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Serum iron and ferritin levels in patients with colorectal cancer in relation to the size, site, and disease stage of cancer

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Abstract: We investigated blood loss from colorectal cancer in 92 men seen between January 1990 and June 1997, in relation to the size and site of the tumor, Dukes stage, pathologic type of cancer, and serum carcinoembryonic antigen (CEA) positivity. We used indirect methods, measuring serum hemoglobin, iron, and ferritin concentrations. The means of these three concentrations were significantly lower in patients with a tumor >3 cm than in those with a tumor ≤3 cm in largest diameter. The means of the three values were lower in patients with proximal colon cancer than in those with distal colon cancer, but only the difference in serum hemoglobin concentration was significant. Cancers of the ulcerative type were found more often in the proximal colon. The proportion of patients with Dukes stage C or D was not different between those with proximal colon cancer and those with distal colon cancer. There was a positive correlation between tumor size and Dukes stage. There were no differences in serum hemoglobin, iron, and ferritin concentrations with respect to the pathologic type of cancer and CEA positivity. These findings show that blood loss from colorectal cancer is closely related to the size and site of the tumor.

Key words: colorectal cancer, serum iron, serum ferritin

Introduction

Hyperferritinemia has often been reported in association with cancers of the digestive organs, such as the liver and pancreas, and increased serum ferritin levels have been documented in gastrointestinal cancer without hepatic metastasis.[1] In colorectal cancer, serum ferritin levels have variously been reported as either increased or decreased.[1–3] However, most patients with advanced colorectal cancer are considered to be in a state of iron deficiency due to continuous bleeding, whether or not anemia is clinically evident.[4] A previous study showed that continuous bleeding from colorectal cancer depleted ferritin stores, lowering the serum ferritin level and resulting in iron deficiency, and therefore, decreased serum iron and ferritin levels were considered indicators of chronic gastrointestinal hemorrhage. It is thought that in advanced colorectal cancer, ferritin is not significant as a tumor marker, but, rather, it reflects a loss of storage iron.[5] In the present study, we investigated the degree of blood loss from colorectal cancer in relation to the size, site, Dukes stage, and pathologic type of cancer, and in relation to serum carcinoembryonic antigen (CEA) positivity. This was done indirectly, by measurements of serum hemoglobin, iron, and ferritin concentrations.

Methods

The study population consisted of 92 men with colorectal cancer seen between January 1990 and June 1997 (age, 41–85 years; mean, 63.7 ± 1.0 years). Women were excluded because they often have iron deficiency due to menstrual blood loss. The 92 patients were stratified into two groups for each parameter; based on (1) the size and (2) site of the tumor, (3) Dukes stage, (4) pathologic type of cancer and (5) serum CEA positivity. (1) According to the size of cancer; largest diameter ≤3 cm (n = 30) and >3 cm (n = 62); (2) according to the site of cancer; proximal colon (cecum, ascending colon, and transverse colon; n = 24) and distal colon (descending colon, sigmoid colon, and rectum; n = 68); (3) according to Dukes stage; A or B (n = 36), and C or D (n = 56); (4) according to the pathologic type of cancer; well differentiated adenocarcinoma (n = 68) and mod-

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erately and poorly differentiated adenocarcinoma (n = 24); (5) according to serum CEA positivity; positive (n = 44) and negative (n = 48). Serum hemoglobin, iron and ferritin concentrations were compared in each of the two groups. The proportion of patients with cancer of the ulcerative type was investigated according to the size and site of the tumor.

Serum iron level was measured by a direct method, using bathophenanthrorine (normal range, 35–180 μg/dl), and the serum ferritin level was measured by radioimmunoassay (RIA) (normal range, 26–240 ng/ml); serum CEA level was also determined by RIA (solid face method) (normal range, below 2.5 ng/ml).

None of the patients had undergone previous abdominal surgery or had taken drugs such as iron preparations or phosphates, that affected serum iron or ferritin levels. All were also confirmed to have no gastroduodenal lesions, inflammatory bowel disease, intestinal diverticulosis, or hemorrhoids by endoscopy, or hematologic diseases such as leukemia or malignant lymphoma, on the basis of clinical manifestations and blood examinations.

All cancers were resected surgically and the resected specimens were sent for histologic examination. The size of the tumor was measured with a ruler immediately after operation and before fixation. The histopathologic analysis of the cancers was obtained retrospectively from pathology reports, and reconfirmed by an experienced pathologist. The cancers were classified into pathologic types on the basis of the Morson classification,[6] adopted by the World Health Organization.

The values for results were expressed as means ± SEM. Overall significance was determined by one-way analysis of variance. The study groups were compared by Student's t-test. P values less than 0.05 (two-tailed) were considered to indicate statistical significance.

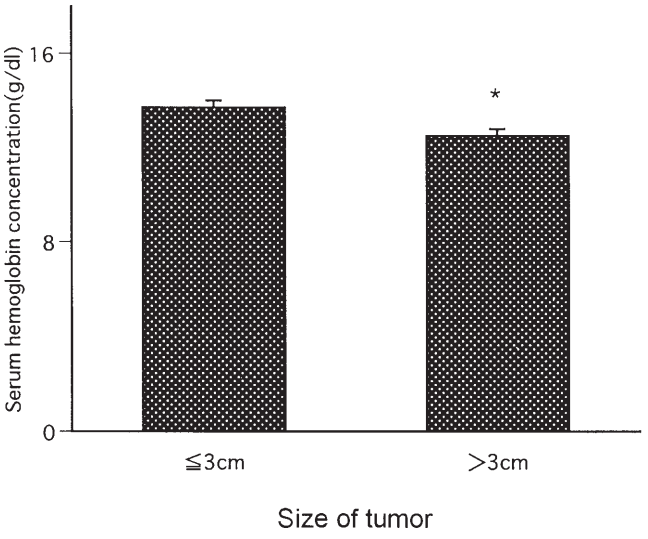

Fig. 1. Serum hemoglobin concentrations (means ± SEM) with respect to tumor diameter. *$P < 0.02$

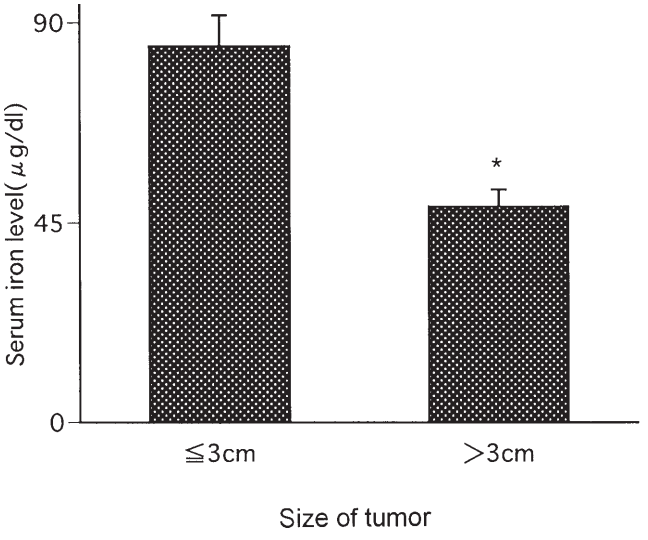

Fig. 2. Serum iron levels with respect to tumor diameter (means ± SEM). *$P < 0.0001$

Results

Eighty-nine of the 92 patients (97%) had a positive fecal occult blood test result (immunological method, using OC-Hemodia [Eiken, Tokyo, Japan]).

Size of tumor

In patients with cancer ≤3 cm and >3 cm largest diameter, the mean serum hemoglobin concentrations were 13.7 ± 0.3 and 12.5 ± 0.3 g/dl, respectively. This difference was significant (Fig. 1; $P < 0.02$). The mean serum iron levels were 84.8 ± 6.9 and 48.7 ± 3.9 μg/dl, respectively; also a significant difference (Fig. 2; $P < 0.0001$). The mean serum ferritin levels were 78.9 ± 14.7 and 43.8 ± 6.0 ng/ml, respectively. Once again, the difference between the two groups was significant (Fig. 3; $P < 0.05$). However, there was no significant difference between the two groups in the proportion of patients with cancer of the ulcerative type (data not shown). The mean ages of patients with cancer ≤3 cm and >3 cm were 66.1 ± 1.9 years and 62.6 ± 1.2 years, respectively (not significant; NS). In patients with cancers whose largest diameter was 2 cm or less, the mean serum iron levels were 87.9 ± 8.7 μg/dl compared with 53.4 ± 4.0 μg/dl in those with tumors of more than 2 cm. There was a significant difference between these two groups ($P < 0.001$). However, there were no significant differences in mean serum hemoglobin and ferritin levels between

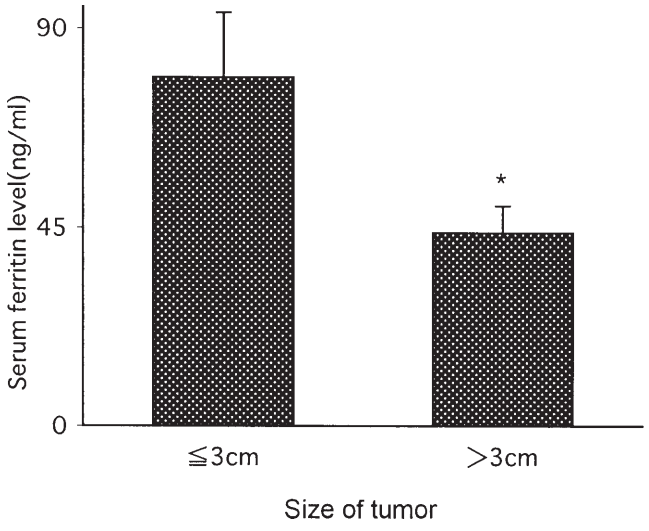

Fig. 3. Serum ferritin levels with respect to tumor diameter (means ± SEM). *$P < 0.05$

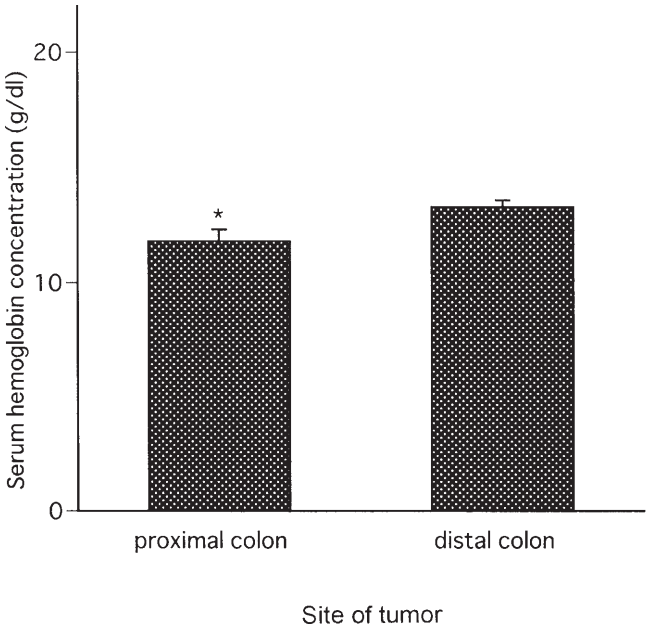

Fig. 4. Serum hemoglobin concentrations in patients with cancer in the proximal colon and those with cancer in the distal colon (means ± SEM). *$P < 0.01$

these two groups (data not shown). In patients with tumors 4 cm or less, there was a significant difference in mean serum hemoglobin, iron, and ferritin levels from these levels in patients whose tumors exceeded 4 cm in size (13.5 ± 0.3 and 12.3 ± 0.4 g/dl; $P < 0.02$; 74.0 ± 5.5 and 47.0 ± 4.8 μg/dl; $P < 0.0005$; 73.5 ± 10.7, and 37.0 ± 6.3 ng/ml; $P < 0.01$, respectively). There was no difference in mean serum hemoglobin, iron, and ferritin levels between patients with tumors 5 cm or less and those whose tumors exceeded 5 cm (data not shown).

Based on the above results, we considered that a tumor size of more than 3 cm is critical for decreasing serum hemoglobin, iron, and ferritin levels.

Site of cancer

The mean serum hemoglobin concentrations in patients with cancer in the proximal colon and distal colon, respectively, were 11.8 ± 0.5 and 13.3 ± 0.3 g/dl. This difference was significant (Fig. 4; $P < 0.01$). However, there were no significant differences in mean serum iron and ferritin levels between the two groups (data not shown). Cancer of ulcerative type was seen in 20 patients in the proximal colon (83%) and in 39 in the distal colon (57%); the difference between the two groups was significant ($P < 0.05$). The mean diameter of the tumor was 4.6 ± 0.4 cm in the proximal colon and 4.2 ± 0.2 cm in the distal colon; there was no significant difference in mean diameter of the tumor between the two sites (data not shown). Thirteen patients with cancers in the proximal colon and 43 patients with cancers in the distal colon were Dukes stage C or D (54% and 63% respectively); this difference was not statistically significant (data not shown).

Dukes stage

In patients with Dukes stage A or B, the mean serum iron levels were 71.8 ± 6.6 μg/dl and in patients with Dukes stage C or D, the mean serum iron levels were 53.2 ± 4.5 μg/dl. This difference was significant (Fig. 5; $P < 0.02$). However, there were no significant differences in mean serum hemoglobin and ferritin concentrations between the two groups (data not shown). The mean diameter of the tumor was 3.0 ± 0.3 cm in patients with Dukes stage A or B, and 5.2 ± 0.2 cm in patients with Dukes stage C or D. This difference between the two groups was significant (Fig. 6; $P < 0.0001$). There was a positive correlation between tumor size and Dukes stage.

Pathologic type of cancer

There were no significant differences in mean serum hemoglobin, iron, and ferritin concentrations between patients with well differentiated adenocarcinoma and those with moderately or poorly differentiated adenocarcinoma (data not shown).

CEA positivity

There were also no significant differences in mean serum hemoglobin, iron, and ferritin concentrations with respect to CEA positivity (data not shown).

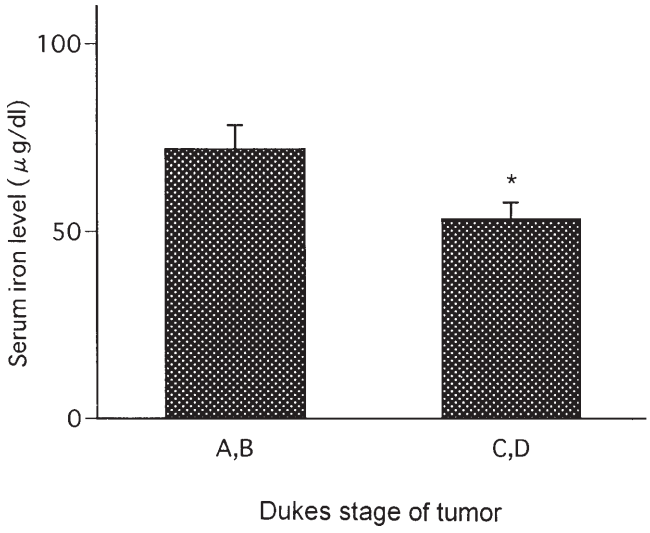

Fig. 5. Serum iron levels with respect to Dukes stage (means ± SEM). *$P < 0.02$

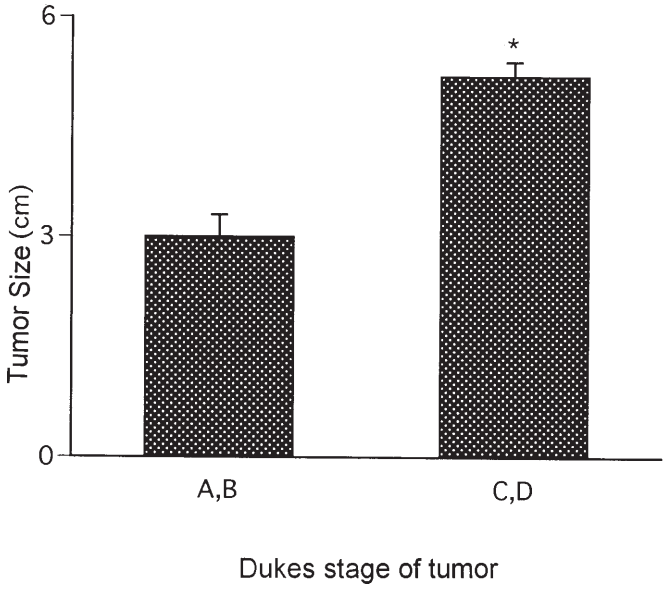

Fig. 6. Tumor size with respect to Dukes stage (means ± SEM). *$P < 0.0001$

Discussion

Occult blood in stool appears to be the most consistent feature associated with colorectal lesions, and positive fecal occult blood tests often lead to the early discovery of colorectal cancers. For this reason, fecal occult blood tests have been used as a method of screening for colorectal cancer.[7–9] Measurements of serum ferritin levels, which allow the detection of iron deficiency even before anemia develops, improve the detection rate of colonic malignancies and polyps when used in combination with stool occult blood testing.[10]

Hyperferritinemia is often observed in patients with liver and pancreatic cancers. A significant increase in serum ferritin level has also been reported in patients with gastric and colorectal cancer.[3] Campo et al.[11] demonstrated, in their immunohistochemical study, that colorectal cancer cells produced ferritin, and Vaughn et al.[12] indicated that the high ferritin content of colonic tumors could be directly responsible for the elevated serum levels of ferritin. However, hyperferritinemia has not often been observed in gastrointestinal cancers in the absence of hepatic metastasis.[1,3,13–15] Harju and Lindberg[2] noted that although low serum ferritin levels, indicating depleted iron stores, were common in patients with gastric or colorectal cancer (40%–50% of patients), the cause was unknown. Niitsu[16] also noted that it was characteristic that serum ferritin level did not increase in gastrointestinal cancer. Furthermore, mean serum iron and ferritin levels have been reported to be significantly lower in patients with advanced colorectal cancer than in controls.[4] In patients with advanced colorectal cancer, the decrease in serum ferritin levels could be caused by depleted ferritin stores, a result of continuous bleeding. Serum iron level would also decrease subsequently, resulting in iron deficiency anemia. Daily blood loss in the feces of control subjects has been reported to be less than 1 ml.[5,17–26] One ml of blood contains approximately 0.5 mg of iron; thus, a steady blood loss of as little as 3–4 ml/day (1.5–2 mg iron) could result in a negative iron balance over a period of time.[27]

In the present study, it appeared that colorectal cancers >3 cm bled more than those ≤3 cm in their largest diameter, as the mean serum hemoglobin, iron, and ferritin concentrations were significantly decreased in patients with the tumors >3 cm compared with concentrations in patients with tumors ≤3 cm. In regard to the relationship between the size of the tumor and blood loss from it, Yoshida and Aisawa[28] reported that the larger the tumor size, the greater the blood loss.

In regard to the site of cancer, blood loss appeared to be greater from tumors in the proximal colon than from those in the distal colon, as the mean serum hemoglobin concentration was significantly lower in patients with the proximal colon tumors. A similar trend was seen in mean serum iron and ferritin levels, although the differences were not significant. This was attributed to the higher proportion of cancer of the ulcerative type in proximal colon, due to the confounding effects of ileal juice and bile. Also, immunological tests for occult blood in stool show higher positivity rates in patients with cancer in the proximal colon than in those with cancer in the distal colon.[29,30] In the present study, all three of the patients who had negative fecal occult blood tests had cancer in the rectosigmoid region.

Winawer et al.[31] reported, in regard to cancers of the right side of the colon, that bleeding was more apt to be slow and the blood, mixed with bowel contents, was more likely to be occult. Patients with cancer in this region gradually become iron-deficient and anemic because of blood loss, and often present with weakness, dizziness, congestive heart failure, angina, or claudication.

In the present study, there was a positive correlation between tumor size and Dukes stage, suggesting that the severity of blood loss from the cancer was related to the Dukes stage. However, blood loss from this cancer was unrelated to the histology of cancer and to serum CEA positivity.

There are several limitations with regard to conclusions drawn on the basis of serum iron and ferritin levels. These two parameters are often increased in patients with liver diseases such as chronic viral hepatitis and cirrhosis (both of which are currently showing increasing incidence in Japan). Also, many women are iron-deficient and often have low serum iron and ferritin levels without anemia because of menstrual blood loss. Nevertheless, serum iron and ferritin levels may be regarded as important indicators of chronic gastrointestinal bleeding, as they can be measured quickly and routinely.[5]

It is concluded that blood loss from colorectal cancer is closely related to its size and site, although this blood loss was assessed indirectly by measurements of serum hemoglobin, iron, and ferritin concentrations.

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