiple, a été utilisé pour mesurer l’association entre la saturation de la transferrine et la présence d’adénomes du côlon.

Résultats. — Des données complètes étaient disponibles pour 124 sujets. L’odds ratio ajusté, pour prédire la présence de polypes chez les patients avec une saturation de la transferrine au-dessus de la médiane, était de 10,9 (IC 4,0—29,5, p < 0,001). Une augmentation de 1 % de saturation de la transferrine a été associée à une augmentation de 1,07 de risque d’avoir un adénome (IC 1,03—1,11, p < 0,001).

Conclusions. — Le statut martial semble directement lié à la présence de polypes adénomateux coliques et pourraient aider à améliorer l’identification des sujets les plus à risque d’avoir un adénome ou un cancer coliques.

© 2008 Elsevier Masson SAS. All rights reserved.

Abbreviations
AVAHCS Amarillo Veterans Administration Health Care System
CD cellular differentiation antigen
CRP C-reactive protein
TTUHSC Texas Tech University Health Sciences Center

Introduction
Colorectal cancer is the third most common malignant neoplasm worldwide [1], and the second cause of cancer deaths in the United States [2]. It is estimated that there will be nearly 150,000 new cases and over 56,700 deaths due to colon cancer in the United States in 2004. The incidence per year ranges from 0.05% in Hispanic men and 0.07% in African American men to 0.03% in Hispanic women and 0.06% in African American women. About 6% of Americans develop the disease within their lifetime [3].

Even though most cases of colorectal cancer occur after 50 years of age [3], 15.5% of cases in male and 13.1% of cases in females are before 55 years of age [4]. Thus, we see that current screening colonoscopy guidelines, which permit screening colonoscopy after 50 years of age, would miss over 50% of colorectal cancers.

Conditions such as familial adenomatous polyposis and hereditary non-polyposis colorectal cancer (inherited as an autosomal dominant manner) predispose to colon cancer. However, these account for only 6% of cases. Other conditions like personal history of colorectal cancer or adenoma, first degree relative with colorectal cancer, first degree relative diagnosed with adenoma before 60 years of age [5], a personal history of ovarian, endometrial or breast cancer and a personal history of inflammatory bowel disease increases the risk of developing cancer [6,7]. However, these high-risk groups account for only 10% of colorectal cancers.

Survey results posted on August 16, 2004 on the National Cancer Institute web site showed lower-risk individuals getting colonoscopies too frequently and delayed diagnosis or screening for higher-risk individuals [9]. For patients with low risk of colon cancer, the cumulative chance of complication could offset the benefits in cancer reduction. In 2000, in the United States, only 39% of people 50 years and older had ever had a colorectal endoscopy.

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, angiodysplasia, 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 [percent-age] = 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 aerodigestive 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 1: Univariate analyses of transferrin saturation and other variables with presence or absence of adenoma.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall [N]</th>
<th>Adenoma [N=45 (36%)]</th>
<th>No Adenoma [N=79 (64%)]</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transferrin saturation</strong></td>
<td>21 (14)</td>
<td>28 (12)</td>
<td>16 (13)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Transferrin saturation above 50th percentile</strong></td>
<td>62 (50)</td>
<td>37 (82)</td>
<td>25 (32)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>62 (50)</td>
<td>8 (18)</td>
<td>54 (68)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>88 (71)</td>
<td>32 (71)</td>
<td>56 (71)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>36 (29)</td>
<td>13 (29)</td>
<td>23 (29)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other cancer</strong></td>
<td>26 (21)</td>
<td>12 (27)</td>
<td>14 (18)</td>
<td>0.24</td>
</tr>
<tr>
<td>Yes</td>
<td>98 (79)</td>
<td>33 (73)</td>
<td>65 (82)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cancer history</strong></td>
<td>25 (20)</td>
<td>12 (27)</td>
<td>13 (17)</td>
<td>0.17</td>
</tr>
<tr>
<td>Yes</td>
<td>99 (80)</td>
<td>33 (73)</td>
<td>66 (84)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age [mean (S.D.)]</strong></td>
<td>70 (10)</td>
<td>71 (10)</td>
<td>70 (11)</td>
<td>0.49</td>
</tr>
<tr>
<td><strong>Hemoglobin [mean (S.D.)]</strong></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.

* Epi Info™.

a 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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</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>Other cancer</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>Cancer history</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>Age</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>Hemoglobin</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 polypos 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, Kynthia Garza, Amy Boyer and Jeremiah Bresnahan for editorial contributions.

References
