Iron Status and Risk of Cancers in the SU.VI.MAX Cohort[1]

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ABSTRACT The aim of the present study was to evaluate the relation between iron status and cancer in a population of middle-aged adults living in France where iron supplementation and iron-fortified foods are rarely used. The SU.VI.MAX study is a randomized, double-blind, placebo-controlled primary prevention trial evaluating the effect of antioxidant supplementation on chronic diseases in women aged 35–60 and men aged 45–60 y. At baseline, concentrations of hemoglobin, serum transferrin and serum ferritin were measured in 10,197 subjects. Data on dietary intake were estimated from six 24-h dietary records completed during the first 2 study years and available for 5287 subjects. All cancer cases that occurred during the 7.5-y follow-up were validated. In men, baseline serum transferrin and serum ferritin concentrations did not differ between subjects with cancers ($n = 467$) and those without. In women, serum ferritin was higher ($P < 0.0001$) and serum transferrin tended to be lower ($P < 0.08$) in cancer cases. Iron status was not related to cancer risk in men, but women with serum ferritin concentrations > 160 μg/L had an increased risk of cancer (odds ratio = 1.88, 95% CI: 1.05,3.35). No relation was found between dietary iron intake and risk of all cancer sites combined for either men or women. Our results suggest that iron status is not a predictor of cancer risk in men, whereas a serum ferritin concentration > 160 μg/L may be associated with an increase in cancer risk in women. J. Nutr. 135: 2664–2668, 2005.

KEY WORDS: • *iron* • *serum ferritin* • *transferrin* • *iron intake* • *cancer* • *prospective study*

It was suggested that the prooxidant properties of iron may have potential deleterious effects (1). Data from experimental studies indicate that high iron stores may induce oxidative stress because of the ability of iron to catalyze the Haber-Weiss and Fenton-type reactions that produce the hydroxyl radical and hydrogen peroxide (2). These species react with all biomolecules and are considered to be very toxic, causing structural damage to macromolecules (e.g., proteins and lipids) and breakage of DNA strands (3). Generation of these reactive oxygen species may deplete antioxidants (4). This disturbance in the equilibrium between prooxidants and antioxidants may contribute to the development of diseases such as cancer (5).

Epidemiologic studies evaluating the relation between iron status and cancer risk have yielded conflicting results to date (1). Some studies showed that body iron stores (assessed by biomarkers) and dietary iron intake were positively associated with subsequent risk of cancer; however, other studies could not confirm this. This discrepancy between the results of epidemiologic studies may be due to the large variability in measurement methods used to assess and define iron status and, to some extent, to the different end points used in these studies; most studies included colon cancer as an end point, although other studies suggested that cancer at other sites may be of greater interest. Finally, studies on iron status and cancer have been conducted mainly in North America or Northern European countries, where iron supplements and iron-fortified foods are widely used.

Therefore, we conducted a prospective study to evaluate the relation between iron status and the risk of cancer in a middle-aged adult population in France where iron supplementation and iron-fortified foods are rarely used.

MATERIALS AND METHODS

Study population. Subjects were part of the SU.VI.MAX study, a double-blind, placebo-controlled, primary prevention trial evaluating the effect of antioxidant supplementation on chronic diseases. Details concerning study rationale, design, methods, and participant characteristics were reported elsewhere (6,7). In brief, 12,741 French adults (7713 women aged 35–60, 5028 men aged 45–60) recruited in 1994 by a multimedia campaign, were randomly allocated to receive

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either a combination of antioxidants [120 mg vitamin C, 30 mg vitamin E, 6 mg β-carotene, 100 μg selenium (as selenium-enriched yeast), and 20 mg zinc (as gluconate)] or a matching placebo, in a single daily capsule. Participants did not have known diseases likely to threaten 5-y survival.

The current analyses included 10,197 subjects (3223 men and 6974 women) for whom serum ferritin measurements at baseline were available and who did not have known inflammatory diseases likely to affect the ferritin level. The protocol was approved by the medical ethics committee of Paris-Cochin (n°706) and the national committee for the protection of privacy and civil liberties.

Cancer ascertainment. Participants were followed prospectively for 7.5 y. They were asked to complete a monthly questionnaire, summarizing treatment compliance and health events, via Minitel (a phone-based French terminal), the internet, or mail. If there was no contact with the participant for a long period, or if the participant failed to appear at the yearly visit, an investigation was launched to determine the reasons. If necessary, an inquiry was made among neighbors and/or the participant's physician. Whatever the sources of information, once a cancer was suspected, all relevant records, including results of diagnostic tests and procedures, were collected from the physicians and hospitals involved or directly from participants. An independent expert committee validated cancers [ICD codes C00-C97, D00-D09 (8)] using pathology reports.

Assessment of iron status. Baseline venous blood samples were obtained using Becton Dickinson mineral-free vacuum tubes from participants who had been fasting for 12 h. Hemoglobin was measured immediately (cyanmethemoglobin method) and blood was kept at 4°C in the dark until centrifugation (300 × *g*, 15 min) and preparation of the aliquots. Aliquots were frozen in polypropylene tubes and transported to the coordination Centre in Paris for storage at −80°C. Serum ferritin and transferrin concentrations were measured using automatic immunoprecipitation on a nephelometer BN II Dade/Behring (precision intra-assay was 2.7% for serum transferrin, and 3.6% for serum ferritin; precision interassay was 2.3 and 3.4%, respectively). The laboratory quality assurance included analysis of serum from standard pools with each run and the use of international standards (markers ProBioQual).

Assessment of dietary intake. Baseline dietary intake was estimated in a subsample of 5287 subjects who completed a 24-h dietary records repeated 6 times during the first 2 study years. They were given a small terminal, specifically developed for the study, loaded with ad hoc software, which enabled subjects to fill out computerized questionnaires off line and to transmit data during a brief telephone connection via the Minitel Telematic Network, which connected them to the main SU.VI.MAX computer server. The Minitel is a small terminal widely used in France as an adjunct to the telephone. At the end of the study, some participants transmitted the data by the Internet instead of Minitel. Subjects were guided by the software's interactive facilities and by an instruction manual for the codification of foods, including photographs for estimations of portion size. Foods were presented in 3 sizes; including intermediate and extreme positions, this yielded 7 choices for estimating the quantity consumed. Photos of the portion sizes were previously validated on 780 subjects in a pilot study (9). Data are also collected on cooking methods, seasonings, types of food (e.g., fresh, frozen, canned), place, and time of dietary intake.

The nutrient intake was estimated using a computerized version of the French food composition table (10) complemented by data based on the McCance and Widdowson's food composition table (11). The mean of the 6 dietary records was calculated to estimate habitual intake.

Baseline height and weight were measured with subjects in underwear and BMI was calculated by dividing weight by the square of height (kg/m^2).

Statistical methods. Because the distributions of serum transferrin and serum ferritin were skewed, median and ranges are presented, whereas means ± SD are presented for the other variables. Follow-up time for each subject was calculated from the date of randomization until the date of cancer diagnosis, the date of death, or September 1, 2002 (end of the follow-up period).

Baseline variables between subjects with cancer and those without were compared using Student's *t* test and χ^2 test where appropriate. Cox proportional-hazards models were used to calculate the relative risk (RR) and its 95% CI. For these analyses, serum ferritin concentrations were categorized according to the following definitions based on data relating ferritin concentration to iron absorption (12): depleted and low status = ferritin ≤30 μg/L; nonreplete and borderline normal status = 31–70 μg/L; replete and adequate status = 71–160 μg/L; and replete and elevated status > 160 μg/L. Subjects were divided in 2 groups according to reference values for serum transferrin concentrations: ≤2 g/L and >2 g/L. Analyses were adjusted for age, smoking, BMI, antioxidant supplementation or placebo groups, and in women also for menopausal status. Statistical analysis were all performed separately for men and women using SAS software version 8.2 (SAS Institute).

RESULTS

Median serum ferritin concentrations were 143.8 μg/L (range: 3–1210) and 36.6 μg/L (range: 3–1000) and median serum transferrin concentrations were 2.47 and 2.51 g/L, in men and women, respectively. For serum ferritin, 18.4% of women and 1.9% of men had concentrations ≤ 15 μg/L, corresponding to totally depleted iron stores, whereas 4.4% of the women and 47.8% of the men had serum ferritin concentrations > 160 μg/L. For serum transferrin, 10.5% of the women and 10.1% of the men had concentrations < 2 g/L. Median follow-up time was 7.54 y during which 467 cancer cases occurred (319 in women, 148 in men).

Subjects who developed a cancer were older and more often smokers (**Table 1**). Men with cancer had a higher BMI than those without cancer. In the subsample in which dietary intake was measured, subjects with and without cancer did not differ for energy, fat, iron intake, or nutrients known to affect iron absorption (fibers, vitamin C, alcohol, calcium, tannins).

In men, hemoglobin, serum transferrin and serum ferritin did not differ between subjects with and without cancer (**Table 2**). In women with cancer, serum transferrin was lower and serum ferritin was higher than in women without cancer and the percentage of women with serum ferritin levels < 30 μg/L (depleted and low) was lower in women with cancer.

No relation between iron status and cancer risk was observed in men (**Table 3**). In women, however, the highest concentration of serum ferritin (>160 μg/L) was associated with an increased cancer risk after multiple adjustments. Serum transferrin was not related to the risk of cancer in either men or women. Analysis of the sample after elimination of subjects in whom cancer was diagnosed in y 1 of the follow-up gave similar results (data not shown).

Colon cancer occurred in 36 subjects, 155 women developed breast cancer, and 43 men prostate cancer. When analyses were performed according to cancer site, there was no relation between serum ferritin or serum transferrin and risk of cancer (data not shown).

No significant relation was found between dietary iron intake and risk of all cancer sites combined in either sex (adjusted for age, smoking, BMI, group of antioxidant supplementation or placebo groups, energy, calcium, vitamin C, fiber, and alcohol intake and menopausal status in women)

DISCUSSION

The data of the present study do not support a role of iron status in the risk of cancer in men but show a potentially deleterious effect of a high iron status in women.

The relation between iron and the risk of cancers is a controversial issue. Although it is hypothesized that iron has a potentially deleterious effect through its prooxidant capacity,

TABLE 1

General characteristics of the study population according to sex and disease status[1]

	Women			Men		
	With cancer	Without cancer	*P* for difference	With cancer	Without cancer	*P* for difference
n	319	6655		148	3075	
Age, *y*	49.1 ± 6.6	46.9 ± 6.5	0.0001	54.2 ± 4.9	51.7 ± 4.7	0.0001
Smoking, %						
Nonsmokers	51.1	55.0	0.001	25.7	34.3	0.07
Former smokers	25.4	29.2		61.1	52.0	
Current smokers	23.5	15.8		13.2	13.7	
BMI, kg/m^2	23.5 ± 3.7	23.4 ± 4.0	0.87	26.3 ± 3.70	25.50 ± 3.20	0.009
Dietary intake						
n	168	3334		87	1698	
Energy, *kJ/d*	7954 ± 1751	7849 ± 1766	0.48	10488 ± 2462	10598 ± 2286	0.66
Total fat, *g/d*	82.3 ± 21.9	81.5 ± 22.9	0.66	105.9 ± 29.3	103.7 ± 25.8	0.45
Fiber, *g/d*	18.2 ± 5.3	18.4 ± 5.7	0.74	22.4 ± 7.6	22.4 ± 7.2	0.98
Alcohol, *g/d*	13.3 ± 12.6	10.9 ± 13.0	0.02	29.7 ± 21.8	29.8 ± 24.4	0.97
Iron, *mg/d*	11.2 ± 2.7	11.0 ± 3.0	0.51	15.3 ± 4.1	15.3 ± 3.9	0.84
Vitamin C, *mg/d*	99.0 ± 45.2	98.1 ± 43.2	0.79	106.7 ± 55.1	101.6 ± 47.5	0.33
Calcium, *mg/d*	883.0 ± 303.0	919.7 ± 310.4	0.13	1018.1 ± 266.4	1040.8 ± 328.5	0.53

[1] Values are means ± SD or %.

epidemiologic studies have so far produced inconsistent results (1). Most of the earlier large prospective studies using biological markers of iron status described a higher risk of total cancer and/or specific locations (colon, rectum, lung) in subjects with high transferrin saturation, serum iron or hemoglobin concentrations (13–17), but some studies found no relation (18,19) or even (in the case of stomach cancer) an inverse association (16).

More recent studies used serum ferritin as a reliable indicator of iron status, because it is now generally accepted that serum ferritin concentrations reflect the amount of body iron stores (20). Two case-control studies found a significantly increased risk of adenomas (intermediate markers of colorectal cancer) in subjects with higher serum ferritin concentrations (21,22). However, one of these studies (21) may have been flawed due to the mode of recruitment of participants: the controls were subjects undergoing colonoscopy because of occult blood in the stools, which could have caused a lower serum ferritin, whereas the patients with adenomas did not have this symptom. The other study showed a positive association only when the second quartile of plasma ferritin was used as a reference group (22). In a third case-control study among subjects who had had at least 1 adenoma removed ≤3 mo before serum ferritin measurement, there was a modest but not significantly increased risk of adenoma recurrence in those with serum ferritin concentrations > 70 μg/L compared with those with lower serum ferritin (23). The effect seemed more pronounced in women than in men. In examining the relation between serum ferritin and proven cancers, one study found that elevated serum ferritin concentrations were significantly associated with a higher risk for primary hepatocellular carcinoma (24); moreover, that elevated risk was confined to the first 3 y of follow-up. For colorectal cancer, Scholefield et al. (25), using samples of serum collected from patients recruited for a screening study on colorectal cancer, did not find significant differences in serum ferritin concentrations between

TABLE 2

Markers of iron status according to sex and disease status[1]

	Women			Men		
	With cancer	Without cancer	*P* for difference	With cancer	Without cancer	*P* for difference
n	319	6655		148	3075	
Hemoglobin, *g/L*	135 ± 10	135 ± 11	0.44	150 ± 10	150 ± 10	0.68
Serum-transferrin, *g/L*	2.46 (1.5–4.9)	2.53 (0.5–5.2)	0.08	2.51 (1.5–4.7)	2.47 (0.8–5.0)	0.25
Serum transferrin, %						
≤2 g/L	13.8	10.3	0.05	10.8	10.0	0.76
>2 g/L	86.2	89.7	89.2	90.0		
Serum ferritin, *μg/L*	44.8 (5.1–345)	36.3 (3.0–1000)	0.002	152.4 (5.1–969)	143.4 (3.0–1210)	0.39
Serum ferritin, %						
≤30 μg/L	28.2	37.8	0.0008	4.1	4.4	0.66
>30–70 μg/L	39.8	36.4		9.5	11.4	
>70–160 μg/L	24.5	21.6		33.8	36.7	
>160 μg/L	7.5	4.3		52.7	47.6	

[1] Values are means ± SD, medians (range), or %.

TABLE 3

Relative risk (RR) for cancer according to serum ferritin and serum transferrin concentrations[1]

	Women			Men		
	n Cancer/no cancer	Crude RR	Adjusted RR[2]	*n* Cancer/no cancer	Crude RR	Adjusted RR[2]
Serum ferritin						
<30 μg/L	90/2514	1	1	6/134	1	1
>30–70 μg/L	127/2419	1.48 (1.13–1.93)	1.39 (0.99–1.94)	14/349	0.92 (0.35–2.39)	0.94 (0.33–2.63)
>70–160 μg/L	78/1437	1.53 (1.13–2.08)	1.11 (0.74–1.67)	50/1129	1.03 (0.44–2.39)	0.91 (0.36–2.31)
>160 μg/L	24/285	2.34 (1.49–3.67)	1.88 (1.05–3.35)	78/1463	1.26 (0.55–2.88)	1.06 (0.42–2.67)
P for trend		0.0006	0.07		0.57	0.89
Serum transferrin						
<2 g/L	44/730	1	1	16/308	1	1
>2 g/L	275/5968	0.71 (0.52–0.98)	1.05 (0.67–1.63)	132/2766	0.94 (0.56–1.37)	0.95 (0.52–1.72)

[1] Values are RR (95% CI) or *n*.
[2] Adjusted for age, smoking, and group of supplementation (and menopausal status for women).

patients with proven colorectal cancer and those without colon disease. Conversely, several studies (nested case-control or cross-sectional), found a significant inverse association between serum ferritin and colorectal cancer (19), prostate cancer (26), stomach cancer (27,28) and (not significant) renal cancer (29). For stomach cancer, one explanation may be that low iron stores are an early sign of occult cancer. Our large prospective study is thus in line with most of the studies in not finding an association, although we observed an increased risk in women with high serum ferritin concentrations only.

It is important to note that due to limited numbers, it was not possible to evaluate specific cancer sites in our study, except for breast and prostate cancers; even then, the numbers may have been too low. On the other hand, a strength of our study is that all cancers included were validated by an independent expert committee and we excluded cancer at baseline as well as the presence of inflammatory disease, which can raise the concentration of serum ferritin without reflecting the level of iron stores. Furthermore, adjustments were made for possible confounding factors. Finally, it is important to mention that the study took place in a country in which few products are iron-fortified and among subjects not taking iron supplements.

The association between iron intake and colorectal cancer or risk of adenomas has also been inconsistent. Although some studies found no or an inverse association (23,30–35), others found a positive association (13,14,19,36,37). Moreover, Bird et al. (22) found a weak U-shaped association with the risk of colorectal polyps (lowest and highest quintiles were associated with increased risk). Recently, Lee et al. (38) found in a large sample of women followed for 15 y that the dietary intake of heme iron was associated with an increased risk of proximal cancer of the colon, especially in alcohol consumers, although a subsequent prospective study carried out by Michaud et al. (39) did not find any association between dietary iron intake and bladder cancer risk. Our results are thus in line with that study.

In conclusion, although iron is involved in in vitro free radical generation, published epidemiologic data on the relation between iron and cancer are inconsistent. After adjustment for confounding factors, our data do not support a major role of iron status or intake in the risk of cancer in men but suggest a potential deleterious effect of high iron status in women. Further studies are warranted to improve our understanding of this difference between genders. It could be related to different types of cancers and/or differences in the nature of thresholds of serum ferritin levels in men and women.

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