Association Between Serum Iron Biomarkers and Breast Cancer

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ABSTRACT

Background: Iron is both essential to life and potentially toxic at higher levels. Epidemiologic studies of iron and breast cancer are sparse, with substantial heterogeneity found in a recent meta-analysis. Evidence based on a comprehensive set of iron biomarkers and a large sample size could help clarify relationships between iron body stores and breast cancer risk.

Methods: A case–cohort sample of 6,008 women, including 3,011 incident cases, has been followed for a median of 7.9 years. We estimated breast cancer HRs with Cox models, including age as the primary time scale and including in turn iron, ferritin, percent transferrin saturation, and their first principal component (PC) both as categorical (quartiles) and continuous measures.

Results: Adjusted HRs for the highest versus lowest quartiles of iron, ferritin, and transferrin saturation (95% confidence interval) were 1.06 (0.90–1.25), 1.03 (0.87–1.23), and 0.94 (0.80–1.12), respectively, and 1.06 (0.90–1.25) for the first principal component (PC). Associations were similar when follow-up time was restricted to ≤4 or >2 years. *Post hoc* analyses suggested low iron stores were associated with reduced breast cancer risk, in both pre- and postmenopause and the obese.

Conclusions: A study with one of the largest sample sizes to date and with all three measures of circulating iron, ferritin, and transferrin saturation does not support a strong association between elevated iron stores and breast cancer risk. Further investigation of low iron may be warranted.

Impact: These results do not support a strong association between iron overload and breast cancer incidence.

Introduction

Iron is essential to life, but potentially carcinogenic at high levels, through mechanisms related to tumor initiation and growth (1). In epidemiologic studies, evidence for an association between cancer and iron status has been mixed, with different biomarkers examined in different populations across varying durations of time. A recent meta-analysis of breast cancer incidence found substantial heterogeneity in associations with higher levels of circulating iron (2). Our aim was to comprehensively assess three common iron biomarkers separately and jointly in relation to breast cancer incidence using data from a large cohort of women.

Materials and Methods

Sample

The Sister Study (3) recruited a cohort of 50,884 women (2003–2009), each of whom had at least one sister who was diagnosed with breast cancer. Participants provided written informed consent and the study was overseen by the Institutional Review Board of the NIH (Bethesda, MD). This analysis uses a case–cohort sample of 6,008 women, including 2,808 incident cases and a randomly selected subcohort of 3,200 women (of whom 222 developed breast cancer during follow-up), through September 2017, data release 7.1. Of the 6,008 women, 5,926 women remained after excluding women with all iron measures missing ($n = 56$), uncertain event status ($n = 9$), follow-up time <1 month ($n = 14$), or unknown event timing ($n = 3$).

Cases were identified as ductal carcinoma *in situ* (DCIS) or invasive incident breast cancer. Tumor hormone status was based on medical records and self-report, in that order of availability (4).

Iron status measures

We used three biomarkers of iron status, serum iron, ferritin, and percent transferrin saturation, assessed in samples provided at cohort enrollment. Ferritin is a circulating iron-binding protein representing iron stores. Percent transferrin saturation indicates the percentage of bound plasma transferrin iron-binding sites, calculated as a function of measured serum iron and unsaturated iron binding capacity (UIBC) as 100[iron/(iron + UIBC)]. The mean intrabatch coefficients of variation were 3.1, 1.4, and 2.7 for iron, ferritin, and transferrin saturation, respectively. A description of laboratory measures is included in the Supplementary Data. We also performed principal components (PC) analysis for the three biomarkers and used the first PC as a summary measure. The first PC explained 72% of the variance for the 3-dimensional marker distribution.

Statistical methods

We used R (5) software with the survival package (6) to fit Cox models with age as the primary time scale to estimate breast cancer HRs for serum iron biomarkers, using the Prentice case–cohort method (7). Iron variables were analyzed as both continuous and divided into quartiles in separate models. We adjusted for baseline smoking, alcohol, education, hormone replacement therapy, age at menarche, age at first birth, oral contraceptive use, body mass index (BMI), menopause status, and a product term between the last two variables. This product term allowed the association with BMI to change after menopause.

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Sensitivity and/or *post hoc* analyses included: (i) restricting the analyses to the first 4 years of follow-up, as more proximate to the baseline iron measures; (ii) restricting by excluding the first 2 years of follow-up, to avoid iron sequestration responses to early carcinogenesis; (iii) estimating breast cancer HRs for particularly low values of ferritin or high values of transferrin saturation, often used as cut-off points for iron deficiency or overload, respectively; (iv) assessing etiologic heterogeneity related to iron levels for invasive versus DCIS, tumor subtypes, and stage, based on case-only logistic analyses; (v) stratifying Cox models based on race/ethnicity and BMI; and (iv) stratifying on pre- and postmenopausal status.

Results

Sample characteristics are shown in **Table 1**. Cases were more educated and less likely to have experienced early menopause than noncases.

Table 1. Baseline characteristics of subcohort and cases of breast cancer.

		Case–cohort	
Variable	**Total**	**Subcohort (no cases)**	**Cases**
N	50,884	2,952	2,974
Baseline age (years)	56 (49–62)	55 (49–62)	57 (50–64)
BMI (kg/m^2)	27 (23–31)	27 (23–31)	27 (24–31)
Waist circumference (in)	33 (30–38)	33 (30–37)	34 (30–38)
Height (cm)	65 (63–66)	64 (63–66)	65 (63–66)
Age at menarche (years)	13 (12–13)	13 (12–13)	13 (12–13)
Time since menopause (years)	4 (0–12)	4 (0–12)	6 (0–13)
Iron (mcg/dL)		92 (73–115)	93 (75–116)
Ferritin (mcg/dL)		67 (36–112)	70 (38–116)
Iron saturation (%)		28 (22–36)	29 (22–36)
Total iron binding capacity (mcg/dL)		328 (300–360)	328 (299–360)
Unsaturated iron binding capacity (mcg/dL)		231 (197–269)	231 (196–269)
Baseline menopause status			
No menopause	17,892 (35)	1,055 (36)	932 (31)
Age ≤ 45 years	5,952 (12)	343 (12)	280 (9)
Age > 45 years	27,040 (53)	1,554 (53)	1,762 (59)
Smoking status			
Never	28,271 (56)	1,609 (55)	1,593 (54)
Former	19,860 (39)	1,185 (40)	1,259 (43)
Current	2,487 (5)	141 (5)	110 (4)
Alcohol status			
Never	1,565 (3)	74 (3)	103 (4)
Past	9,751 (20)	573 (20)	472 (16)
Current	36,879 (77)	2,157 (77)	2,305 (80)
Education			
<high school degree	627 (1)	34 (1)	30 (1)
Completed high school	7,177 (14)	455 (15)	397 (13)
Some college, no degree	9,957 (20)	573 (19)	534 (18)
Associate or technical degree	7,224 (14)	420 (14)	405 (14)
Bachelor's degree	13,714 (27)	776 (26)	826 (28)
Graduate level degree	12,170 (24)	694 (24)	781 (26)
Hormone replacement therapy (ever yes/no)	29,275 (63)	1,659 (61)	1,736 (64)
Birth control (ever yes/no)	43,118 (85)	2,515 (86)	2,491 (84)
Age at first birth (years)			
No birth	9,293 (18)	551 (19)	547 (18)
<20	9791 (19)	575 (19)	540 (18)
>20–24	12,808 (25)	751 (25)	759 (26)
>24–29	11,571 (23)	675 (23)	662 (22)
>29–55	7,421 (15)	400 (14)	466 (16)
Race/ethnicity			
Non-Hispanic White	42,558 (84)	2,463 (83)	2,554 (86)
Non-Hispanic Black	4,462 (9)	266 (9)	222 (7)
Hispanic	2,515 (5)	144 (5)	113 (4)
Other	1,334 (3)	79 (3)	84 (3)
BMI categories (kg/m^2)			
<18.5	563 (1)	25 (1)	26 (1)
18.5–24.9	18,875 (37)	1,111 (38)	1,056 (36)
25.0–29.9	16,149 (32)	934 (32)	953 (32)
30.0–34.9	8,800 (17)	509 (17)	551 (19)
35.0–39.9	3,958 (8)	230 (8)	232 (8)
40.0 +	2,519 (5)	140 (5)	156 (5)

Table 2. Breast cancer risk associated with increasing levels of iron-related biomarkers, Sister Study case–cohort sample.

Biomarkers	Quartile of iron-related biomarker				Linear trend over quartiles[a]
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Iron (μg/dL)					
Median	63	85	103	133	
Ranges	(5–74)	(74–93)	(93–115)	(115–340)	
Unadjusted	Reference	1.15 (0.99–1.33)	1.08 (0.93–1.25)	1.14 (0.98–1.32)	1.03 (0.99–1.08)
Adjusted[b]	Reference	1.07 (0.91–1.26)	1.08 (0.92–1.27)	1.06 (0.90–1.25)	1.02 (0.97–1.07)
Ferritin[c] (μg/dL)					
Median	22	50	88	157	
Ranges	(5–36.25)	(36.25–67)	(67–113)	(113–1625)	
Unadjusted	ref	1.05 (0.90–1.21)	1.09 (0.93–1.26)	1.06 (0.91–1.23)	1.02 (0.97–1.07)
Adjusted[b]	Reference	0.99 (0.84–1.17)	1.05 (0.89–1.24)	1.03 (0.87–1.23)	1.02 (0.96–1.07)
Transferrin saturation (%)					
Median	19	26	33	42	
Ranges	(2–22)	(22–29)	(29–36)	(36–90)	
Unadjusted	Reference	1.01 (0.88–1.17)	1.10 (0.95–1.28)	1.02 (0.88–1.19)	1.02 (0.97–1.06)
Adjusted[b]	Reference	0.92 (0.78–1.07)	1.06 (0.89–1.25)	0.94 (0.80–1.12)	1.00 (0.95–1.05)
First PC[d]					
Median	−1.5	−0.3	0.5	1.5	
Ranges	(−9.9 to −0.799)	(−0.799–0.147)	(0.147–0.976)	(0.976–5.12)	
Unadjusted	Reference	1.18 (1.02–1.37)	1.11 (0.95–1.28)	1.11 (0.96–1.29)	1.03 (0.98–1.07)
Adjusted[b]	Reference	1.12 (0.95–1.32)	1.04 (0.88–1.23)	1.06 (0.90–1.25)	1.01 (0.96–1.06)

[a]Iron covariate in quartile units.
[b]Adjusted for baseline smoking, alcohol, education, hormone replacement therapy, age at menarche, age at first birth, oral contraceptive use, menopause status, BMI, and a product term between the last two variables.
[c]Log transformed.
[d]The first PC explains 72% of the variance and represents loadings of 0.63, 0.40, and 0.66 for the iron, ferritin and transferrin saturation measures, respectively.

There was little evidence of an association between the three serum iron biomarkers, or the first PC of those three measures, and breast cancer risk (**Table 2**). Adjusted HRs [95% confidence interval (CI)] for fourth versus first quartile of exposure and breast cancer were: iron [1.06, (0.90–1.25)], ferritin [1.03 (0.87–1.23)], transferrin saturation [0.94 (0.80–1.12)], and the first PC [1.06 (0.90–1.25)].

Sensitivity analyses were consistent with the primary findings, further supporting the absence of any strong association with breast cancer. The *post hoc* analyses (Supplementary Tables S1–S8) largely aligned with the primary findings. Case-only analyses did not provide evidence for an association between higher iron levels and cancer subtype or stage (Supplementary Tables S7 and S8). However, analyses by BMI subgroups suggested overall decreased risk for the lowest quartile compared with others (Supplementary Table S2). If we compare the lowest with the grouped top three quartiles, the adjusted HRs (95% CI) were 0.72 (0.56–0.92) for iron and 0.84 (0.66–1.09) for ferritin among women with a BMI ≥ 30 kg/m^2 (Supplementary Table S3). Similarly, stratified analyses for the premenopausal group indicated decreased risk for those with low iron stores (Supplementary Table S4). Comparing the lowest quartile with the top three quartiles, the adjusted HRs (95% CI) were 0.70 (0.51–0.97) for iron, 0.73 (0.54–0.99) for ferritin, 0.71 (0.52–0.96) for transferrin saturation, and 0.64 (0.47–0.88) for the first PC (Supplementary Table S4). Iron stores tend to increase postmenopausally, but there was also evidence for protection for those who still had low ferritin postmenopausally (Supplementary Tables S5 and S6).

Discussion

There was little evidence of association between iron overload and breast cancer incidence in the Sister Study. These findings, from one of the largest studies to date, are similar to those of another U.S. cohort (8), but contrast with studies from other countries, some of which found either strong positive or inverse associations between serum ferritin levels and breast cancer (2). Our exploratory analyses suggested reduced risk at the lowest levels of ferritin and iron, particularly among obese women, a group with increasing numbers worldwide. However, little evidence exists in this large U.S. sample to support an association between iron overload and breast cancer.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

A. Von Holle: Conceptualization, formal analysis, visualization, writing–original draft, writing–review and editing. **K.M. O'Brien:** Writing–review and editing. **D.P. Sandler:** Supervision, funding acquisition, investigation, writing–review and editing. **R. Janicek:** Writing–review and editing, responsible for the sample handling and laboratory assessments. **C.R. Weinberg:** Conceptualization, supervision, funding acquisition, investigation, methodology, writing–original draft, project administration, writing–review and editing.

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