Iron is required for proliferation of normal and neoplastic cells [13-17]. The relationship between iron and cancer risk appears to be more obvious in the colon due to its high concentrations of iron. It has been suggested that the protective effect of dietary fiber observed in human colorectal cancer may be due to iron chelation by phytic acid in dietary fiber [18,19]. The Haber-Weiss cycle that results in synthesis of hydroxyl radical and other oxidants has been demonstrated in vitro and in vivo, and for iron delivered parenterally or enterally [18]. Multiple epidemiologic studies have shown a positive correlation between iron and colorectal cancer, including examination of effects of genetics, dietary fiber, dietary iron, and total body iron stores [10,13,14,20,21].
several serum iron indices (serum ferritin, serum iron and transferring saturation) and colon cancer risk in a nested case-control study within the alpha-tocopherol, beta-carotene cancer prevention study cohort which included 130 colorectal cancer cases and based on a 276-item food frequency questionnaire [30]. Cross et al. [30] however, found the serum Unsaturated Iron Binding Capacity (UIBC) associated with an elevated risk for colon cancer.

In addition to association with colorectal cancer, studies have found that iron overload also has a positive relationship with the development of precancerous lesions. There is evidence showing that unabsorbed dietary iron increases free radical production in the colon to a level that could cause damage to the mucosa and crypt cell proliferation [31,32]. Results from animal studies showed that iron supplementation in rats led to cytotoxic events. These cytotoxic events include decreased manganese superoxide dismutase activity, increased lipid peroxidation and free radical generating capacity in the colon and cecum, and elevated colonic aberrant crypt foci [22,33-37]. Cytoplasmic staining for the iron storage protein ferritin was detected in both colonic adenoma and colorectal cancer, and expression of ferritin has been found to be positively associated with the degree of dysplasia and tumor size [38]. Examination of resected polyps and colorectal carcinomas showed an association of colonic adenoma progression to carcinoma with an increased expression of iron import proteins and a decreased expression of iron export proteins [39,40].

Controversial association between body iron load and colorectal carcinogenesis is listed in (Table 1).

### Mechanisms of Iron-mediated Carcinogenesis

In the colon, iron increases the production of Reactive Oxygen Species (ROS) from peroxidases via the Fenton reaction, which may cause cellular toxicity and pro-mutagenic lesions [41-43]. Lipids, DNA, and proteins are targeted by these ROS. Iron-overload was shown to induce oxidative DNA damage in the form of DNA breaks and oxidized bases in the human colon carcinoma cell line HT29 clone 19A when the tumor cells were incubated with ferric-nitrito triacetate (Fe-NTA) or with hemoglobin [42]. Hemoglobin was used as a source of physiological iron and was found to be as efficient in inducing DNA damage as Fe-NTA in a clear-cut concentration-effect relationship [42]. DNA damage incubated with Fe-NTA or with hemoglobin was two-six fold of the control [42]. Iron increased damage two-three fold over the control at concentration which have been reported to be physiologically available (200-500μM) [17,42]. It has also been demonstrated that cells localized near the stem cells of the colon crypt were more susceptible to oxidative stress than colon cells located on the luminal part of the crypt [44].

Recent studies also suggest that iron-mediated ROS may target specific genes in Fenton reaction-induced cancer. A Fe-NTA-induced rat Renal Cell Carcinoma (RCC) model showed increased numbers of oxidatively modified DNA bases including 8-oxoguanine and a major lipid peroxidation product, 4-hydroxy-2-nonenal [45-47]. Gpt delta transgenic mice showed deletion and single nucleotide substitutions at G:C sites to be preferred mutations in the kidney treated with Fe-NTA [45,48]. Microsatellite analysis in F1 hybrid rats revealed that p15 and p16 tumor suppressor genes were targeted and either homozygously deleted or methylated at the promoter region [49]. This led to the proposal of 'fragile' sites in the genome susceptible to oxidative stress [45]. Gene expression microarray and array-based comparative genome hybridization analyses identified target oncogenes in Fe-NTA-induced RCC. A tyrosine phosphatase, ptprr1, was found to be highly expressed in RCC and at the chromosomal region of amplification (4q22). This model showed that iron-mediated oxidative stress induced

<table>
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<th>Correlation</th>
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<tr>
<td>Elevated serum iron was associated with increased risk, strongest in the distal colon and significant in females. Mean transferrin saturation was higher in cases compared to controls (50.7 versus 28.7%), but TIBC did not predict the occurrence of colorectal cancer.</td>
<td>[10]</td>
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<td>Mean transferrin saturation and differences in TIBC and serum iron were higher in men who developed cancer than those who did not. When divided into 5 groups on the basis of baseline transferrin saturation, the combined risk of cancer occurrence associated with moderate elevations.</td>
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<td>Mean total iron-binding capacity was significantly lower and transferrin saturation was significantly higher than men who remained free of cancer. The risk of cancer in men in each quartile of transferrin-saturation level relative to the lowest quartile rose incrementally. Among women, a post hoc examination associated with very high transferrin saturation.</td>
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<td>Mortality in postmenopausal women was inversely related to TIBC; the relative risk for the highest tertile of TIBC, adjusted for age, smoking and alcohol intake was 0.05 (95% confidence interval (CI): 0.007-0.39). There was association between body iron stores and mortality due to cancer was observed in men.</td>
<td>[20]</td>
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<td>Excess risk of colorectal was found in subjects with transferrin saturation level exceeding 60%. The adjusted relative risk was 3.04 for colorectal cancer. High iron stores may increase the risk of colorectal cancer.</td>
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<td>Elevated relative risk was observed in hereditary hemochromatosis heterozygotes in males for colorectal cancer (RR, 1.28; CI, 1.07-1.53), colonic adenoma (RR, 1.29; CI, 1.08-1.53 for females and 1.24; CI, 1.05-1.46 for males), and stomach cancer in females (RR, 1.37; CI, 1.04-1.79).</td>
<td>[24]</td>
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<td>Individuals carrying the HFE Tyr282 allele (homo- and heterozygotes) in combination with homozygosity for the TFR Ser142 allele are at increased risk for neoplasia, including colorectal cancer. The odds ratio for three neoplasms (including CRC) increased for HFE Tyr homozygotes and compound heterozygotes in combination with TFR Ser homozygosity.</td>
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<td>There was a significantly increased risk of colorectal cancer associated with higher total iron intake [odds ratio (OR) = 2.50; 95% confidence interval (CI) suggesting a role of luminal exposure to excessive iron but does not support a role for increased body iron stores in CRC development.</td>
<td>[29]</td>
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<td>There were no associations between the risk of colorectal cancer and any serum iron indices except for serum ferritin, which showed a significant inverse association. This suggests a role of luminal exposure to excessive iron but does not support a role for increased body iron stores in CRC development.</td>
<td>[29]</td>
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<tr>
<td>There was an inverse association between serum ferritin, iron and transferrin and colorectal cancer risk and a suggestion of an inverse association between dietary iron and colorectal cancer risk. However, serum unsaturated iron binding capacity was positively associated with colon cancer risk.</td>
<td>[30]</td>
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<td>In men, transferrin saturation was inversely associated with risk of colon and rectal carcinoma. No cases observed with transferrin saturation. There was no evidence that the risk of epithelial cancer (all sites combined) is related to transferrin saturation level or to iron deficiency (5%) or overload (≥60%).</td>
<td>[26]</td>
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Table 1: Summary of association between body iron load and the development of colorectal cancer.
genomic amplification of ptprz1 which results in activation of β-catenin pathways during carcinogenesis [45,50].

It has also been proposed that iron can induce early signaling pathways that modulate activities of oxidative-responsive transcription factors such as activator protein 1 (AP-1) and nuclear factor kappa B (NFκB) [22]. AP-1 and NFκB binding sites are found in promoters of many genes such as interleukin-6 (IL-6). Activation of these transcription factors may lead to upregulation of cytokine genes, and over-expression of IL-6 caused by iron may lead to chronic inflammation and carcinogenesis [22,51].

Other possible mechanisms for iron carcinogenesis include effects of iron on the immune system. Tumoricidal activity of macrophages was markedly suppressed by phagocytosed erythrocytes, erythrocyte lysate, hemoglobin, iron salts or iron dextran [22,52]. The ratio of CD4 and CD8 positive lymphocytes were lowered by iron [53]. Studies in mice have also shown iron to reduce both macrophage and tumor cell-derived nitric oxide release, which promotes carcinogenesis [54].

Iron itself may facilitate cancer growth by serving as a nutrient. Iron is required for cell proliferation and is a constituent of proteins that catalyze key reactions including oxygen sensing, energy metabolism, respiration, and DNA synthesis [22,55]. Tumor cells express more transferrin receptors, resulting in higher cellular iron uptake for growth than normal cells [22].

Another interesting aspect of iron carcinogenesis is the synergistic effect iron may have with non-amidated gastrins in the development of CRC. Non-amidated gastrins include progastrin and Ggly. CRCs have been found to express progastrin in greater amounts than normal colon cells, and patients with CRC have increased circulating concentrations of Gamide and total gastrins [40,56,57]. It has also been recognized that ferric ions were essential for the biological activities of non-amidated gastrins with the proposal that gastrins catalyze the loading of transferrin with iron [40]. Although precise mechanisms underlying the involvement of gastrins in iron homeostasis are unknown, this synergistic effect of non-amidated gastrins and iron on CRC development is strongly suggested [40]. (Figure 1) summarizes the main mechanisms involved in iron-mediated carcinogenesis.

**Conclusion**

Many epidemiologic and experimental studies have shown a positive association between dietary and body iron stores with the development of colorectal cancer and precancerous lesions. However, the risk of iron intake for the development of CRC is controversial. There are a few studies showing no association between the risk of colorectal cancer and body iron levels or dietary iron uptake and that iron supplement or serum ferritin concentration is not linked to the recurrence of colorectal adenoma. Inverse associations between the risk of colorectal cancer and body iron levels or dietary iron uptake have also been reported.

The mechanisms of possible iron carcinogenesis are not unclear. Based on in vitro evidence, it is proposed that iron can induce early signaling pathways that modulate oxidative-responsive transcription factors, or that iron suppresses tumoricidal activity of macrophages and lowers the ratio of CD4 and CD8 positive lymphocytes. Emerging research shows that certain genomic sequences may be vulnerable to oxidative damage. This illustrates the complex interplay of genetic and metabolic alterations in chemical carcinogenesis.
References


