A Possible Link Between Iron Deficiency and Gastrointestinal Carcinogenesis

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There is definitive evidence that iron overload induces oxidative stress and DNA damage, which can enhance carcinogenic risk. However, other evidence suggests that iron deficiency and anemia also increase oxidative stress and DNA damage, which might increase carcinogenesis risk, especially in the gastrointestinal (GI) tract. The aim of this review is to provide essential background information for the accurate interpretation of future research on iron deficiency and increased GI cancer risk. Based on clinical, epidemiological, and experimental evidence, we discuss how iron deficiency might contribute to increased cancer risk through the impairment of several iron-dependent metabolic functions that are related to genome protection and maintenance (e.g., immune responses against cancer-initiated cells, metabolism of toxic compounds, and redox regulation of DNA biosynthesis and repair). Some epidemiological studies have indicated increased risk of GI tumors among individuals with low iron intake or low somatic iron stores, and in vivo data from rodent cancer models indicates the early progression of GI tumors during iron deficiency. Given the preliminary but consistent evidence relating iron deficiency to cancer risk and the fact that iron deficiency affects about one third of the world’s population, further studies are needed to define the extent to which iron deficiency might increase GI cancer risk.

Iron Overload and Carcinogenesis

The subcutaneous injection of Fe-nitriloacetic acid is a well-characterized renal murine cancer-induction system (1). Iron containing mixtures or compounds, such as furnace fumes (2), asbestos (3), magnetite (4), and iron salts induce oxidative stress as their main carcinogenic activity (5,6).

A meta-analysis has shown a weak but significant association between heme iron, the main source of iron in meat, and the risk of GI cancer (7), depending on the population studied. For example, although several studies have detected an increase in intestinal cancer using heme as a marker of iron intake [e.g., (8–10)], a recent cohort study of 49,654 Canadian women did not find any association between iron intake, heme iron, or iron from meat with risk of GI cancer (11). Heme iron is more bioavailable than inorganic iron (12) and is also genotoxic (13). It must be noted, however, that when eating meat, significant levels of saturated fat, preservatives, and/or cooking by-products are consumed along with heme iron (14), some of which have known carcinogenic potential (15). Indeed, it is difficult to estimate the independent contribution of each genotoxin in cooked meat to overall cancer risk.

Iron overload, as measured by high serum ferritin (SF) and/or transferrin saturation (TS), is associated strongly with a general increase in mortality and to a weaker and more controversial extent with increased cancer risk (16). Some reviews have shown that TS > 60% substantially increased the risk of GI cancer (17–19) synergistically with alcohol (11) and fat consumption (20,21). Conversely, one study of 35- to 60-yr-old subjects in a double-blind, placebo-controlled, primary prevention trial
evaluating the effect of antioxidants supplementation on chronic diseases in France, a country with low intake of iron supplements, showed no association between iron intake, somatic iron status, and GI cancer (22). Another case-control study of elderly Californian subjects undergoing endoscopy screening for intestinal polyps that measured iron consumption and somatic iron status showed that when subjects using iron supplements were excluded from analysis, higher iron intake was not linked to an increased incidence of polyps (23).

IRON DEFICIENCY AND BODY IRON STATUS
Iron deficiency (ID) is the most prevalent global micronutrient deficiency, particularly among poor children and women (24). Anemia, a hallmark of severe ID, affects about 50% of 5- to 14-yr-old children and pregnant women (25). It is well established that ID can irreversibly affect brain development (26), impair immunity (27), and lead to increased oxidative stress and decreased antioxidant defenses (28–30).

As reviewed by Trost et al. (31), ID can be viewed as a continuum: iron depletion, iron-deficient erythropoiesis (IDE), and iron deficient anemia (IDA). During iron depletion, functional and transport iron levels remain normal, but somatic iron stores are reduced, leaving little or no reserves available if the body requires more iron. During IDE, both storage and transport iron levels are low. Red blood cell production is diminished, resulting in insufficient iron for growth and homeostasis. Finally, during IDA, storage, transport, and functional iron are severely decreased, which can lead to impaired function in multiple organ systems (31). The current adult Dietary Reference Intake (DRI) for iron recommends 8 mg/day (males and post-menopausal women), 18 mg/day (fertile women), and 27 mg/day (pregnant women) as adequate intake to prevent IDA (12).

Transferrin (Tf) is the principal iron transporter in serum. Each Tf molecule can bind two molecules of iron and along with serum ferritin (SF), which can store up to 4,500 molecules of iron, contains the vast majority of serum iron (SI) (24). The serum of a typical healthy man contains approximately 30 µM Tf, of which about 28% (32) is saturated by iron (SI ≈ 18 µM) (33), 5.5 nM ferritin (34), and virtually zero (far less than 1 µM) nontransferrin bound iron (NTBI) (35). However, the best marker for somatic iron status is still controversial, particularly because it has been very difficult to unravel how iron metabolism works (36). Bone marrow sample staining is a highly accurate method for measuring iron, but this is impractical for population studies. SF correlates highly with bone marrow staining, but it can fluctuate widely during infections. SI and total iron binding capacity (TIBC), measured indirectly by the unsaturated binding capacity of serum, are used to calculate transferrining saturation (TS; TS = SI/TIBC) (37). ID is generally associated with reduced SI and increased transferrin levels, as evidenced by higher TIBC and lower TS levels in individuals with marked anemia (18,37). TIBC correlates inversely with total iron status in people with normal or depleted iron levels (38). Indeed, although these parameters are not as reliable as the gold standard of bone marrow staining, they are routinely used in evaluating iron status (18).

AIM, SCOPE, METHODS, AND STRUCTURE OF THE REVIEW
We will not discuss further the relationship between iron overload and carcinogenesis. Instead, our aim is to discuss the evidence that exists in the scientific literature that suggests a link between ID and GI cancer; this evidence has often been reported as inconsistencies between iron overload and cancer risk. For this review, primary studies were identified in Pubmed and the Web of Sciences using the following search terms: cancer, tumor, DNA damage, oxidative stress, iron, iron deficiency, anemia, transferrin, ferritin, gastrointestinal tract, mouth, esophagus, stomach, colon, rectum, and colorectum. Additional studies were identified by cross-referencing primary studies.

We will first discuss the clinical evidence linking upper GI tract carcinogenesis to ID. In the next section, we will discuss epidemiological studies linking stomach and colorectal cancer to ID. In the following section, we will present evidence from rat models of links between ID and carcinogenesis. Later, we will discuss how the impairment of several iron-dependent metabolic functions might be related mechanistically to genomic instability, a fundamental cause of cancer. Finally, we will weigh the evidence linking ID to increased GI cancer risk.

CLINICAL AND EPIDEMIOLOGICAL EVIDENCE LINKING ID TO UPPER GI CARCINOGENESIS: PATTERSON-KELLY SYNDROME
The role of ID as a carcinogenic condition was first suggested at the beginning of the 20th century in association with sideropenic dysphagia by Paterson (39) and Kelly (40). Sideropenic dysphagia was first described in the literature as early as 1893 and was later named Paterson-Kelly syndrome (PKS) and Plummer-Vinson syndrome (41). PKS is generally associated with nail defects, lip and tongue abnormalities, stomatitis, chronic gastritis, malabsorption, and esophageal webs (42,43). PKS was once common in Northern regions and endemic in some parts of rural Sweden (44) but became less prevalent due to improved nutrition; today, it is restricted to middle aged and elderly women and children (45,46). Although the link between ID, PKS, and cancer risk is controversial, the effective amelioration of PKS with iron treatment (47) and the higher incidence of cancer in PKS patients provide some evidence of a link between these conditions. However, given the rarity of the syndrome in regions with endemic ID, it is likely that other dietary or environmental factors are involved (48).

Anatomic studies in ID individuals and lab animals have shown fibrosis, epithelial atrophy, and epithelial hyperplasia in association with chronic inflammation, which are typical features of PKS (44,49), and submucous fibrosis—an oral precancerous condition common in iron deficient individuals (50).
Chronic inflammation is strongly associated with increased cancer risk in several organs such as the GI tract, liver, and lungs (51). In parallel with inflammation, decreased esophageal motility has been observed in anemic individuals (52), possibly due to impaired mitochondrial function and/or low neuronal nitric oxide synthetase activity (52). Accordingly, ID and impaired heme biosynthesis increase mitochondrial DNA damage and mitochondrial deterioration via a poorly understood mechanism (53,54). Mitochondrial impairment has been linked to cancer, aging, and most neurodegenerative diseases (55).

Although some authors have not detected carcinogenicity in PKS patients (56), others associate PKS with increased GI tract cancers (57,41). From an epidemiological point of view, an estimated 4–15% of individuals with PKS develop carcinomas of the upper alimentary system according to analysis of 4 follow-up studies of the association between PKS syndrome and carcinoma of the upper alimentary tract (58). Moreover, an analysis of Swedish Cancer Registry and Hospital statistical data (44) showed that nutritional improvement throughout the 20th century reduced the incidence of PKS and influenced the pattern of hypopharyngeal cancer, particularly among women in northern Sweden.

According to the case-control studies summarized in Table 1, there is also evidence that individuals with higher iron intake have lower risk for developing upper GI carcinomas (59) and oral precancerous lesions associated with smoking (60,61).

**EPIDEMIOLOGICAL STUDIES RELATING GI CANCER RISK IN THE STOMACH AND COLORECTUM TO ID**

According to two cohort studies, low body stores of iron, as measured by SF (62) or transferrin and ferritin combined (63), are associated with increased incidence of stomach cancer in Japanese and Japanese-descendant Hawaiians (Table 1). Associations were also observed between colorectal cancer and low TS (18) in California males in a cohort study and between this cancer and SF levels (64) in New York women in a case-control nested study. In another cohort study with Finnish subjects, it was shown that individuals with higher TIBC, that is, reduced body iron stores, were more likely to develop rectal cancers (17). Moreover, cohort studies of American men and postmenopausal women (65) showed that they had 5- or 31-fold higher risks of developing gastrointestinal cancer if they were ID or anemic two years before cancer diagnosis, respectively. In agreement with these data, other case-control studies of Harrison et al. (18) showed that higher iron intake is associated with lower incidence of intestinal adenocarcinoma (Table 1). Along the same lines, Broitman et al. (67) showed that ID individuals had an extremely high incidence (>90%) of preneoplastic stomach lesions unassociated with bleeding (25% with superficial gastritis, 50% with chronic atrophic gastritis and 20% with gastric atrophy with intestinal metaplasia) after histological analyses of 104 hypochromic, anemic Colombian patients presenting abdominal symptoms without cancer or peptic ulcers (as evaluated by gastroscopy).

One very interesting case-control study with elective endoscopy in 50- to 75-yr-old Californian subjects by Bird et al. (23) showed that low or high iron intake can increase the odds of colorectal polyps, generating a “U” shaped curve of risk vs. iron intake, although the risk for higher intake was reduced when individuals with supplementation were excluded from analysis. In another case-control study evaluating the anticarcinogenic potential of antioxidants in 50- to 69-yr-old male Finnish subjects, Cross et al. (68) showed that the risk of colorectal carcinoma decreased in a dose-dependent manner with increasing dietary iron intake. Figure 1 summarizes the odds ratio data from both studies according to iron intake. In general, one would expect a daily intake of about 20 mg/day of iron to minimize the risk to polyps and colorectal cancer. This value is higher than the current DRI of iron for older adults (8 mg/day) and lower than the upper level (UL) of 45 mg/day (12). It is lower than the 87 mg/day iron found in the Paleolithic diet, which also had much higher levels of antioxidants (69).

Low somatic iron stores also seem to be related to increased cancer risk in tissues other than the GI tract. For example, Ali et al. (70) showed that high serum levels of ferritin and nitrite, but not total SI, were associated with decreased renal cancer...
TABLE 1
Epidemiological evidence linking iron deficiency and increased gastrointestinal (GI) cancer risk<sup>a</sup>

<table>
<thead>
<tr>
<th>GI Region/Evidence</th>
<th>Study Characteristics and Population</th>
<th>Reference No.</th>
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<tbody>
<tr>
<td><strong>Upper dietary tract and esophagus</strong></td>
<td>Strong dose-response relationship between increased intake of iron and decreased risk of adenocarcinomas of the esophagus and gastric cardia (ACEGC); individuals with high dietary intakes of iron were less likely to develop cancer of the larynx and esophagus (OR = 0.5, CI 95% = 0.3–0.9)</td>
<td>Case-control study based on endoscopy diagnostic and data of a self-administered Health Habits and History Questionnaire responded to 1–2 yr preceding the exam in New York, conducted in 95 incident cases with the pathological diagnosis of ACEGC, 67 patients with adenocarcinomas of the distal stomach, and 132 cancer free controls (59,121)</td>
</tr>
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<td><strong>Stomach</strong></td>
<td>2.5-fold higher risk of precancerous oral lesions among women in the lower quartile of iron intake in relation to the 2nd and 3rd quartiles among smokers</td>
<td>Case control study in India with 226 cases of precancerous oral lesions and equal number of controls (all smokers) (61)</td>
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<td>Protective linear effect of iron intake against precancerous oral lesions among smokers</td>
<td>Case control study in India with 485 cases of precancerous oral lesions and 487 controls of 19 rural cities of India (all smokers) (60)</td>
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<td>Individuals with lower serum ferritin, but not transferrin, had threefold more stomach cancers than those in the higher quartile of ferritin level</td>
<td>Case control study in a cohort of 20,000 atomic bomb survivals from Hiroshima and Nagasaki, including 233 stomach cancer cases and matched controls whose serum was collected and frozen at least 5 yr before cancer diagnostics (62)</td>
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<td>Inverse association between stomach cancer incidence and serum ferritin or transferrin</td>
<td>Case-control study in Hawaiian men of Japanese origin, including 121 cases and 121 controls whose sera was collected about 20 yrs ago and thawed after diagnosis (63)</td>
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<td></td>
<td>Higher dietary intake of iron and other nutrients was associated with a lower incidence of gastric adenocarcinoma</td>
<td>Case-control study based in endoscopy diagnostic and data of a self-administered Health Habits and History Questionnaire responding 1–2 yr preceding the exam in New York, conducted in 134 cases and 131 controls (66)</td>
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Colorectum

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<tr>
<th>Statement</th>
<th>Study Details</th>
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<tr>
<td>Higher risk of rectal cancer among women with high TIBC (reduced iron stores)</td>
<td>Cohort study with 14-yr follow-up in 41,276 Finnish subjects</td>
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<tr>
<td>Negative association between TS and the risk of colon and rectal carcinoma in men</td>
<td>Cohort study with 20 yr follow-up in 2,150 Californians aged 20–84 yr</td>
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<td>Individuals consuming low (&lt;11.6 mg/day) or high (&gt;27.3/mg day) iron diets had higher risk of colorectal polyps in comparison to those consuming adequate amounts of iron, in a “U”-shaped curve trend</td>
<td>Case-control study with 965 California men and women aged 50–75 yr subjected to sigmoidoscopy evaluation</td>
</tr>
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<td>Significant inverse association between serum ferritin and the risk of colorectal cancer</td>
<td>Nested case-control study with average follow-up of 4.7 yr in 105 incident cases of colorectal cancer and 523 individually matched control women in New York City</td>
</tr>
<tr>
<td>The proportion of individuals diagnosed with GI malignancy was 31 and 5 times higher among men and postmenopausal women anemic and with iron deficiency, respectively</td>
<td>Cohort of 9,024 Americans with 2-yr follow-up</td>
</tr>
<tr>
<td>Increasing iron intake, serum ferritin, serum iron, and TS reduced the OR for colon but not for rectal cancer in a trend-like manner</td>
<td>Nested case-control study within the α-tocopherol, β-carotene cancer prevention (ATBC) study in male Finnish smokers aging 50–69 years including 130 colorectal cancer cases and 260 matched controls whose serum was collected and frozen at least 5 yr before diagnostics</td>
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*Abbreviations are as follows: OR, odds ratio; CI, confidence interval; PKS, Paterson-Kelly syndrome; TIBC, total iron binding capacity; TS, transferrin saturation.
risk, although this association was not statistically significant. Kuvibidila et al. (21) measured serum ferritin, SI, TIBC, and TS in serum samples from prostate cancer patients and controls and observed that prostate cancer patients had significantly lower mean concentrations of serum ferritin and TS than controls, suggesting that high somatic iron stores are less common in men with prostate cancer compared to those without this malignancy.

Abnormal iron levels also seem to affect the prognosis of GI cancer patients. Lorenzi et al. (71) evaluated the survival of 97 colorectal patients who underwent curative or palliative surgeries in a 5-yr follow-up study. They observed that patients with low or high serum ferritin levels had shorter survival periods than patients with normal levels. Likewise, Tseng et al. (72) studied the relationship between dietary iron and the recurrence of colorectal adenoma in 419 controls and 247 cases (at least one adenoma removed within 3 mo of enrollment) for 4 yr and found that dietary iron was inversely related to adenoma risk but was significantly related only for higher intake levels. The odds ratio was 0.32 for the higher intake group (median intake of 20.9 mg/day) in relation to the lower intake group (11 mg/day). Anemia as evaluated by hemoglobin levels is common in about 25–45% of colorectal cancer cases, which could be due to colorectal bleeding, a common manifestation in colorectal cancer. Anemia can impair colon cancer survival due to nutritional or immune deficiency (71), and the evaluation of body iron has been suggested as a screening method for GI cancer (73). Increased serum ferritin levels can also affect approximately 30% of colon cancer patients, since ferritin is often overexpressed in tumors. This condition might impair colon cancer survival prognosis due to the noxious effects associated with iron accumulation (71).

Two major confounding factors might interfere with defining the carcinogenic potential of ID in the GI. First, insufficient iron intake is likely to be associated with the lack of several other nutrients, or to a general undernourishment pattern, which might act synergistically in promoting cancer. Second, GI bleeding is linked to GI cancer and is sometimes a major cause of anemia. Notwithstanding, most studies report that GI bleeding is detected in only a small percentage of older anemic subjects (74).

**EXPERIMENTAL EVIDENCE USING RODENT CANCER MODELS RELATING ID TO INCREASED GI CANCER RISK**

Experimental evidence also supports that ID—due to blood loss (venisection), an iron depleted diet, or both—accelerates the emergence of oral/liver tumors (49,75) and increases the incidence of colonic/duodenal tumors (76) in rats exposed to model carcinogens (Table 2). Despite the fact that blood loss could induce physiological effects (such as lower oxygen tension) other than ID, these data support a potential role for ID in enhancing susceptibility to carcinogens. However, further animal studies could evaluate whether uninduced tumor incidence increases as a consequence of ID. Given the physiological differences between humans and rodents and evidence from epidemiological studies, population studies should be also carried out to evaluate the effect of ID in carcinogenesis.

**GENERAL PHYSIOLOGICAL EFFECTS OF ID RELATED TO INCREASED CARCINOGENESIS RISK**

Table 3 summarizes molecular and metabolic functions that are impaired by ID and evidence linking such impairment to genomic instability and cancer. Atamna et al. (53,77) have shown that heme deficiency and the consequent imbalance in iron-containing mitochondrial enzymes leads to DNA damage, oxidative stress, and mitochondrial decay, which are known to be important in cancer development.

**TABLE 2**

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Study Characteristics and Model</th>
<th>Reference No.</th>
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<tr>
<td>Iron deficient rats showed a change in the site of tumors from colon to liver and much earlier emergence of liver tumors (126 vs. 245 days) than iron replete rats</td>
<td>Assessment of tumors in liver, GI, kidney, lungs, and ear channels in Lewis male rats treated subcutaneously with dimethylhydrazine and fed normal or low iron diets</td>
<td>(49)</td>
</tr>
<tr>
<td>Similar incidence but earlier development (183 vs. 229 days) of oral squamous cell carcinomas in anemic rats in comparison to nonanemic rats; variation in tumor distribution, with iron deficiency being associated with lingual abnormalities</td>
<td>Assessment of oral tumors in Charles River rats fed a normal diet or a low iron diet and repeatedly venisectioned whose palate was painted with 4-Nitroquinilone-N-oxide</td>
<td>(75)</td>
</tr>
<tr>
<td>Significant higher overall incidence of proximal GI tumors (colonic and duodenal) in iron-deficient rats (66%) than in the control group (46%) as well as evidence of altered hepatic cells</td>
<td>Assessment of the incidence of GI tumors in Fischer 344 rats fed diets with different iron levels treated with dimethylhydrazine by gastric intubation</td>
<td>(76)</td>
</tr>
<tr>
<td>Molecule Impaired</td>
<td>Metabolic Function Impaired</td>
<td>Enzyme Impaired</td>
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<tr>
<td>-------------------</td>
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<tr>
<td>DNA</td>
<td>DNA synthesis</td>
<td>Ribonucleotide reductase</td>
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<tr>
<td></td>
<td>DNA repair</td>
<td>DNA glycosylase (BER system)</td>
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<td></td>
<td></td>
<td>MMR system</td>
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<tr>
<td>Cytochromes</td>
<td>Metabolization of xenobiotics</td>
<td>P450 family</td>
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<td></td>
<td>Oxidative metabolism</td>
<td>Mitochondrial complex IV</td>
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<td></td>
<td></td>
<td>Cytochrome C oxidase</td>
</tr>
<tr>
<td>Peroxidases</td>
<td>Trigger apoptosis</td>
<td>MPO</td>
</tr>
<tr>
<td></td>
<td>Kill pathogens</td>
<td>CAT</td>
</tr>
<tr>
<td></td>
<td>Neutralize ROI</td>
<td>CAT</td>
</tr>
<tr>
<td></td>
<td>Trigger apoptosis</td>
<td>NOS</td>
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*Abbreviations are as follows: BER, base excision repair; MMR, mismatch repair; MPO, myeloperoxidase; ROI, reactive oxygen species; CAT, catalase; NOS, nitric oxide synthase.*
hallmarks of aging. For example, iron is a key component in cytochrome C oxidase, and this enzyme, which plays a key role in oxidative metabolism, is an important intermediate in the apoptotic cascade (78). Indeed, it has been shown ID impairs apoptosis in blood cells (79,80).

ID has been shown to cause oxidative damage due to the abnormal assembly of mitochondrial electron transport chains (81). In the same vein, Walter et al. (54) showed that ID or excess impaired liver mitochondrial metabolism and increased mtDNA damage, and ID led to increased levels of oxidants in polymorphonuclear leukocytes. Providing further in vivo evidence that reduced iron impairs genomic stability, Aslan et al. (82) observed increased DNA damage and reduced antioxidant defenses in the leukocytes of anemic women. This evidence confirms the role of iron in DNA synthesis and repair and in other cellular functions related to genomic stability.

Iron is a functional component of ribonucleotide reductase (RR) (83), the enzyme that converts ribonucleotides to deoxyribonucleotides. Inhibitors of RR, such as hydroxyurea, have leukemogenic potential (84,85). Interestingly, there is evidence of higher leukemia risk in children whose mothers were anemic during pregnancy, and iron supplementation in association with folic acid during pregnancy substantially reduces leukemogenic risk (86–88). The role of iron as a poorly understood functional component of DNA repair glycosylases has also been described (89). DNA glycosylases are responsible for the excision of DNA lesions in the Base Excision Repair system (BER), which repairs a wide range of base lesions including 8-oxoguanine. Defects in BER have been described in several procarcinogenic conditions (90). Iron is also present in alkyltransferases (91) and seems to play a fundamental role in XPD family DNA helicases (92). Moreover, defects in the iron-containing DNA glycosylase MUTYH are directly associated with colorectal cancer (93). Additionally, iron chelators and hypoxia have been linked to the downregulation of some genes of the mismatch repair system (MMR). Defects in MMR enzymes have been linked to hereditary nonpolyposis colon carcinoma (94) and to sporadic colorectal cancer in some populations (95). Nevertheless, there are no studies to date that directly evaluate the effect of ID on DNA repair enzymes.

The impairment of antioxidant defenses and the increase of oxidized lipids or proteins or susceptibility to oxidative damage during oxidative stress is well known (28,96,97). Moreover, antioxidant depression can be extremely noxious in the GI tract, particularly because the GI tract is exposed to oxidants to a greater degree than other body tissues (98). Myeloperoxidases (MPO) are cytotoxic heme-containing enzymes secreted by phagocytes (99) that have multiple targets such as multicellular worms or parasites, bacteria, viruses, and host cells (51,100). There is increasing evidence that MPO deficiency increases the susceptibility of infection and malignant tumors. Since MPO deficiency can occur as a consequence of ID (101), there might be a link between ID-induced MPO impairment and genomic instability. Similarly, catalase (CAT), an enzyme required for the neutralization of hydrogen peroxide, contains 4 porphyrin heme groups. CAT activity seems to be related to body iron status as measured by hemoglobin content (102). Interestingly, CAT overexpression might be associated with the blockage of cell cycle progression or the induction of apoptosis in cells with damaged DNA (103). Recent studies have linked iron-containing enzymes to oxygen sensing, for example, in nitric oxide synthase (89). Indeed, iron is also a cofactor for nitric oxide synthase (NOS), and ID can suppresses ileal NOS activity (104). The blockage of nitric oxide production, which also occurs during iron overload, reduces the tumorocidal activity of macrophages that secrete nitric oxide to inhibit iron-containing enzymes, DNA synthesis, mitochondrial respiration, and citric acid cycle enzymes of microbes and tumor cells (105).

Finally, enzymes of the cytochrome P450 superfamily contain heme and are involved in the metabolism of most xenobiotic compounds. In rats, the concentration of cytochrome P450 is higher in the duodenum and in mature villous cells (43). In humans, P450 is expressed more highly in the intestine than in the others parts of the GI tract: Its expression is maximal in the upper region of the intestine, reduces from the duodenum to the jejunum, and reduces acutely toward the ileum. This intestinal region has a significant xenobiotic absorptive function. CYP metabolism might serve as a barrier to the systemic uptake of xenobiotics, including drugs, by facilitating excretion to the lumen of the intestine or by bioactivation of xenobiotics, with consequent binding to enterocyte macromolecules and removal with sloughed-off enterocytes (106). Iron deprivation substantially reduces P450 activity in the intestine (107). Rao and Jagadeesan (108) studied the effects of iron deprivation on xenobiotic metabolism in rats and observed a decrease of several phase I (activating) and phase II (conjugating) enzymes but no change in P450, depending on whether they studied the liver or extrahepatic tissues (kidney, lung, and GI tract).

WEIGHT OF EVIDENCE OF THE RELATIONSHIP BETWEEN ID AND INCREASED RISK OF GI CANCER

The summarized studies suggest a potential link between ID and increased GI cancer risk (Tables 1 and 2). Many of these studies have shown that iron has a dual effect, being carcinogenic either in overload or deficiency situations. In fact, a “U” shaped dose-response pattern named Bertrand’s rule is typical for most macronutrients and micronutrients (109,110). The data of Walter et al. (54), Bird et al. (23), and Cross et al. (68) (Fig. 1) support the potential “U” shaped curve for, respectively, DNA damage, preneoplastic lesions, and colorectal cancer according to iron intake. This trend agrees with the concept that only a defined physiological range for most nutrients favors health and genomic stability (111–114). According to the data in Fig. 1, a daily intake of around 20 mg/day of iron would reduce the risk of colorectal cancer. This amount is above the current DRI (8–24 mg for adults), below the UL (45 mg/day) (12), and much lower than the level of iron ingested in the Paleolithic diet (85 mg/day).
(69). Therefore, further studies focusing on iron intake levels are suggested.

Despite clinical evidence and animal studies supporting a relationship between ID and GI cancer risk, and although ID is by far the most prevalent micronutrient deficiency, there is a lack of well-controlled studies evaluating whether adequate iron intake can minimize cancer risk. For this reason, in this review, we sought to provide essential baseline information for the accurate interpretation of future research on ID and cancer risk. The evidence posed by the epidemiological studies we summarize (Table 1) can be classified as II-2-good according to the “Current methods of the U.S. Preventive Services Task Force” (115). In the “hierarchy of research design,” class II-2 is defined as “well-designed cohort or case-control analytic studies, preferably from more than one center or research group.” Regarding internal validity, evidence can be classified as good, since the studies show consistent results, are well designed, are conducted in representative populations, and evaluate health outcomes directly.

The summarized evidence can be also classified as Class 1 according to the “hierarchy of robustness,” as defined by the Joint Panel of the World Research Fund and the American Institute for Cancer Research (116); this hierarchy ranks human and animal experimental studies in evaluating the role of dietary and physical activity in the risk/prevention of human cancer. Class 1 refers to a) in vivo data from controlled human feeding studies, b) data from genetically modified models of human diseases, and c) in vivo studies using rodent cancer models designed to investigate modifiers of the cancer process (116).

There is no strong evidence of increased GI cancer incidence in iron-deficient populations, possibly because no systematic study has been performed, although some research has been carried out in India (60,61) and Colombia (67). The potential for reverse causality is a critical issue in evaluating the relationship between ID and GI cancer risk. For example, it is not known to what extent cancer-derived GI bleeding could lead to reduced body iron stores.

ID surely correlates with the deficiency of other nutrients. Diet and lifestyle have complex interactions in determining cancer risk, and there is evidence that malnourishment impairs immunity and DNA repair capacity (117,118). Vegetarians, who tend to have nutrient imbalances, do not display higher GI cancer incidence than omnivores (119). Whereas on one hand vegetarians and vegans tend to have lower body stores of iron, zinc, and vitamin B12 due to lower intake of animal products, on the other hand they have a generally healthier diet and lifestyle than nonvegetarians and a higher intake of cancer-protecting phytonutrients (119,120). The complex interplay between diet and lifestyle in cancer risk/prevention is still far from being elucidated. For iron, one problem lies in defining the best marker of body stores and another lies in considering the interplay of this nutrient with other micronutrients, genetic polymorphisms, and nutritional peculiarities in populations under evaluation (e.g., the extent of iron supplement consumption). The different nutritional demands of various organs further complicate the evaluation of the effects of ID.

We also summarized growing evidence that ID might hamper key physiological functions related to genomic maintenance, apoptosis, and immune response against malignant cells. This leads to the concept that ID cells might not be able to synthesize and repair DNA properly. Moreover, ID cells might be impaired in P450 function for metabolizing toxic compounds in phagocytosing malignant cells, in detoxifying reactive oxygen intermediates, in triggering apoptosis, and in responding properly to oxygen tension fluctuations (Table 3). These and other mechanisms regarding cancer risk and nutrient deficiency should be investigated. One possible avenue would be to evaluate the DNA repair capacity of ID cells/individuals.

Given the preliminary but consistent evidence relating ID to GI cancer risk and the fact that ID affects about one third of the world’s population, we suggest that the carcinogenic risk of ID and anemia should be further monitored in epidemiological studies specifically to evaluate this condition.

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