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Association of iron with colorectal cancer

E. D. Weinberg

Department of Biology and Program in Medical Sciences, Indiana University, Bloomington, IN, USA

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Many studies indicate that animals and humans burdened with excess iron are at increased risk of neoplasia at various sites. This review focuses on inquiries that involve iron and colorectal cancer. Relevant studies reported in the past decade are briefly described and evaluated. The studies in animal models and in relatively large groups of humans point to a positive association of excessive iron with colorectal oncogenesis. Phytic acid, a chelator of iron and zinc, may be useful in withholding iron from the carcinogenic process. Sufficient evidence is available to justify construction of long-term prospective studies in humans in which would be monitored (i) levels of iron and phytate intake, (ii) serum transferrin iron saturation and ferritin, (iii) fecal levels of iron and hydroxyl radicals, and (iv) appearance of colorectal polyps, adenomas and carcinomas.

Keywords: colorectal cancer, iron, phytic acid

Introduction

A recent editorial on diet and cancer suggested that "any attempt to isolate one single (dietary) factor in carcinogenesis may be futile" (Modan 1992). Nevertheless, the author urged that intervention studies be undertaken for promising leads. The present review summarizes evidence from animal models and humans of one such lead: the association of excessive iron with colorectal cancer. The evidence accumulated to date may be sufficient to justify initiation of an intervention study.

A review of the association of iron with neoplasia noted that "animals and humans burdened with excess iron appear to have a greater than normal risk of developing one or more primary neoplasms" (Weinberg 1981). Moreover, the sites of the tumors "tend to be associated with the site of deposition of the metal". Examples include the development of (i) sarcomas at sites of intramuscular injection of the metal (Weinberg 1992a), (ii) lung cancer and mesotheliomas in persons who inhaled iron either from industrial sources of the metal, asbestos varieties that contain iron and/or iron-loaded cigarette tobacco and paper (Weinberg 1993), and (iii) hepatocellular carcinoma in hemochromatotic, siderotic and/or alcoholic patients whose livers are burdened with excess iron (Kew 1990). A fourth example is the subject of this paper, i.e. the association of colorectal cancer with excessive iron either in the blood supply and/or in the lumen of the large intestine.

Address for correspondence: E. D. Weinberg, Department of Biology and Program in Medical Sciences, Indiana University, Bloomington, IN 47405, USA. Fax: (+1) 812 855 6705.

Carcinogenic mechanisms of iron

Iron can be carcinogenic in three ways. First, ferric ions are reduced by superoxide and the ferrous product is reoxidized by peroxide to regenerate ferric ions and to yield hydroxyl radicals (Cerutti 1985, Loeb *et al.* 1988, Babbs 1990, Sahu 1992). Such activated forms of oxygen as hydroxyl radicals can alter normal cells by initiating autoxidation chain processes, by addition of double bonds, by abstraction of hydrogen from allyl carbon atoms, and by oxidation of sulfhydryl, thioether and amino functions. Cellular consequences include enhanced radiosensitivity, mutation, sister chromatid exchange, chromosomal aberrations and oncogenesis.

Secondly, in addition to initiation of the cancer process, iron can promote the growth of transformed cells by inhibiting host defenses. Several research groups have reported that excessive iron inhibits activity of CD4 lymphocytes (de Sousa 1989, Djeka & Brock 1992). Moreover, the tumorcidal action of macrophages has been found to be markedly suppressed by phagocytosed erythrocytes, erythrocyte

lysate, hemoglobin, iron salts or iron dextran. In contrast, erythrocyte ghost membranes, latex spheres, myoglobin and dextran were inactive (Weinberg & Hibbs 1977). In a subsequent study, tumorcidal activity of macrophages was suppressed by iron dextran, carbonyl iron or iron-containing ferritin, but not by deferrated dextran, carbon particles or apoferritin (Green *et al*. 1988). As little as 1.3 pg iron per cell was inhibitory.

The third way in which iron is carcinogenic is that of serving as an essential nutrient for unrestricted tumor cell multiplication. Although normal and neoplastic cells have a similar qualitative requirement for iron, the continuous proliferation of the tumor cells necessitates an enhanced, and perhaps diversified, supply of the metal (Weinberg 1984, 1992a). Thus tumor cells are much more likely to express transferrin receptors, to produce their own transferrin or transferrin-like proteins and to obtain iron from non-transferrin sources than are normal cells. Moreover, even when hosts activate a powerful iron depletion defense mechanism that causes tumor cells to halt production of DNA, the non-proliferating cells often can survive by obtaining energy via iron-independent glycolysis (Weinberg 1992b).

The colonic environment: replete with iron

In the contest between host iron witholding defense mechanisms and the exceptional ability of tumor cells to acquire the metal, the colonic environment would appear to favor success of the neoplasm. Extraordinary quantities of unabsorbed iron reach the lumen of the colon especially in individuals who consume processed foods adulterated with inorganic iron and/or vitamin supplements containing the metal. Even persons who attempt to ingest only the US Recommended Daily Allowance of 15 mg of iron normally will absorb only 1 mg (or 1.5 mg if a menstruating female) per day. Besides the large quantity of unabsorbed dietary iron, smaller amounts accumulate daily in faeces from normal bood loss (0.4 mg) and from normal biliary excretion (0.18 mg). In iron overloaded persons, additional amounts would be available from the blood supply to the mucosa of the large intestine.

Babbs (1990) has estimated that feces can contain as much as 320 μM iron, which is at least 10-fold higher than in most tissues. He has noted that bile pigments in feces (as well as heme if bleeding is present) keep iron soluble at near neutral pH values and promote catalysis of hydroxyl radical formation. In patients with untreated ulcerative colitis or Crohn's disease, mucosal bleeding would augment the supply of iron (Babbs 1992). Patients with these conditions have, respectively, a 10- to 20-fold increased risk or a 4- to 7-fold increased risk of developing colorectal cancer as compared with the general population (Levin 1988).

The higher incidence of colorectal cancer in pre-menopausal women as compared with men of the same age may be a consequence of the difference in use of iron supplements (Nelson 1992). For example, in the US in 1986, approximately 23% of females in the 18–50 year age group used iron supplements; in males, the rate was only 16%.

Studies in animal models

In the initial study (Siegers *et al*. 1988), 19 male mice given 20 mg kg^{-1} dimethylhydrazine (DMH) s.c. weekly for 10 weeks developed a mean tumor rate of 2.4/mouse after 20 weeks. The tumors were localized exclusively in the distal segment of the colon. A set of 18 mice similarly treated with DMH but fed a diet adulterated with 3.5% iron fumarate developed a mean tumor rate of 13.2/mouse. The tumors were localized in the distal colon and rectum. The animals fed excess iron had a 6.5-fold increase in mucosal iron concentration in the proximal and distal segments of the colon.

Subsequently, in a different laboratory, rats were given 10 weekly injections of 20 mg/kg DMH (Nelson *et al*. 1989). On a basal diet of 35 mg kg^{-1} iron, the tumor incidence was 20%. On a diet of 580 mg kg^{-1} iron, the incidence rose to 63%. With a diet of 580 mg kg^{-1} iron plus 2500 mg kg^{-1} inositol hexaphosphate (phytic acid), a chelator of iron and zinc, the tumor incidence was lowered to 20%. Another group of rats, on basal iron diet, was given DMH and five parenteral injections of 15 mg kg^{-1} iron dextran. A control group was given DMH and injections of plain dextran. The animals given parenteral iron had a 1.86-fold increase in colon tumors as compared with the rats given plain dextran.

In a third laboratory (Ullah & Shamsuddin 1990), 29 rats were given six weekly i.m. injections of 8 mg kg^{-1} body weight azoxymethane (AOM). Seventeen developed cancers of the large intestine; the tumors had a mean volume of 2070 ± 840 mm^3. An experimental set of 20 rats, injected with AOM, were given 1% sodium phytate at pH 7.4 in drinking water. Only six of the latter set developed tumors in the large intestine; the mean volume was 268 ± 110 mm^3 ($P = 0.001$). Animals fed sodium

phytate had a slight reduction in serum iron and zinc, respectively, of 14 and 9.6%.

Studies in humans

In the initial study (Stevens *et al.* 1988), blood iron profiles and estimated dietary intake of iron were obtained for a group of 3355 US males. Four years later, the subjects were monitored for cancers. Selected results are contained in Tables 1 and 2. A significant association between colon cancer and iron intake, as well as between this cancer and transferrin iron saturation and serum iron was observed. However, the estimate of dietary iron intake was based on the subjects' single 24 h recall which may not be a good reflection of long-term dietary intake. Moreover, use of iron supplements apparently was not included in the estimates.

In a group of 5228 women in the same study, 149 developed cancer in 6 years. Those subjects who had a transferrin iron saturation $\geq 36.8\%$ (similar to the highest quartile in males) had a relative risk of 1.5 for development of neoplasms. However, specific cancer sites were not identified nor was a history of iron supplementation included.

Subsequently, an 8 year case-control study (Freudenheim *et al.* 1990) of diet and rectal cancer was conducted. Cases were matched with neighborhood controls for age and sex. Two hundred and seventy seven case control pairs of males and 145 case control pairs of females were interviewed regarding consumption of 129 foods. Unfortunately, information on use of iron supplements and blood iron profiles was not presented. The likelihood of rectal cancer increased with increasing intake of dietary iron in males (Table 3) but not in females.

The third study (Nelson *et al.* 1992) on the possible role of iron in human colorectal cancer risk involved 27 US military personnel with early cancers, 154 with benign adenomas and 169 tumor-free controls. Body iron burden was evaluated by means of the serum ferritin assay. A linear increase in risk of colonic neoplasia was associated with increasing concentration of serum ferritin. Results for patients with adenomas are summarized in Table 4. It should be noted that when synthesized to sequester toxic quantities of the metal, ferritin is a useful estimate of body iron status. However, production of the protein also is a component of iron withholding

Table 3. Odds ratios of rectal cancer in males for each quartile of dietary iron intake (n = 277 pairs)[a–c]

1 (low)	2	3	4 (high)
1.00	1.19 (0.72, 1.96)	1.32 (0.79, 2.20)	2.15 (1.29, 3.57)

[a]Derived from a portion of Table 4 of Freudenheim *et al.* (1990).
[b]Values in parentheses are 95% confidence intervals.
[c]P for trend < 0.01.

Table 1. Mean iron values according to the site of cancer[a]

Cancer site	No. of men	Transferrin iron saturation (%)	Serum iron (μM)	Dietary iron (mg day^{-1})
None	3113	30.7	19.0	14.1
Colon	12	38.6*	22.6*	19.2*
Rectum	10	33.7	21.2	12.6
All others	220	34.3	19.7	13.4

[a]Derived from a portion of the data in Table 1 of (Stevens *et al.* 1988). *$P < 0.05$ as compared with values in men without cancer.

Table 2. Relative risk estimates for quartiles of transferrin iron saturation[a,b]

Cancer site	No. of men	Transferrin iron saturation quartile (%)			
		≤ 22.8	22.9–29.1	29.1–36.7	≥ 36.8
Colon	12	1.00	1.76 (0.41, 20.4)	3.11 (0.27, 35.3)	4.69 (0.45, 48.7)
All types	232	1.00	1.01 (0.67, 1.52)	1.10 (0.74, 1.64)	1.37 (0.94, 2.01)

[a]Derived from a portion of the data in Table 4 of Stevens *et al.* (1988).
[b]Values in parentheses are 95% confidence intervals.

Table 4. Odds ratios of colonic adenomas for each quartile of serum ferritin ($n = 154$)[a]

1 (low)	2	3	4 (high)
1.00	1.43	2.31	3.43

[a]Data derived from Nelson *et al.* (1992).

defense against such inducers of inflammation as microbial and neoplastic cell invaders. Thus in future clinical studies, it would be desirable to include one or more additional measures of body iron.

In other human studies, attempts have been made to determine if dietary fiber might protect against colorectal neoplasia. In one inquiry (Giovannucci *et al.* 1992), 170 cases of adenomas of the left colon or rectum were documented in 7284 US males. All sources of dietary fiber (vegetables, fruits, grains) were associated with decreased risk of adenoma. The relative risk of adenoma in the highest quintile of fiber intake as compared with the lowest quintile was 0.36 (CI = 0.22–0.60) (P for trend < 0.0001). In a group of 56 women, decreased fiber intake raised the risk of occurrence of adenomatous polyps (Neugut *et al.* 1993). However, in the 130 men in this study, the protective effect of fiber was not observed.

In the study on rectal cancer cited above (Freudenheim *et al.* 1990), risk decreased with increasing intake of dietary fiber from vegetables but not from grains. Results of that study (Freudenheim *et al.* 1990) and the investigation on adenoma and fiber (Giovannucci *et al.* 1992) are discordant with the hypothesis of Graf and Eaton (1985) that the most important antineoplastic principle in fiber is phytic acid. The latter authors have noted that fruits and vegetables can have high fiber but low phytate. However, fibers low in phytate might still be anticarcinogenic by other mechanisms. For example, they could reduce fecal transit time, lower concentration of free bile acids and fecal mutagens, and serve as fermentation substrates with resulting decrease in colonic pH (Babbs 1990).

The iron withholding capability of phytate has been well documented in both animal models and in human studies. For example, the inhibitory effect of bran on iron absorption in humans was found to be due to its content of phytate rather than to its content of fiber (Brune *et al.* 1992). The antineoplastic action of phytate would necessitate not only a withholding of the metal from absorption but also retention of iron by the phytate chelate as the latter passed through the colorectal lumen.

Intestinal absorption of inorganic iron is increased by concurrent ingestion of ethanol (Weinberg 1990). The solvent may act by stimulating gastric acid secretion thereby maintaining ferric ions in solution until they reach the duodenum or by reducing the ability of enterocytes to withhold the metal from absorption. Moreover, inordinate consumption of ethanol is associated with the formation of desialyated transferrin which contributes to hepatic siderosis, an iron metabolism disorder (Mihas & Tavassoli 1991). Several studies have evaluated possible associations between ethanol ingestion and colorectal cancer. Unfortunately, the studies did not include an evaluation of body iron status or extent of cirrhosis.

In a group of 13074 retired persons, 100 men and 120 women developed colorectal cancer (Wu *et al.* 1987). Relative to non-daily drinkers, those who ingested 1 oz per day of ethanol had an increased risk of 1.1 (males) and 1.2 (females), whereas heavier drinkers of each sex had an increased risk of 1.5. In a different survey of 10572 persons, 203 developed colon and 66 rectal cancer (Klatsky *et al.* 1988). The increase in risk associated with 1, 2 or 3 drinks per day, respectively, for colon cancer was 1.16, 1.59, and 1.71; for rectal cancer, 1.42, 2.28, and 3.17.

In an inquiry (Cope *et al.* 1991) involving 66 patients (30 women) with colorectal adenomatous polyps and 86 controls (48 women), the relative risk was increased three-fold in persons who consumed 6–10 drinks per week. The relative risk for persons who both drank ethanol and smoked cigarettes was 12.7 (CI = 3.02–53.42). Inasmuch as approximately 1 μg of iron is inhaled in the mainstream smoke of each pack of cigarettes (Weinberg 1993), smokers as well as drinkers become overburdened with iron. In subsequent studies, body iron values should be determined for drinkers and/or smokers in both the patient and control groups.

In a 6 year study of 88751 women, the risk of colon cancer was increased 2.49-fold in subjects who consumed mammalian sources of meat daily as compared with those who ate these forms of meat less than once per month (Willett *et al.* 1990). Although mammalian meat is an important source of iron, the study contained no evaluation of iron status either in feces or in blood of the subjects.

Excessive iron is intimately involved in ischemic myocardial injury (Sullivan 1989). Accordingly, Sullivan (1982) has proposed that daily ingestion of aspirin may be preventing myocardial infarction by causing a reduction in body iron burden. In a recent study in adult males (Meyer *et al.* 1992), ingestion of

1.3 g aspirin per day increased fecal blood loss 8-fold over controls. This quantity of blood would contribute ~3.3 mg iron per day to the lumen of the large intestine. Thus it might be predicted that aspirin ingestion could increase the risk of colorectal cancer. However, in a 6 year study of 662 424 adults, the relative risk of death from colon cancer among men and women who ingested aspirin at least 16 times per month (as compared with non-use) was 0.6 and 0.4, respectively (Thu *et al.* 1991). The reduction in blood iron apparently is more important in protection against colorectal cancer than is any possible danger to the host of increased lumenal iron.

Future directions

Several recent studies in animal models and in moderately large groups of humans point to a positive association of excessive iron with colorectal oncogenesis. As a corollary, phytic acid (a chelator of iron and zinc) may be useful in withholding iron from the carcinogenic process. Sufficient evidence is available to support construction of long-term prospective studies in humans in which would be monitored (i) levels of iron intake from *all* sources, (ii) serum levels of transferrin iron saturation and ferritin at appropriate intervals, (iii) fecal levels of iron and hydroxyl radicals, and (iv) appearance of colorectal polyps, adenomas and carcinomas.

Variables to be tested would include ingestion of fibers with different amounts of phytic acid. Note, however, that administration of iron supplements to human subjects would be unethical. Indeed, Nelson (1992) has observed that "iron doping of healthy individuals to improve performance may well have dire health consequences not less severe than anabolic steroids. For now, iron supplements are best reserved for medical therapy of a specific illness, symptomatic iron deficiency anaemia".

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