

However, Shaheen et al. (1) may have underestimated the strength of the association between colon cancer risk and HFE gene mutations because of the potential for delayed diagnosis of colon cancer among HFE gene mutation carriers who often have elevated levels of stored iron. Increased stored iron may delay the diagnostic sign of anemia because, for a given rate of microbleeding, a subject with more stored iron will require more time to exhaust iron stores and then compromise erythropoiesis. Because HFE gene mutation carriers tend to have elevated levels of stored iron, they might be less likely than age-matched control subjects without HFE gene mutations to be diagnosed with an existing colon cancer because they would require more time to develop anemia.

Healthy subjects without any stored iron, i.e., iron-depleted subjects, might not only be protected from the potentially prooxidant and carcinogenic effects of excessive iron, as suggested by Shaheen et al. (1), but would also be more likely to develop anemia early if they did develop a microbleeding colon cancer. Blood contains approximately 0.5 mg of iron per mL. Typical, middle-aged North American men have approximately 1000 mg of stored elemental iron. For a colonic lesion that sheds 2 mL of blood per day, 1000 days of bleeding would have to pass before iron deficiency anemia would appear. A period of 1000 days would often be enough for a cancer to progress to an inoperable stage. In an iron-depleted subject with essentially no stored iron, an excess iron loss of 1 mg per day would produce anemia in a matter of days to weeks rather than over months to years.

An effect of stored iron in delaying cancer diagnosis argues against the traditional view that stored iron is benign. Recommendations that iron depletion be avoided are not based on controlled clinical trials, but rather, on long-standing, customary practices. Stored iron is iron in excess of that needed to maximize hemoglobin levels. There is no good evidence that stored iron has any beneficial function except to prevent anemia from chronic blood loss. (Clearly, no amount of stored iron can prevent anemia in the event of sudden blood loss.) However, this "protective" effect of stored iron may also function to defer symptoms and delay diagnosis of colon

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### **Re: Association Between Hemochromatosis (HFE) Gene Mutation Carrier Status and the Risk of Colon Cancer**

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Shaheen et al. (1) recently reported that carriers of hemochromatosis (HFE) gene mutations have a statistically significantly increased risk of colon cancer. Taken together with other recent findings (2), these results suggest that heterozygosity for hemochromatosis confers increased risk of both colon cancer and cardiovascular disease in the approximately 15% of the U.S. population who are HFE gene mutation carriers.

cancer or other diseases associated with slow chronic bleeding. Given the emerging role of iron in cardiovascular diseases (2,3–5), carcinogenesis (1), diabetes (6), and infectious diseases (7), as well as its potential for delaying cancer diagnosis, the burden of proof should rest with those who believe that stored iron is safe. Shaheen et al. (1) state that limiting iron intake as a way to lower cancer risk is “highly speculative.” However, this idea is not unreasonable considering that the safety of stored iron has not been established in scientifically objective studies.

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## NOTES

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## RESPONSE

Dr. Sullivan points out an interesting and plausible source of bias in our study (1). Subjects with colon cancer often present with iron deficiency anemia. If subjects with an HFE gene mutation have higher iron stores on average than subjects without HFE gene mutations, subjects with HFE gene mutation would present with more advanced stages of

colon cancer because of the delayed onset of iron deficiency. If subjects with HFE gene mutations and very advanced cancers died before they could be included in our study, their differential loss would skew our results. As Dr. Sullivan notes, this bias, if it existed, might have caused us to underestimate the strength of the association between colon cancer and HFE gene mutations.

We, too, were concerned that subjects with HFE mutations who developed cancer might present with more advanced or inoperable stages of disease. Because our study included both those with operable and inoperable cancers, this was a testable hypothesis. We compared the tumor stages at diagnosis (classified as *in situ*, local, regional, or distant) of subjects who had an HFE mutation with those who did not. We found no statistically significant differences in tumor stage at diagnosis, based on HFE gene mutation status. We also asked whether those with HFE gene mutations had different symptoms at presentation than those without such mutations. Again, no statistically significant differences were noted.

Given these results, it is unlikely that we substantially underestimated the association between HFE gene mutations and colon cancer because of this potential bias. Moreover, we minimized the time between diagnosis and enrollment into the study by use of the rapid ascertainment system of the North Carolina Cancer Registry: study subjects were identified at a median of 34 days after their diagnosis. Thus, even in subjects presenting with very advanced disease, this period of time seems unlikely to allow for loss of a substantial number of participants due to death from cancer.

Although we agree with Dr. Sullivan that limiting iron intake to lower cancer risk may not be unreasonable conceptually, it may not be prudent to limit dietary iron intake until studies demonstrate that such measures are effective. Dietary changes to avoid intake of iron, if done in an unsupervised way, could promote less healthy eating in general, which might increase the individual's risk of other conditions, such as heart disease. However, as more data emerge regarding the effects of iron stores on the risk of disease, long-standing practices, such as the fortification of foods with iron and the routine addition of iron to multivitamins, should be revisited. It

is likely that the “right” amount of iron will differ from individual to individual, and our current “one-size-fits-all” approach will need tailoring to fit our developing understanding of the role of iron in disease.

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## NOTE

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