Cancer Causes Control (2007) 18:1047–1053
DOI 10.1007/s10552-007-9058-9

ORIGINAL PAPER

Does excess iron play a role in breast carcinogenesis? an unresolved hypothesis

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Received: 5 April 2007 / Accepted: 20 August 2007 / Published online: 6 September 2007

Abstract Free iron is a pro-oxidant and can induce oxidative stress and DNA damage. The carcinogenicity of iron has been demonstrated in animal models, and epidemiologic studies have shown associations with several human cancers. However, a possible role of excess body iron stores or of elevated iron intake in breast carcinogenesis has received little attention epidemiologically. We propose that iron overload and the disruption of iron homeostasis with a resulting increase in free iron may contribute to the development of breast cancer, and we summarize the relevant evidence from mechanistic studies, animal experiments, and studies in humans. Over time a high intake of iron can lead to iron overload. Furthermore, body iron stores increase in women following menopause. Reactive oxygen species produced by normal aerobic cellular metabolism can lead to the release of free iron from ferritin. In the presence of superoxide radical and hydrogen peroxide, stored ferric iron (Fe^{3+}) is reduced to ferrous iron (Fe^{2+}), which catalyzes the formation of the hydroxyl radical (*OH). *OH in turn can promote lipid peroxidation, mutagenesis, DNA strand breaks, oncogene activation, and tumor suppressor inhibition, increasing the risk of breast cancer. In addition to its independent role as a proxidant, high levels of free iron may potentiate the effects of estradiol, ethanol, and ionizing radiation—three established risk factors for breast cancer. In order to identify the role of iron in breast carcinogenesis, improved biomarkers of body iron stores are needed, as are cohort studies which assess heme iron intake. Ultimately, it is important to determine whether iron levels in the breast and iron-induced pathology are higher in women who go on to develop breast cancer compared to women who do not.

Keywords Iron · Heme iron · Reactive oxygen species · Lipid peroxidation · Breast neoplasms

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Introduction

Iron, an essential micronutrient and the most abundant transition metal in the human body, plays an important role in a variety of physiological functions, including oxygen transport, electron transport, energy production, and DNA synthesis [1, 2]. However, as a transition metal, iron has loosely bound electrons in its outer shell and catalyzes the production of reactive oxygen species (ROS), resulting in increased oxidative stress, mutations, DNA single and double strand breaks, and oncogene activation [1, 3–7]. Oxidative stress is a disturbance in the balance between the production of ROS and antioxidant defenses, resulting in a relative excess of ROS [8, 9]. ROS, or free radicals, are compounds containing an unpaired electron, which is unstable and can react with DNA and other molecules within the cell. Current thinking posits that DNA damage caused by ROS is a critical factor in the carcinogenic process [9, 10]. The carcinogenicity of iron has been demonstrated in animal models [6, 11, 12], and elevated iron levels were associated with increased risk of several human cancers in some studies [13–17].

The possibility that iron plays a role in the development of breast cancer has received little attention epidemiologically, despite the fact that it has biological plausibility. We propose here that excess body iron stores and/or elevated dietary intake of iron may increase the likelihood that free

iron will be released from storage, inducing oxidative DNA damage and, thereby, contributing to increased risk of breast cancer.

Evidence for the hypothesis

Iron homeostasis

Due to its toxicity, sensitive mechanisms have developed to regulate free iron. Most iron is bound to proteins, is not bioavailable and, therefore, is unable to induce adverse health effects [6]. Individual cells must maintain an internal iron balance supplying adequate iron for physiologic functions but controlling free iron that could induce reactive oxygen species. All mammalian cells produce the iron-storage protein ferritin to sequester iron. The ferritin molecule has a cage-like structure which can fit up to 4,500 iron atoms in its core [18]. Another protein, transferrin, is responsible for transporting iron in the blood and delivering it to cells bearing transferrin receptors [18]. Iron homeostasis can be disturbed by a variety of factors, including ROS generated by infection and inflammation, alcohol, and possibly other factors [1, 3, 19, 20].

Iron as a pro-oxidant

The "free" or "catalytic" form of iron mediates the production of reactive oxygen species via the Fenton and Haber-Weiss reactions, thereby inducing oxidative stress [1, 6]. This process can be initiated when superoxide (O_2*–), a by-product of aerobic cell metabolism, but also produced in response to inflammation and infection, releases ferric iron (Fe^{3+}) from ferritin and hemosiderin in the cell. Fe^{3+} is reduced to ferrous iron (Fe^{2+}), which, in the presence of superoxide and hydrogen peroxide (H_2O_2), can catalyze the formation of the hydroxyl radical (*OH). The hydroxyl radical is an extremely powerful oxidizing species and can affect all classes of macromolecules, promoting lipid peroxidation, mutagenesis, DNA strand breaks, oncogene activation, and tumor suppressor gene inhibition [3, 5]. Free iron is essential in initiating and sustaining the chain reaction of lipid peroxidation [3, 7].

Reactive oxygen species and lipid peroxidation in breast cancer

A number of studies suggest that oxidative stress and lipid peroxidation may play a role in breast carcinogenesis, although the evidence is inconsistent. Elevated *OH-DNA adducts as well as single and double strand DNA breaks have been reported in women with invasive breast cancer [21–23]. In addition, malondialdehyde, the major end-product of peroxidative breakdown of polyunsaturated fatty acids, has been shown to be significantly increased in the blood of breast cancer patients compared to that of controls [24–27], as well as in the urine of women with mammographic dysplasia [28, 29]. Levels of malondialdehyde-DNA adducts have also been shown to be significantly higher in normal breast tissue from breast cancer patients compared to normal breast tissue from control women [30]. In a large, recent case–control study [31], levels of 15-F_{2t}-isoprostane, another marker of lipid peroxidation, were positively associated with risk of breast cancer, showing a significant dose-response relationship. However, levels of 8-oxodeoxyguanosine, the most abundant type of ROS-induced DNA damage, were not associated with breast cancer. In a comparison of lipid peroxidation products in cancerous and noncancerous breast tissue from 23 breast cancer cases, Punnonen et al. [32] found no evidence of increased lipid peroxidation products in cancerous tissue. Specifically, they found no difference in the level of diene conjugation, whereas levels of thiobarbituric-acid-reactive material in the cancerous tissue were slightly decreased as compared to noncancerous tissue.

Iron suppresses host defenses

Iron and its binding proteins play a role in immune regulation, and both iron deficiency and iron overload can have deleterious effects on host defenses [33, 34]. Iron overload has been shown to alter the distribution of T-lymphocyte subsets and to suppress the action of helper T (CD4) cells [34–36] and the tumoricidal action of macrophages and monocytes [34, 37]. In hereditary hemochromatosis patients, iron overload increases the numbers and activity of suppressor T (CD8) cells and decreases the numbers and activity of CD4 cells, resulting in increased CD8/CD4 ratios [34]. Thus, excess iron levels could impair immune surveillance for cancer cells [33].

Prevalence of iron overload

While iron deficiency has been a major concern in both developing and developed societies, recent perspectives suggest that iron overload may be more of a problem than iron deficiency in Western countries due to the fortification of cereals, the use of iron-containing supplements, and a high intake of red meat [1, 3, 5–7, 12, 38, 39]. Iron overload refers to an excess of total body iron, most of which is bound to the iron storage compounds ferritin and hemosiderin [39]. Studies in which blood ferritin levels were

measured in postmenopausal women indicate that approximately 10% of older women have elevated ferritin levels [39, 40].

Body iron levels accumulate with age

Mammals have no mechanism for eliminating excess iron. Rather, iron levels are reduced in a basically unregulated manner only through blood loss, pregnancy, and cell desquamation [41]. Control of body iron concentrations is achieved through regulation of the amount of iron absorbed through the gastrointestinal tract. Regulation of iron absorption is complex and is poorly understood [41]. In American men, iron stores increase with increasing age [39]. In women, iron levels are stable during the menstruating years, but following menopause they increase till about age 60 and reach a plateau [38, 40]. It has been suggested that the accumulation of iron with increasing age in conjunction with the age-related decline of endogenous antioxidant defenses, such as catalase, superoxide dismutase, and glutathione, plays a role in breast carcinogenesis [42]. A crucial question in regard to a possible etiologic role of iron in breast carcinogenesis is whether iron levels in breast tissue increase with age.

In animal experiments, iron enhances chemical carcinogenesis and growth of transplanted mammary tumors

In animal experiments, iron enhances chemically-induced mammary carcinogenesis. Excess iron intake has been shown to increase the incidence of carcinogen-induced mammary tumors in rats [43–45] and estrogen-induced kidney tumors in Syrian hamsters [12]. In a study in which iron-deficient and iron-replete rats were treated with DMBA, cumulative mammary tumor incidence was lowest in the iron-deficient rats [46]. Refeeding of iron-deficient rats attenuated the effects of iron deficiency [46]. Mammary tumors transplanted into DBA/2 mice fed on a low iron diet were significantly smaller compared to transplanted tumors in mice on a normal iron diet [47]. In another experiment, Fisher rats were transplanted with 13762NF mammary adenocarcinoma and divided into four groups: normal diet, normal diet plus treatment with deferoxamine mesylate (an iron chelator), low iron diet, and low iron diet plus deferoxamine mesylate (DEF) treatment [48]. Both a low iron diet and DEF treatment individually decreased the tumor yield, but the greatest inhibitory effect on tumor growth was seen in rats treated with DEF and fed a low iron diet.

Iron replaces zinc in zinc-finger proteins

Zinc may protect against carcinogenesis through its antioxidant activity and through other mechanisms [49]. The antioxidant activity of zinc may result from: its presence in copper-zinc superoxide dismutase, one of the prime lines of defense against ROS; its ability to prevent hydroxyl radical formation by competing for binding sites with pro-oxidant transition metals, such as iron and copper; and its role in regulating metallothionein, a potent hydroxyl radical scavenger [50–53]. Animal studies clearly demonstrate that zinc deficiency causes oxidative DNA damage, DNA strand breaks, and DNA fragmentation [51]. In addition to its antioxidant activity, zinc performs a critical role in the replication and transcription of DNA through zinc-finger proteins [49]. Many proteins involved in both base and nucleotide excision repair are zinc-finger or zinc-associated proteins, and zinc deficiency appears to adversely affect these processes [49, 51–53]. One of the mechanisms by which iron may contribute to carcinogenesis is by replacing zinc in zinc-finger proteins [50]. Specifically, when redox iron is substituted for zinc in zinc-finger proteins, it generates free radicals and causes DNA damage [50].

Iron is required for neoplastic growth and accumulates in malignant breast tissue

Cancer cells have a high iron requirement and a high level of transferrin receptors [5, 54]. Tissue ferritin levels have been shown to be six-fold higher in breast cancer tissue compared to normal or benign breast tissue [55, 56]. In addition, levels of transferrin and transferrin receptor proteins have been shown to be higher in breast cancer tissue compared to normal or benign tissue [57–59]. Marcus and Zinberg [59] reported that, compared to women without breast cancer, in whom levels of serum ferritin were normal, 41% of women with preoperative breast cancer had elevated serum ferritin levels. A recent study reported that iron levels in breast cancer biopsy tissue were 5 times higher than levels in breast tissue from women without breast cancer [60]. It is not clear from these studies, however, whether excess iron is present prior to the development of cancer or whether its presence is a by-product of carcinogenesis.

Iron may interact with estradiol, ethanol, and ionizing radiation in breast carcinogenesis

Excess iron may act synergistically with other agents which play a role in breast carcinogenesis. Current evidence suggests that the metabolism of estradiol to catechol

estrogen and to semi-quinones and quinones is a key step in breast carcinogenesis [61]. Iron may enhance estrogen-induced carcinogenesis via a number of steps which favor the production of mutations and DNA damage. For example, iron may replace zinc in the zinc finger-like structures of the DNA-binding domain of the estrogen receptor, and in the presence of hydrogen peroxide and ascorbate, the "iron finger" of this modified estrogen receptor can generate free radicals [12]. Furthermore, estrogen administration increases iron accumulation in hamsters and facilitates iron uptake by cells in culture [12]. At the same time, metabolic redox cycling of estrogen metabolites produces superoxide radicals, which in turn release iron from its storage in ferritin. In animal experiments, the incidence and number of kidney tumor nodules in hamsters treated with estradiol plus a diet enriched with iron were significantly increased (two- to four-fold) compared to those observed in animals fed an iron-poor diet plus estradiol [12].

Alcohol consumption, which is consistently associated with breast cancer risk in epidemiologic studies [62], may potentiate the effects of iron. Several studies have shown that blood ferritin levels and other markers of iron overload are increased in women consuming greater amounts of alcohol [38, 40, 63–65]. In addition, alcohol may act as a trigger releasing free iron from storage in ferritin [42].

Exposure to ionizing radiation particularly in adolescence increases the risk of breast cancer [66], and Stevens et al. [67] have proposed that elevated iron levels in the body may increase radiation sensitivity.

Figure 1 presents a schema showing how iron overload might increase the risk of breast cancer, either independently or in concert with ethanol, estradiol levels, and ionizing radiation. Possible interactions between iron and these agents require confirmation and elucidation.

Clinical and epidemiologic studies of iron and breast cancer risk

A small number of ecologic, cross-sectional, case–control, and cohort studies have examined the association of iron with breast cancer risk. With one exception, these studies have failed to show a positive association of excess body iron level or of iron intake with risk of breast cancer. An ecological study correlating nutritional survey data with mortality from different cancers in Germany found no association at the population level between dietary iron intake and mortality from breast cancer [68]. A second ecological study conducted in 65 mostly rural counties in China found no association between plasma levels of iron and breast cancer mortality [69]. A clinical study from Taiwan [25] found no difference in serum iron levels between breast cancer cases and controls. In a case–control study in southeast England [70], dietary iron intake was inversely associated with breast cancer risk (OR for extreme quartiles 0.49, 95% CI 0.23–1.01, p for trend = 0.03). In a case–control study from Germany [71], a relatively high iron intake showed a nonsignificant reduced risk (OR for extreme quartiles 0.66, 95% CI 0.37–1.27, p for trend 0.06).

Four cohort studies have addressed the association of iron in relation to breast cancer risk. Knekt et al. [16] assessed serum iron, total iron-binding capacity, and transferrin saturation levels in a cohort study in Finland. Positive associations were seen with cancers of the colorectum and lung but not with breast cancer (n = 192 cases) for subjects with transferrin saturation >60%. Garland et al. [72] examined the association of toenail levels of iron and several other trace elements in a cohort of 62,641 women who provided toenail clippings and were followed for 4 years. Among 433 cases of breast cancer and 459

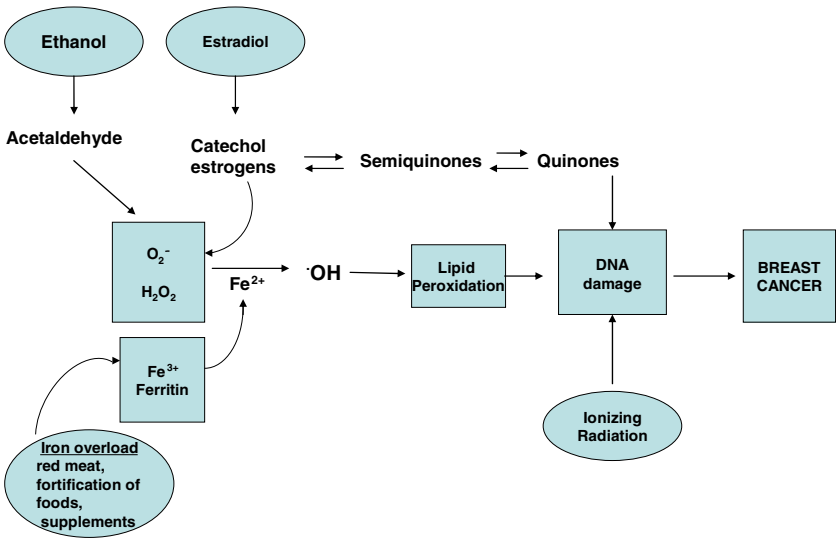

Fig. 1 How excess iron might increase the risk of breast cancer independently or synergistically with ethanol, estradiol, and ionizing radiation

matched controls, the odds ratio comparing the highest to the lowest quintile of toenail iron adjusted for established breast cancer risk factors, was 0.89 (95% CI 0.56–1.40). Using data from the Iowa Women's Health Study, Lee et al. [73] found no overall association of dietary intake of iron or heme iron with breast cancer, but reported an association of both iron and heme iron intake with breast cancer risk among women who consumed 20+ grams of alcohol per day. More recently, in an analysis of nearly 2,500 breast cancer cases ascertained during 16 years of follow-up of a cohort of 49,654 Canadian women, Kabat et al. [74] found no association of dietary intake of iron or heme iron with breast cancer and no evidence of effect modification by alcohol consumption or use of hormone replacement therapy.

A recent case–control study nested within a cohort of 9,315 women with benign breast disease reported that iron levels in breast tissue were significantly higher in women who subsequently developed breast cancer compared to breast tissue levels in controls. The positive association with breast cancer was observed among postmenopausal women (multivariate-adjusted odds ratio for highest versus lowest quintile: 2.77, 95% CI 1.25–6.13, p for trend 0.008) but not among premenopausal women [75].

Finally, two cohort studies, which followed hemochromatosis patients [76, 77] found a greatly increased risk of hepatocellular carcinoma but not of other cancers; however, the number of female hemochromatosis cases in both studies was small.

Recommendations for further research

In clinical and case–control studies, one cannot rule out an effect of disease on measurement of serum or breast tissue iron levels or on reported dietary intake. This is not an issue in cohort studies. To date, cohort studies have mostly used biomarkers including serum iron, serum ferritin, transferrin saturation level, total iron-binding capacity, and toenail iron levels, as well as dietary iron and supplemental iron intake computed from food-frequency questionnaires. However, these markers may be inadequate. Due to the fact that iron stored in iron proteins is tightly bound, serum iron (also known as transferrin iron), serum ferritin, transferrin saturation level, and total iron-binding capacity do not provide direct markers of bioavailable iron, which is responsible for the adverse effects of iron [6]. This may explain the inconsistent results of epidemiologic studies of the association of iron with various cancers [6]. Huang has emphasized the need for better biomarkers of iron overload for use in epidemiologic studies [6]. Although serum ferritin levels correlate well with total body iron stores, two individuals with the same ferritin level can have very different amounts of iron [6]. For this reason, Huang has proposed that the molar ratio of iron to ferritin may provide a better marker of cancer risk than ferritin alone [6]. Toenail iron levels are a potentially useful marker of body iron stores, but they need to be validated [78].

Heme iron, an organic form of iron, which represents two-thirds of total body iron, is more bioavailable than inorganic iron and may provide a more informative marker of potential iron toxicity [6]. Upon consumption, the heme proteins contained in cooked and processed meat are hydrolyzed to amino acids and peptides, and the heme groups are absorbed and transported by the blood to every organ and tissue [79]. To date, only two cohort studies have addressed the association of iron and heme iron intake with breast cancer risk [73, 74]. One of these was published in abstract form only [73]. Further studies addressing the association of heme iron intake may be relevant to breast cancer, in view of the finding in some, but not all, studies that red meat consumption is associated with increased risk of breast cancer [80–83]. Such studies should measure heme iron intake using validated food-frequency questionnaires, should assess intake of different types of meat and heme iron at multiple points during follow-up, and should include data on use of iron supplements.

With regard to both biomarkers of iron stores and markers of dietary intake, there is a need to elucidate the relationship of these markers to actual iron levels in breast tissue. It is equally important to determine whether iron levels in the breast are higher in women who go on to develop breast cancer compared to women who do not, as one recent study [75] has shown. Finally, the possibility that free iron simply adds to oxidative damage or interacts with established breast cancer risk factors, including estradiol, ethanol, and ionizing radiation, deserves further study.

Conclusions

A high intake of iron in developed societies may, over time, lead to a physiologic state of iron overload in postmenopausal women. Iron overload favors the production of reactive oxygen species, lipid peroxidation, and DNA damage, and may contribute to breast carcinogenesis independently or by potentiating the effects of estradiol, ethanol, and ionizing radiation. Epidemiologic studies incorporating validated biomarkers of body iron stores as well as intake of iron and heme iron are needed, as are studies elucidating whether elevations in breast tissue iron levels precede the development of cancer. If excess body iron levels or a high dietary iron intake are shown to contribute to the development of breast cancer, it might be feasible to reduce the risk of

the disease through restriction of iron intake or through the use of iron chelators.

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