# Cancer as a Ferrotoxic Disease: Are We Getting Hard Stainless Evidence?

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Iron is an essential mineral to all human tissues. Incorporated in the heme complex, it is necessary for the hemoglobin-borne transport of oxygen and generation of ATP in the electron transport chain. But iron may also have direct toxic effects, and iron uptake is consequentially tightly regulated in the human body (1). Recognizing the pro-oxidative properties of iron and its tendency to accumulate with age in properly nourished individuals, investigators have hypothesized that iron might be involved in the causation of many of the chronic diseases that are linked to a Western lifestyle (2–4), and believers have coined the term "ferrotoxic" disease (5). For example, sex differences in iron levels have been hypothesized to contribute to the differences between men and women in the risk of cardiovascular disease (6).

Iron has long been suggested to play a role in carcinogenesis (7), based on evidence from animal model studies (7,8) and on results—admittedly inconsistent—from observational studies in humans using various laboratory markers of iron status (4,9,10). Although there is little doubt that large excess levels of iron in hereditary hemochromatosis is a strong risk factor for liver cancer (11), the combined literature offers limited support for important associations with nonhepatic cancers (12,13). The outstanding question is whether lesser variation in iron levels may have any influence on the risk of hepatic and nonhepatic cancer in humans.

Several pathways for iron-induced carcinogenesis have been suggested. Iron-induced oxidative stress may cause lipid peroxidation and direct damage to DNA and proteins (7). Excess iron may also hamper some of the protective mechanisms that cells are believed to otherwise activate to limit the damaging effects of oxidative stress. Along these lines, iron has predominantly been considered an early-stage carcinogen. However, it has also been suggested that iron may influence carcinogenesis at later stages, perhaps as a nutrient and a facilitator of tumor growth (7,14).

In this issue of the Journal, Zacharski et al. (14) have taken the contentious issue about iron-induced carcinogenicity in humans to new heights by presenting the results from a randomized, single-blinded clinical trial of stored iron reduction through repeated phlebotomies. Observational studies in blood donors have yielded some (15–18) although not unreserved (18) support for an association of reduced cancer risk with blood letting, but the possibility of confounding from particularly active blood donors' presumably healthier lifestyle has precluded firm conclusions. A flawless randomized trial is the only way to eliminate such confounding. Therefore, the results of the study of Zacharski et al. (14) are of considerable interest. However, these results almost seem to be too good to be true: quite remarkably, the 636 patients who were randomly assigned to iron reduction, followed for an average of 4.5 years (range 2.5–6 years), were found to have a lower rate of visceral cancer occurrence (hazard ratio [HR] = 0.65, 95% confidence interval [CI] = 0.43 to 0.97; $P$ = .036) than the 641 patients in the control arm. Patients who developed cancer in the iron reduction group had higher mean ferritin levels across all follow-up visits than those in the same intervention arm who did not develop cancer, suggesting that the treatment advantage could have been even bigger if compliance had been better. Furthermore, the 38 iron-reduced patients who developed cancer during follow-up had lower risks of death from cancer (HR = 0.39, 95% CI = 0.21 to 0.72; $P$ = .003) and all-cause mortality (HR = 0.49, 95% CI = 0.29 to 0.83; $P$ = .009) in the fairly short period that passed between cancer diagnosis and end of follow-up than the 60 control patients who were also diagnosed with cancer.

Zacharski et al. (14) should be congratulated on their efforts. Their trial is both innovative and well executed; its only major limitation is that it was not designed to study cancer as the outcome and that the present report is based on an ad hoc analysis. This could have been a serious threat to the validity of the conclusions if the investigators had dredged data for many specific outcomes or combinations of outcomes. In this case, however, it seems as if the cancer analyses were second on the list after cardiovascular outcomes, and the authors commendably restricted themselves to only one aspect, namely incidence of total visceral cancer. It is not clear, however, what is meant by "visceral" cancer and why the authors chose this as the outcome and not total cancer.

Are the findings biologically plausible? Strikingly, cumulative risk curves for the intervention and control groups began to separate at 6 months, ie, after only one phlebotomy. In fact, almost all the effects observed in the present study between the phlebotomy arm and control arm regarding cumulative incidence were seen within the first 2 years of entry to the study. The authors speculate that late-stage effects of iron depletion on already established tumors might be prominent, but we remain skeptical. The observed risk difference is unexpected in terms of both timing and magnitude. Moreover, although a higher proportion of lung cancers in the control group may partly explain the observed marked advantage for iron-depleted vs nondepleted cancer patients as far as cancer-specific and all-cause mortality is concerned, there are

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few, if any, strong mechanistic explanations for such an advantage. Therefore, the possibility of bias must be seriously entertained.

Although follow-up data were recorded by a blinded observer, it is our understanding that participating patients were managed by physicians who could not be kept blinded to intervention or ferritin measurements. Hence, detection bias cannot be excluded. Serial measurements of hemoglobin, hematocrit, and ferritin could conceivably have signaled the presence of incipient cancers in the control group, whereas this signal may have been less interpretable in the intervention arm, leading to earlier diagnosis in the control group. The better survival among iron-depleted cancer patients is inconsistent with this speculation, though.

Another possibility to consider is inadequate randomization. The sophisticated allocation scheme is well described, but the description is not unequivocal with regard to concealment and unpredictability. It should be noted that this was a multicenter study and that close to half of the patients assessed for eligibility were excluded before randomization (19). Because the intervention was experimental and might have been perceived by some as adventurous (the mean blood volume required for removal to achieve ferritin reduction was calculated as 970 mL), it would not be surprising if some clinicians had considered withholding patients whose general condition was poor and/or consistent with impending serious disease—without necessarily being reflected in the investigated baseline characteristics accounted for previously—had they known that allocation to the iron depletion arm was coming up (19). The scenarios above are only examples of pitfalls even in well-conducted randomized trials, and we have no special reason for alleging that these biases have indeed affected the present study. However, the results are so unexpected that all possibilities for bias must be carefully examined. For the present, the results have to be interpreted with caution.

Some words of caution should perhaps also be expressed regarding the external validity of the findings. The study was conducted among almost exclusively elderly and predominantly white men with peripheral artery disease. The extent to which the results, if they prevail, may be extrapolated to other populations is therefore uncertain and warrants further study. The choice of a study population with an increased vulnerability may perhaps explain why Zacharski et al. (14) found such a pronounced association and may help explain the surprisingly short induction time, 6 months, before the cumulative incidence of the two study groups began to diverge.

Despite the abundance of iron in nature, iron deficiency remains a large public health threat, both in developing countries and also, to a lesser extent, in the Western world. Meanwhile, evidence supporting possible adverse effects of also moderately increased iron levels is accumulating. Zacharski et al. (14) have brought us some of the way, but we need more studies to clarify the role of iron in carcinogenesis and to concentrate on whether iron depletion may lower the incidence of cancer, slow tumor growth, or perhaps even both. Even if adequate iron therapy, intravenous or oral, should not be withheld where indicated, a cautious standpoint toward iron supplementation where no proper indication exists is perhaps advisable.

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