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Cancer Epidemiology, Biomarkers & Prevention

Review

Iron and Cancer Risk—A Systematic Review and Meta-analysis of the Epidemiological Evidence

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Abstract

Iron has been suggested as a risk factor for different types of cancers mainly due to its prooxidant activity, which can lead to oxidative DNA damage. Furthermore, subjects with hemochromatosis or iron overload have been shown to have a higher risk of developing liver cancer. We have systematically reviewed 59 epidemiologic studies, published between 1995 and 2012, reporting information on total iron, dietary iron, heme iron, and biomarkers of iron status and cancer risk. Furthermore we conducted meta-analysis for colorectal [relative risk (RR), 1.08; 95% confidence interval (CI), 1.00–1.17], colon (RR = 1.12; 95% CI, 1.03–1.22), breast (RR = 1.03; 95% CI, 0.97–1.09), and lung cancer (RR = 1.12; 95% CI, 0.98–1.29), for an increase of 1 mg/day of heme iron intake. Globally, on the basis of the systematic review and the meta-analysis results, a higher intake of heme iron has shown a tendency toward a positive association with cancer risk. Evidence regarding high levels of biomarkers of iron stores (mostly with serum ferritin) suggests a negative effect toward cancer risk. More prospective studies combining research on dietary iron intake, iron biomarkers, genetic susceptibility, and other relevant factors need to be conducted to clarify these findings and better understand the role of iron in cancer development. *Cancer Epidemiol Biomarkers Prev; 23(1); 1–20. ©2013 AACR.*

Introduction

Iron is an essential element for human life (1). Nevertheless, an excess of iron is toxic (2) and therefore iron metabolism is a very well-regulated process (3). Up until recent years, the focus surrounding iron intake by the Public Health sector was related to iron deficiency. In fact, it still represents the world's most common nutritional deficiency (4). However, the other side of this double-edged sword, iron excess, is getting more relevance in recent research of chronic diseases and also cancer. A complete review of the potential mechanisms and pathways involved in iron-induced carcinogenesis can be found elsewhere (5).

A typical Western diet provides a daily amount of 10 to 20 mg of iron, although only a small percentage is absorbed. There are 2 types of iron in foods, the heme (organic) and the non-heme (inorganic) fraction. Heme iron represents a small proportion of total iron, it is present mostly in red meat and can be absorbed more easily (between 15% and 40%) than inorganic iron due to the insolubility of iron salts (6). The non-heme iron represents the major fraction of total iron, it is present in both animal and vegetal (mainly in cereals, legumes, and some vegetables) but has a wider range of absorption (1%–40%). In humans, the absorption of iron takes place mainly in the proximal part of the intestine, and it is influenced by body iron stores, hypoxia, and erythropoietic activity (7). This absorption is greatly enhanced by vitamin C (especially the inorganic iron fraction) and decreased by dietary calcium (which affects both inorganic and heme iron; ref. 3). Most circulating iron is bound to transferrin, a minimal part of iron is free or bound to albumin and iron stored in cells is bound to ferritin. Serum ferritin has been recognized as the best indicator of body iron stores, although many clinical conditions elevate these concentrations. Serum iron is considered a less specific marker for body iron stores, whereas transferrin saturation has been shown to reflect tissue iron stores reasonably well (8).

Carcinogenicity of iron has been clearly shown in animal models (9) and human experiments (10). Non–protein-bound iron ("free" or catalytic iron) is a prooxidant, as its participation in the redox cycling is associated with the generation of reactive oxygen species (ROS) such as the hydroxyl radicals. ROS are highly reactive molecules capable of inducing lipid peroxidation and oxidative damage to DNA (2). In addition, heme iron, mainly found in red meat, can be involved in carcinogenesis by acting as a nitrosating agent (11), forming *N*-nitroso compounds that are known carcinogens (12). This could explain the association between

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red meat intake, the main source of heme iron, and certain types of cancer (13).

In some conditions, like in hereditary hemochromatosis, genetic mutations in the HFE gene leads to an accumulation of this mineral in the parenchymal cells of the liver and other tissues, causing iron overload (14). This condition is associated with an increased risk of hepatocellular carcinoma, predominantly in patients with cirrhosis (15). Moreover, in subjects with HFE mutation, there are also suggestions of increased risk for other types of cancer (16, 17).

Although evidence concerning meat intake and cancer risk is consistent, it is not conclusive for iron intake (13). The World Cancer Research Fund report included only evidence for colorectal cancer risk in relation to dietary and heme iron intake, all of them before 2006 (13). It was precisely around this moment when more cohort study articles on heme iron and other cancer types started to be published in the literature. Recently, 2 meta-analysis focused on iron intake were published on colorectal cancer (18, 19). However, epidemiologic evidence regarding other cancer types has not been systematized. To our knowledge, there is not a systematic review of all cancer types and iron in the literature. We propose in this systematic review a global overview of the available epidemiologic evidence on dietary iron and iron biomarkers, with different cancer types.

Materials and Methods

Search strategy

In this systematic review, we conducted a PubMed search to identify epidemiologic studies on the association of iron and the risk of developing cancer published between 1995 and 2012. Query terms used for the PubMed database search included the terms "iron," "heme," "biomarkers," "dietary," "cancer," and "risk." In addition, we complemented this search manually after exploring references of the retrieved articles from the PubMed search. When only abstracts were available from the PubMed database, we contacted the correspondent author to get the full article.

Inclusion and exclusion criteria

Included publications for this review were epidemiologic studies with a prospective or a case–control design. Furthermore, the exposures of interest were dietary iron, total iron, heme iron, iron biomarkers (more information can be found in exposure definition and classification), and the outcome of interest was cancer. All studies gathered for this review gave information on the effect estimates, as well as the corresponding 95% confidence intervals (CI).

We did not consider reviews of the literature and experimental studies (*in vitro*, animal, and human studies). We also excluded one article (20) that provided a combined effect estimate for different cancer types without referring to cancer-specific effects.

Data extraction

The following data were gathered from the included studies: general study information (first author, publication year, journal, and country); study design (prospective or case–control, follow-up period or recruitment period, cohort size, number of cases and number of controls); subject's description (age and gender); exposure information (type of dietary assessment method and iron biomarkers); study results [the most valid odds ratio or relative risks (RR), adjusted for relevant confounders, and 95% CI for the highest vs. the lowest categories of the exposure variable measured in each included article, and adjustments for confounding factors].

Publications versus studies

As some publications measured different exposure variables and others provided results for different types of cancer, we counted them as separate studies and presented their results independently. This will explain the disparity in the number of publications and number of results presented later in this review.

Exposure definition and classification

Iron from dietary sources. In this review, *dietary iron* refers to iron from foods only and *total iron* refers to iron from foods plus iron supplement intake. We included all studies that presented information on heme iron intake, from all food sources. Some studies estimated heme iron using their own database, which included only meat sources (this information was included in Tables 1 and 3; ref. 21). The methodology behind heme iron assessment will be commented on in more detail the discussion section later in this review.

Iron biomarkers. We retrieved available data on *serum ferritin*, *serum transferrin*, *total iron-binding capacity*, *transferrin saturation*, *serum iron*, and *toenail iron*. This range of biomarkers in combination allows for reliable assessment of iron status and, therefore, of the adequacy of iron intake (8). Iron is transported in the circulation bound to transferrin, which maintains iron in a redox-inert state and delivers it to tissues (22). Transferrin is the main plasma transport protein responsible for iron distribution and serves as a storage sink for sequestering iron extracellularly until iron is needed, then allowing it to reach target tissues (23). Circulating serum levels, although modest, show a strong positive correlation with tissue stores of ferritin (8). When iron is not immediately needed by the organism, it is stored in the cells as ferritin, and the relatively small quantities of ferritin in the plasma are proportional to the quantity stored intracellularly (8). Plasma/Serum ferritin is a sensitive indicator of iron stores (8), although its main limitation is that chronic infection or inflammation elevates the concentration 2 to 3 times higher than values representing iron stores (24). Total iron-binding capacity (TIBC) measures the ability of plasma proteins to bind iron and reflects the fraction of transferring-free places to bound iron (22). Transferrin saturation has been shown to reflect tissue iron stores

Table 1. Characteristics of the population in the cohort studies

Author (ref), country, study	Cohort/cases (cancer type)	Sex/age	Follow-up	Assessment	Exposure		
					Variable	Value ♀	Value ♂
Cross and colleagues (35),[a] USA, NIH-AARP Diet and Health Study	300,948/2,719 (colorectal)	♀♂/50–71 y	7.2	124 item FFQ[b]	Heme iron (μg/1,000 kcal)	150.3[c]	
					Dietary iron (mg/1,000 kcal)	8.2[c]	
					Total iron (mg/d)	21.5[c]	
Zhang and colleagues (36), USA, NHS and HPFUS	115,061/2,114 (colorectal)	♀♂/NHS 30–55 y and HPFUS 40–75 y	22	61–130 item FFQ	Heme iron (mg/d)	1.1[c]	1.2[c]
Balder and colleagues (37), Netherlands, Netherlands Cohort Study	120,852/1,535 (colorectal)	♀♂/55–69 y	9.3	150-item FFQ	Heme iron (mg/d)	0.92[c]	1.08[c]
					Dietary iron (mg/d)	11[c]	13[c]
Hara and colleagues (38), Japan, Japan PH Center-based Prospective Study	85,097/1,284 (colorectal)	♀♂/45–74 y	5	138-item FFQ[b]	Heme iron (mg/d)	0.44[d]	0.61[d]
Lee DH and colleagues (39), USA, Iowa Women's Health Study	34,708 438 proximal + 303 distal (colon)	♀/55–69 y	15	127-item FFQ	Heme iron (mg/d) proximal and distal	1.16–1.64[e]	
Kabat GC and colleagues (40), Canada	49,654/617 (colorectal)	♀/40–59 y	16.4	86-item FFQ	Heme iron (mg/d)	1.99–2.40[e]	
					Dietary iron (mg/d)	12.90–13.82[e]	
Larsson and colleagues (41), Sweden, Swedish Mammography Cohort	61,433/547 (colon)	♀/40–75 y	14.8	FFQ	Heme iron (mg/d)	1.04–1.52[e]	
Ekblom and colleagues (42), Sweden, Northern Sweden Health and Disease Study	NA/226 (colorectal)	♀♂/50.3–60.25	NA	Dietary NA Blood sample	Plasma ferritin (μg/L)	60.8–180.3[f]	
					Plasma transferrin saturation (%)	28.7–46.8[f]	
					Plasma TIBC (μmol/L)	48.1–57.3[f]	
					Plasma iron (μmol/L)	15.1–23.2[f]	
Cross and colleagues (43), Finland, Alfa-tocopherol, Beta-carotene cáncer prevention study	29,133 130 cases: 73 (colon) + 57 (rectal) (colorectal)	♂/50–69 y	14.2	276-item FFQ Blood sample	Dietary iron (mg/d)	19[c]	
					Serum iron (μg/dL)	124[c]	
					Serum ferritin (ng/mL)	141[c]	
					Transferrin saturation (%)	38[c]	
					TIBC (μg/dL)	326[c]	
Kato and colleagues (25), USA, New York University Women's Health Study cohort	15,785/105 (colorectal)	♀/34–65 y	4.7	FFQ Blood sample	Total iron (mg/d)	13.7[d]	
					Serum iron (μg/dL)	83[d]	
					TIBC (μg/dL)	325.2[d]	
					Transferrin saturation (%)	25.8[d]	
					Serum ferritin (ng/mL)	88.4[d]	
Wurzelmann and colleagues (44), USA, National Health and Nutrition Examination Survey I and National Health Evaluation Follow-up study	11,317/156 (colorectal)	♀♂/31–74 y	15	FFQ + 24h-R	Dietary iron (mg/d)	9.6[d]	13.5[d]
					Serum iron (μg/dL)	96.7[d]	106.1[d]

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Table 1. Characteristics of the population in the cohort studies (Cont'd)

Author (ref), country, study	Cohort/cases (cancer type)	Sex/age	Follow-up	Assessment	Exposure		
					Variable	Value ♀	Value ♂
Jakzsyn and colleagues (59), Europe, European Prospective Study into Cancer and Nutrition	481,419/444 (gastric)	♀♂/35–70 y	8.7	88–266 item FFQ	Heme iron (mg/d)	1.02[g]	
Cook and colleagues (60), Finland, Alfa-tocopherol, Beta-carotene cáncer prevention study	29,133/341 (gastric)	♂/50–69 y	22	276-item FFQ	Dietary iron (mg/d)	18[d]	
					Total iron (mg/d)	22[d]	
				Blood sample	Serum iron (μg/dL)	117[d]	
					Serum ferritin (ng/mL)	156[d]	
					Transferrin saturation (%)	36[d]	
					TIBC (μg/dL)	329[d]	
Cross and colleagues (58)[a], USA, National Institutes of Health - AARP Diet and Health study	303,156/505 (esophageal) 532 (gastric)	♀♂/50–71 y	10	124-item FFQ[b]	Heme iron (μg/1,000 kcal)	154.2[c]	
Steffen and colleagues (68), Europe, European Prospective Study into Cancer and Nutrition	348,738/151 (esophageal)[g]	♀♂/35–70 y	11.8	FFQ[b]	Heme iron (μg/1,000 kcal)	245[c]	
Kabat and colleagues (50)[a], USA, NIH-AARP Diet and Health Study	116,674/3,396 (breast)	♀/50–71 y	6.5	124-item FFQ[b] + FFQ with meat-cooking module	Dietary iron (mg/d)	8.2[c]	
					Heme iron (mg/d)	124.6[c]	
Kabat GC and colleagues (51), Canada, Canadian National Breast Screening Study	49,654/2,545 (breast)	♀/40–59 y	16.4	86-item FFQ	Dietary iron (mg/d)	12.90–13.82[e]	
					Heme iron (mg/d)	1.99–2.40[e]	
Ferrucci and colleagues (52)[a], USA, PLCO Cancer Screening Trial	52,158/1,205 (breast)	♀/55–74 y	5.5	124-item FFQ	Dietary iron (mg/1,000 kcal)	8.3[c]	
					Heme iron from meat (mg/1,000 kcal)	0.14[c]	
Tasevska and colleagues (69)[a], USA, NIH-AARP Diet and Health Study	46,7976/6,361 (lung)	♀♂/50–71 y	8	124-item FFQ[b] + FFQ with meat-cooking module	Heme iron (μg/1,000 kcal)	125.2[c]	171.1[c]
Tasevska and colleagues (70)[a], USA, PLCO Cancer Screening Trial	99,579/782 (lung)	♀♂/55–74 y	8	124-item FFQ[b] + DHQ[c] + meat-cooking module	Heme iron (μg/1,000 kcal)	136[c]	191[c]
Lee DH and colleagues (71), USA, Iowa Women's Health Study	34,708/700 (lung)	♀/55–69 y	16	127-item FFQ	Heme iron (mg/d)	1.65[c]	
Genkinger and colleagues (81), Sweden, Swedish Mammography Cohort	60,895/720 (endometrial)	♀/40–76 y	21	67-item FFQ + 96-item FFQ[b]	Heme iron (mg/d)	1.13[c]	
					Dietary iron (mg/d)	13.62[c]	

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Table 1. Characteristics of the population in the cohort studies (Cont'd)

Author (ref), country, study	Cohort/cases (cancer type)	Sex/age	Follow-up	Assessment	Exposure		
					Variable	Value ♀	Value ♂
Kabat and colleagues (82), Canada, Canadian National Breast Screening Study	34,148/426 (endometrial)	♀/40–59 y	16.4	86-item FFQ	Dietary iron (mg/d) Heme iron (mg/d)	12.90–13.82[e] 1.99–2.40[e]	
Jakzsyn and colleagues (83), Europe, European Prospective Study into Cancer and Nutrition	481,419/1,001 (bladder)	♀♂/35–70 y	8.7	FFQ	Heme iron (mg/d)	1.02[c]	
Molina-Montes and colleagues (84), Europe, European Prospective Study into Cancer and Nutrition	477,202/865 (pancreatic)	♀♂/25–70 y	11.3	FFQ[b]	Dietary iron (mg/d) Heme iron (mg/d)	11.9[c] 0.9[c]	14.3[c] 1.4[c]
Jakzsyn and colleagues (85), Europe, European Prospective Study into Cancer and Nutrition	139,005/4,606 (prostate)	♂/35–70 y	11	FFQ	Heme iron (mg/d)	1.45[c]	

Abbreviation: NA, not available.
[a]Heme iron estimation according to NCI database (only meat food sources).
[b]FFQ validated with 14-, 28-, or 1-week dietary records.
[c]Median.
[d]Mean.
[e]Percentile 40 and 60.
[f]25th–75th percentile.
[g]Only squamous cell carcinoma.

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Table 2. Characteristics of the population in the case–control studies

Author (ref), study, and/or country	Study base and period	Cases/controls (cancer type)	Control information Sex/age	Assessment	Exposure	
					Variable	Value
Kallianpur AR and colleagues (53); Shanghai Endometrial Cancer Study; China	Population (1996–1998 and 2002–2005)	3,452/3,474 (breast)	♀/25–70	76-item FFQ	Dietary iron (NA)	NA
Adzersen and colleagues (54); Heidelberg, Germany	Hospital (1998–2000)	310/353 (breast)	♀/25–75	161-item FFQ	Dietary iron (mg/d)	11.2[a]
Levi and colleagues (55); Swiss Canton of Vaud, Switzerland	Hospital (1993–1999)	289/442 (breast)	♀/23–74	79-item FFQ	Dietary iron (mg/d)	12.3[a]
Cade and colleagues (56); Southampton and Portsmouth, England	Hospital (1990–1992)	220/825 (breast)	♀/50–65	25-item FFQ + 141 FFQ[b]	Dietary iron (mg)	12.7[a]
Pelucchi and colleagues (61); Milan, Italy	Hospital (1997–2007)	230/547 (gastric)	♀♂/22–80	78-item FFQ	Dietary iron (NA)	NA
Corneé and colleagues (62); Marseille, France	Hospital (1985–1988)	92/128 (gastric)	♀♂/NA	Dietary history questionnaire	Dietary iron (mg/d)	12[a]
Ward and colleagues (63); Nebraska, USA	Population (cases: 1988–1993; controls: 1992–1994)	124 (esophageal)[c] and 154 (gastric)/449 (esophageal and gastric)	♀♂/≥21	Health Habits and History Questionnaire 1	Dietary iron (μg/d) Heme iron (mg/d)	13.4[a] 1,038[a]
O'Doherty and colleagues (26); FINBAR study, Ireland	Population (2002–2005)	224/256 (esophageal)[c]	♀♂/cases were <85 and controls 35–84	FFQ	Energy adjusted dietary iron (mg/d) Energy-adjusted heme iron (mg/d)	14.0[d] 1.2[d]
				Blood sample	Serum iron (μg/dL) Ferritin (ng/mL) Toenail iron (ppm)	93.48[d] 125.97[d] 10.36[d]
Levi and colleagues (45); Swiss Canton of Vaud, Switzerland	Hospital (1992–1997)	223/491 (colorectal)	♀♂/27–74	FFQ	Dietary iron (mg/d)	13.4[a]
Sun and colleagues (46); Newfoundland, Labrador and Ontario; Canada	Population (1997–2006)	1,760/2,481 (colorectal)	♀♂/20–74	170-item FFQ	Total iron (mg/d)	24.5[d]
Zhou and colleagues (72); Massachusetts General Hospital, USA	Hospital (1992–2000)	923/1,125 (lung)	♀♂/≥18	126-item FFQ	Energy-adjusted dietary iron (mg/d) Energy-adjusted heme iron (mg/d)	1.3[a] 1.0[a]

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Table 2. Characteristics of the population in the case–control studies (Cont'd)

Author (ref), study, and/or country	Study base and period	Cases/controls (cancer type)	Control information Sex/age	Assessment	Exposure	
					Variable	Value
Richie Jr and colleagues (86); New York, USA	Hospital (NA)	65/85 (oral)	♀♂/NA	Blood sample	Serum iron (μg/dL) men	110[d]
					Serum iron (μg/dL) women	102[d]
					Transferrin saturation (%) men	22.7[d]
					Transferrin saturation (%) women	22.8[d]
					TIBC (μg/dL) men	399[d]
					TIBC (μg/dL) women	376[d]
					Ferritin (ng/mL) men	188[d]
					Ferritin (ng/mL) women	131[d]

Abbreviation: NA, information not available.

[a]Median.

[b]The latter was filled at home.

[c]Only adenocarcinoma.

[d]Mean.

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Table 3. RRs for cancer risk within the highest versus lowest categories of iron (diet and biomarkers)

Author, year, country (ref), study, and/or country	*n* cases	Measured variable	Exposure categories: Lowest	Highest	Comparison	Units	Adjusted RR (95% CI)	P_{trend}
Colorectal								
A: Prospective								
Cross and colleagues (35);[a] NIH-AARP Diet and Health Study; USA	2,719	Heme iron	48.1	335.8	Q5 vs. Q1	mg/1,000 kcal	1.13 (0.99–1.29)	0.022
		Dietary iron	5.9	11.4	Q5 vs. Q1	mg/1,000 kcal	0.75 (0.65–0.87)	<0.001
		Total iron	10.8	36.1	Q5 vs. Q1	mg/d	0.75 (0.66–0.86)	<0.001
Zhang and colleagues (36); Nurses' Health Study and Health Professionals Follow-up Study; USA	2,114	Heme iron (♀)	<0.78	>1.30	Q5 vs. Q1	mg/d	1.10 (0.93–1.30)	0.51
		Heme iron (♂)	<0.90	>1.60	Q5 vs. Q1	mg/d	Combined sex	
		Total iron (♀)	<10.9	>22.7	Q5 vs. Q1	mg/d	1.09 (0.93–1.30)	0.37
		Total iron (♂)	<12.6	>24.6	Q5 vs. Q1	mg/d	Combined sex	
Balder and colleagues (37); Netherlands Cohort Study; Netherlands	1,535	Heme iron (♂)	0.60[b]	1.85[b]	Q5 vs. Q1	mg/d	1.16 (0.87–1.55)	0.27
		Heme iron (♀)	0.47[b]	1.54[b]	Q5 vs. Q1	mg/d	1.22 (0.89–1.68)	0.22
		Total iron (♂)	8.5[b]	15[b]	Q5 vs. Q1	mg/d	1.34 (0.93–1.93)	0.12
		Total iron (♀)	9.5[b]	17[b]	Q5 vs. Q1	mg/d	1.08 (0.72–1.62)	0.90
Hara and colleagues (38); Japan Public Health Center-based Prospective Study; Japan	1,284	Heme iron (♂)	0.24[b]	0.77[b]	Q4 vs. Q1	mg/d	1.06 (0.79–1.42)	0.6
		Heme iron (♀)	0.23[b]	0.67[b]	Q4 vs. Q1	mg/d	0.88 (0.61–1.29)	0.4
Lee DH and colleagues (39);[c] Iowa Women's Health Study; USA	741	Heme iron (proximal colon)	≤0.76	≥2.05	Q5 vs. Q1	mg/d	2.18 (1.24–3.86)	0.01
		Heme iron (distal colon)	≤0.76	≥2.05	Q5 vs. Q1	mg/d	0.90 (0.45–1.81)	0.77
Kabat GC and colleagues (40); Canada	617	Heme iron	<1.58	≥2.95	Q5 vs. Q1	mg/d	1.06 (0.80–1.42)	0.99
		Dietary iron	<11.90	≥14.99	Q5 vs. Q1	mg/d	1.07 (0.80–1.43)	0.94
Larsson and colleagues (41);[c] Swedish Mammography Cohort; Sweden	547	Heme iron	<0.67	≥2.06	Q5 vs. Q1	mg/d	1.31 (0.98–1.75)	0.03
		Heme iron (≥20 g/w alcohol)	<0.67	≥2.06	Q5 vs. Q1	mg/d	2.29 (1.25–4.21)	0.007
Ekblom and colleagues (42); Northern Sweden Health and Disease Study	225	Plasma ferritin (full group)	NA	NA	Q5 vs. Q1	μg/L	0.48 (0.27–0.88)	0.015
		Serum TIBC (full group)	NA	NA	Q5 vs. Q1	%	2.24 (1.22–4.15)	0.005
		Plasma iron (age < 59 y)	NA	NA	Q5 vs. Q1	μmol/L	1.25 (0.57–2.72)	0.35
		Plasma iron (age ≥ 59 y)	NA	NA	Q5 vs. Q1	μmol/L	0.85 (0.45–1.62)	0.91
		Transferrin saturation (age < 59 y)	NA	NA	Q5 vs. Q1	%	1.02 (0.45–2.31)	0.99
		Transferrin saturation (age ≥ 59 y)	NA	NA	Q5 vs. Q1	%	0.46 (0.22–0.93)	0.18
Cross and colleagues (43); ATBC: α-tocopherol, β-carotene cancer prevention study cohort, Finland	130	Dietary iron	≤14.4	>22	Q4 vs. Q1	mg/d	0.4 (0.1–1.1)	0.06
		Serum ferritin	≤88	>221	Q4 vs. Q1	ng/mL	0.4 (0.2–0.9)	0.09
		Serum iron	≤97	>153	Q4 vs. Q1	μg/dL	0.7 (0.3–1.5)	0.41
		Serum transferrin saturation	≤29.7	>47.3	Q4 vs. Q1	%	0.6 (0.3–1.3)	0.24
		Serum TIBC	≤300	>351	Q4 vs. Q1	μg/dL	1.4 (0.7–3.2)	0.28

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Table 3. RRs for cancer risk within the highest versus lowest categories of iron (diet and biomarkers) (Cont'd)

Author, year, country (ref), study, and/or country	*n* cases	Measured variable	Exposure categories				Adjusted RR (95% CI)	P_{trend}
			Lowest	Highest	Comparison	Units		
Kato and colleagues (25); New York University Women's Health Study cohort; USA	105	Total iron	NA	NA	Q4 vs. Q1	mg/d	1.17 (0.6–2.3)	0.44
		Serum iron	NA	NA	Q4 vs. Q1	μg/dL	0.85 (0.5–1.6)	0.52
		Serum ferritin	NA	NA	Q4 vs. Q1	ng/mL	0.40 (0.2–0.8)	<0.01
		Serum transferrin saturation	NA	NA	Q4 vs. Q1	%	0.63 (0.3–1.2)	0.11
		Serum TIBC	NA	NA	Q4 vs. Q1	μg/dL	1.81 (0.9–3.5)	0.10
Wurzelmann and colleagues (44); NHANES + NHEFS; USA[c]	136	Dietary iron	NA	NA	Q4 vs. Q1	mg/d	3.35 (1.74–6.46)	<0.001
	126	Serum iron	NA	NA	Q4 vs. Q1	μg/dL	1.36 (0.77–2.41)	0.24
B: Case–control								
Sun and colleagues (46); Newfoundland, Labrador and Ontario; Canada	1,760	Total iron	12.6[b]	36.7[b]	Q5 vs. Q1	mg/d	1.34 (1.01–1.78)	0.02
Levi and colleagues (45); Swiss Canton of Vaud, Switzerland	223	Dietary iron	9.4[b]	18[b]	T3 vs. T1	mg/d	2.43 (1.2–5.1)	<0.05
Breast								
A: Prospective								
Kabat and colleagues (50);[a] NIH-AARP Diet and Health Study; USA	3,396	Dietary iron	<6.8	≥10.1	Q5 vs. Q1	mg/1,000 kcal	1.02 (0.90–1.15)	0.94
		Heme iron	<62.9	≥216.7	Q5 vs. Q1	μg/1,000 kcal	1.01 (0.89–1.14)	0.97
Kabat and colleagues (51); Canada	2,545	Dietary iron	<11.90	≥14.99	Q5 vs. Q1	mg/d	0.97 (0.85–1.10)	0.63
		Heme iron	<1.58	≥2.95	Q5 vs. Q1	mg/d	1.03 (0.90–1.18)	0.25
Ferrucci and colleagues (52);[a] Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; USA	1,205	Dietary iron	≤6.9	>10.3	Q5 vs. Q1	mg/1,000 kcal	1.25 (1.02–1.52)	0.03
		Heme iron (from meat)	≤0.07	>0.23	Q5 vs. Q1	mg/1,000 kcal	1.12 (0.92–1.38)	0.59
B: Case–control								
Kallianpur AR and colleagues (53); Shanghai Endometrial Cancer Study; China	3,452	Dietary iron	NA	NA	Q4 vs. Q1	NA	1.32 (0.97–1.80)	0.08
Adzersen and colleagues (54); Heidelberg, Germany	310	Dietary iron	<9.0	>14.3	Q4 vs. Q1	mg/d	0.66 (0.32–1.33)	0.06
Levi and colleagues (55); Swiss Canton of Vaud, Switzerland	289	Dietary iron	9.0[b]	16.8[b]	T3 vs. T1	mg/d	1.21 (0.65–2.26)	0.3
Cade and colleagues (56); Southampton and Portsmouth, England	220	Dietary iron	NA	NA	Q4 vs. Q1	NA	0.49 (0.23–1.01)	0.03

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Table 3. RRs for cancer risk within the highest versus lowest categories of iron (diet and biomarkers) (Cont'd)

Author, year, country (ref), study, and/or country	*n* cases	Measured variable	Exposure categories				Adjusted RR (95% CI)	P_{trend}
			Lowest	Highest	Comparison	Units		
Gastric								
A: Prospective								
Jakzsyn and colleagues (59); EPIC-Europe; Europe	444	Heme iron	0.36[b]	1.97[b]	Q4 vs. Q1	mg/d	1.67 (1.20–2.34)	0.002
Cook and colleagues (60); ATBC: α-tocopherol, β-carotene cancer prevention study cohort (a); Finland	341	Dietary iron[d]	<1.22	≥1.53	Q4 vs. Q1	mg/1,000 kcal/d	1.05 (0.60–1.85)	0.931
		Serum ferritin	<96	≥241	Q4 vs. Q1	ng/mL	0.69 (0.44–1.09)	0.108
		Serum iron	<92	≥146	Q4 vs. Q1	μg/dL	0.84 (0.53–1.33)	0.463
		Serum transferrin saturation	<28.65	≥44.10	Q4 vs. Q1	%	0.92 (0.58–1.45)	0.721
		Serum TIBC	<295	≥362	Q4 vs. Q1	μg/dL	0.91 (0.57–1.46)	0.708
Cross and colleagues (58);[a] NIH-AARP Diet and Health Study, USA	532	Heme iron (gastric cardia)	48.8[b]	347.7[b]	Q5 vs. Q1	μg/1,000 kcal	0.83 (0.53–1.30)	0.256
		Heme iron (gastric non-cardia)	48.8[b]	347.7[b]	Q5 vs. Q1	μg/1,000 kcal	0.72 (0.48–1.08)	0.531
B: Case–control								
Pelucchi and colleagues (61); Milan, Italy	230	Dietary iron	NA	NA	Q4 vs. Q1	NA	0.56 (0.27–1.15)	0.10
Corneé and colleagues (62); Marseille, France	92	Dietary iron	NA	NA	T3 vs. T1	NA	0.41 (0.19–0.89)	0.02
Ward and colleagues (63);[a] Nebraska, USA	154	Heme iron	98 to <660	>1,440	Q4 vs. Q1	μg/d	1.99 (1.00–3.95)	0.17
		Dietary iron	<10.6	>17.3	Q4 vs. Q1	mg/d	1.71 (0.75–3.18)	0.21
Esophageal								
A: Prospective								
Cross and colleagues (58);[a] NIH-AARP Diet and Health Study, USA	505	Heme iron ESCC[e]	48.8	347.7	Q5 vs. Q1	μg/1,000 kcal	1.25 (0.64–2.42)	0.944
		Heme iron EADC[f]	48.8	347.7	Q5 vs. Q1	μg/1,000 kcal	1.47 (0.99–2.20)	0.063
Steffen and colleagues (68); EPIC-Europe; Europe	151	Heme iron ESCC[e]	<116	426–460	Q5 vs. Q1	μg/1,000 kcal	0.99 (0.90–1.10)	NA
B: Case–control								
Ward and colleagues (63);[a] Nebraska, USA	124	Dietary iron	<10.6	>17.3	Q4 vs. Q1	mg/d	1.67 (0.51–5.44)	0.31
		Heme iron	98 to <660	>1,440	Q4 vs. Q1	μg/d	3.04 (1.20–7.72)	0.01
O'Doherty and colleagues (26); FINBAR study, Ireland	224	Dietary iron	<12.76	≥15.44	Q4 vs. Q1	mg/d	0.50 (0.25–0.98)	0.06
		Heme iron	<0.74	≥1.39	Q4 vs. Q1	mg/d	3.11 (1.46–6.61)	<0.01
		Toenail iron	<5.48	≥11.52	Q4 vs. Q1	ppm	0.40 (0.17–0.93)	0.07
Lung								
A: Prospective								
Tasevska and colleagues (69);[a] NIH-AARP Diet and Health Study; USA	6,361	Heme iron (♂)	≤90.2	>285.2	Q5 vs. Q1	μg/1,000 kcal	1.25 (1.07–1.45)	0.02
		Heme iron (♀)	≤63.2	>217.2	Q5 vs. Q1	μg/1,000 kcal	1.18 (0.99–1.42)	0.002
Tasevska and colleagues (70);[a] Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; USA	782	Heme iron (♂)	≤106	>317	Q5 vs. Q1	μg/1,000 kcal	0.91 (0.65–1.28)	0.37
		Heme iron (♀)	≤72	>227	Q5 vs. Q1	μg/1,000 kcal	0.89 (0.62–1.29)	0.78

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Table 3. RRs for cancer risk within the highest versus lowest categories of iron (diet and biomarkers) (Cont'd)

Author, year, country (ref), study, and/or country	*n* cases	Measured variable	Exposure categories			Units	Adjusted RR (95% CI)	P_{trend}
			Lowest	Highest	Comparison			
Lee DH and colleagues (71); Iowa Women's Health Study; USA	700	Heme iron (0 vit C)	≤0.77	≥2.44	High vs. Low categories	mg/d	1.27 (0.67–2.40)	0.75
		Heme iron (>700 mg vit C)	≤0.77	≥2.44	High vs. Low categories	mg/d	8.97 (1.29–62.51)	0.02
Zhou and colleagues (72); Massachusetts General Hospital, USA	923	Dietary iron	≤10.76	≥16.24	Q5 vs. Q1	mg/d	1.45 (1.03–2.06)	0.01

Abbreviation: NA, not available.

[a]Heme iron estimation according to NCI database (only meat food sources).

[b]Median.

[c]Colon cancer.

[d]mg/1,000 kcal/d.

[e]Esophageal squamous cell carcinoma.

[f]Esophageal adenocarcinoma.

reasonably well and reflects the percentage of places that are bound by iron in the transferrin molecule (25). Toenail iron was measured only in one of the studies of this revision and it is known to be a more stable measure of iron exposure (26).

Overall, with iron overload, biomarkers will reflect bigger values, with the exception of TIBC, which will vary inversely with iron stores. It is also important to mention that iron biomarkers have reference values (27) that can change with circadian rhythm, sex, infection, and inflammation, among other factors.

Meta-analysis

Often summarizing the state-of-the-art review of epidemiologic studies involves a quantitative meta-analysis, which typically provides a combined measure of the effect (i.e., RR). However, this assumes there is a common assessment of such an effect across all studies, whereas in many instances, the studies reflect a huge variability of results. In this case, trying to explain the observed differences may be more interesting that just providing an overall estimate that could prove difficult to interpret. This is particularly important when heterogeneity does not only reflect underlying differences in populations but also rather methodologic differences in the study design, the actual exposure and outcomes being measured, and the exposure dose to which the relative measures of effect refers to. The latter is a strong drawback in interpreting the results of some meta-analyses that summarize effect estimates of highest versus lowest levels of exposure. In fact, people classified in the highest category of exposure in one study may be placed in the lowest category in another.

Despite the above-mentioned limitations, we decided to supplement our systematic review with a meta-analysis; however, we restricted this approach by applying the following criteria: (i) we did not combine different indicators of exposure (i.e., dietary iron, heme iron, biomarkers of iron status); (ii) we did not consider broad groups of cancers (i.e., gastrointestinal tumors, head and neck cancers); (iii) we did not combine prospective and case–control studies; when available, the former were preferred; (iv) we included only studies where it was available/or it was possible to compute a summary measure of effect for a given amount of exposure (dose–response analysis); and (v) we conducted a meta-analysis only when there were at least 3 studies available. After reviewing all the studies included in the systematic review fitting the established criteria, we carried out a meta-analysis of prospective studies assessing the relationship between heme iron intake and cancers of the colon and rectum (colorectal cancer), colon, breast, and lung.

For each study of the 4 meta-analyses, we used the most fully adjusted effect estimate available, usually the HR as an estimate of the RR. When only categorical results were published, we calculated the trend in RR for 1 mg/d of heme iron intake using the median of each category (i.e., tertiles, quartiles, quintiles), estimated, when necessary, as category midpoint. The trend RR (for 1 mg heme iron)

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with corresponding 95% CI was computed assuming linearity of logRRs, by means of a method based upon generalized least squares (28). Overall RRs were estimated using a random-effect model (29). Heterogeneity across studies was assessed by means of the Cochran's Q and the I^2 statistic (30).

Results and Discussion

Study characteristics

After an initial search defined in Material and Methods, we identified a total of 88 articles, from which we excluded 58 after reviewing their abstracts. The main reasons for the exclusion were non-dietary iron, different outcome, systematic reviews, and one meta-analysis on colorectal cancer. In a second phase, after consulting the full articles, we added 10 publications that resulted in a total of 40 publications. In this phase, we had to discard 3 publications (31–33) as we did not receive the full articles after these had been requested of the correspondent authors, totaling 37 publications to review. From these, we retrieved results from a total of 56 studies (39 prospective and 17 case–control) that we reviewed independently according to the exposure variable (dietary iron, total iron, heme iron, and iron biomarkers). The provenance of the publications analyzed in this review was mostly European and North American (around 90%). Detailed information about these studies can be found in Tables 1 and 2. Results from colorectal, breast, gastric, esophageal, and lung cancers can be found in Table 3 (we showed detailed results only for cancer types with 4 or more publications gathered in this review). A summary of the main associations for all cancer types can be found in Table 4, and Fig. 1 shows the meta-analysis results for colorectal, colon, breast, and lung cancers and heme iron intake.

Colorectal and colon cancers

Colorectal cancer is the most common cancer in developed countries (34) and it is the most represented cancer type in this review with 21 studies in total (17 colorectal and 4 colon cancer studies; refs. 25, 35–46). Three colorectal (2 case–control and 1 prospective) and 1 colon cancer (prospective) studies looking into dietary and total iron showed a positive association, and 3 of them were statistically significant [RR, 3.35; 95% CI, 1.74–6.46 (ref. 44); RR, 2.43; 95% CI, 1.2–5.1 (ref. 45); RR, 1.34; 95% CI, 1.01–1.78 (ref. 46)]. A large prospective study, with 2,719 colorectal cases, found a statistically significant negative association with both dietary and total iron (RR, 0.75; 95% CI, 0.65–0.87 for dietary iron and RR, 0.75; 95% CI, 0.66–0.86 for total iron; ref. 35). The same tendency was shown when looking only at colon cancer (RR, 0.78; 95% CI, 0.66–0.92 for dietary iron and RR, 0.73; 95% CI, 0.62–0.84 for total iron). Regarding heme iron, Lee and colleagues were the first authors to report a statistically significant positive association between heme iron and proximal colon cancer, using information from 741 cases of the Iowa Women's Health Study (RR, 2.18; 95% CI, 1.24–3.86; ref. 39). Following the results of this study, in the Swedish Mammography Cohort (41), there was also evidence of a statistically significant positive association, but only among women who consumed 20 or more grams of alcohol per week (RR, 2.29; 95% CI, 1.25–4.21). Two other studies found a positive association between heme iron and colorectal cancer but it was not statistically significant (35, 37). In a meta-analysis of 5 prospective

Table 4. Summary of the main association between iron (diet and biomarkers) and different cancer types

	Dietary iron		Heme iron intake		Biomarkers of iron overload[a]	
Tumor	Case–control	Prospective	Case–control	Prospective	Case–control	Prospective
Colorectal	2[b] (2[b])	8[b] (1) [2]		7 (2)		4 [3]
Breast	4	3 (1)		3		
Gastric	3 [1]	1	1	2 (1)		1
EAC		2 [1]	2 (2)	2	1 [1]	
Lung	1 (1)			3 (2)		
Endometrial		2 (1)		2 (1)		
Bladder				1		
Pancreatic		1		1		
Prostate				1		
Oral						1[c]

NOTE: n (n) [n]: n = number of studies, (n) = studies with a statistically significant positive association between exposure and cancer risk, [n] = studies with a statistically significant negative association between exposure and cancer risk.

[a]Biomarkers of iron overload refer to high levels of serum ferritin, transferrin saturation, toenail iron, and low levels of TIBC.

[b]Includes 1 case–control study and 3 prospective studies with total iron intake (with supplements).

[c]Serum ferritin statistically significant positive association with cancer risk and serum iron and transferrin saturation statistically significant negative association with cancer risk.

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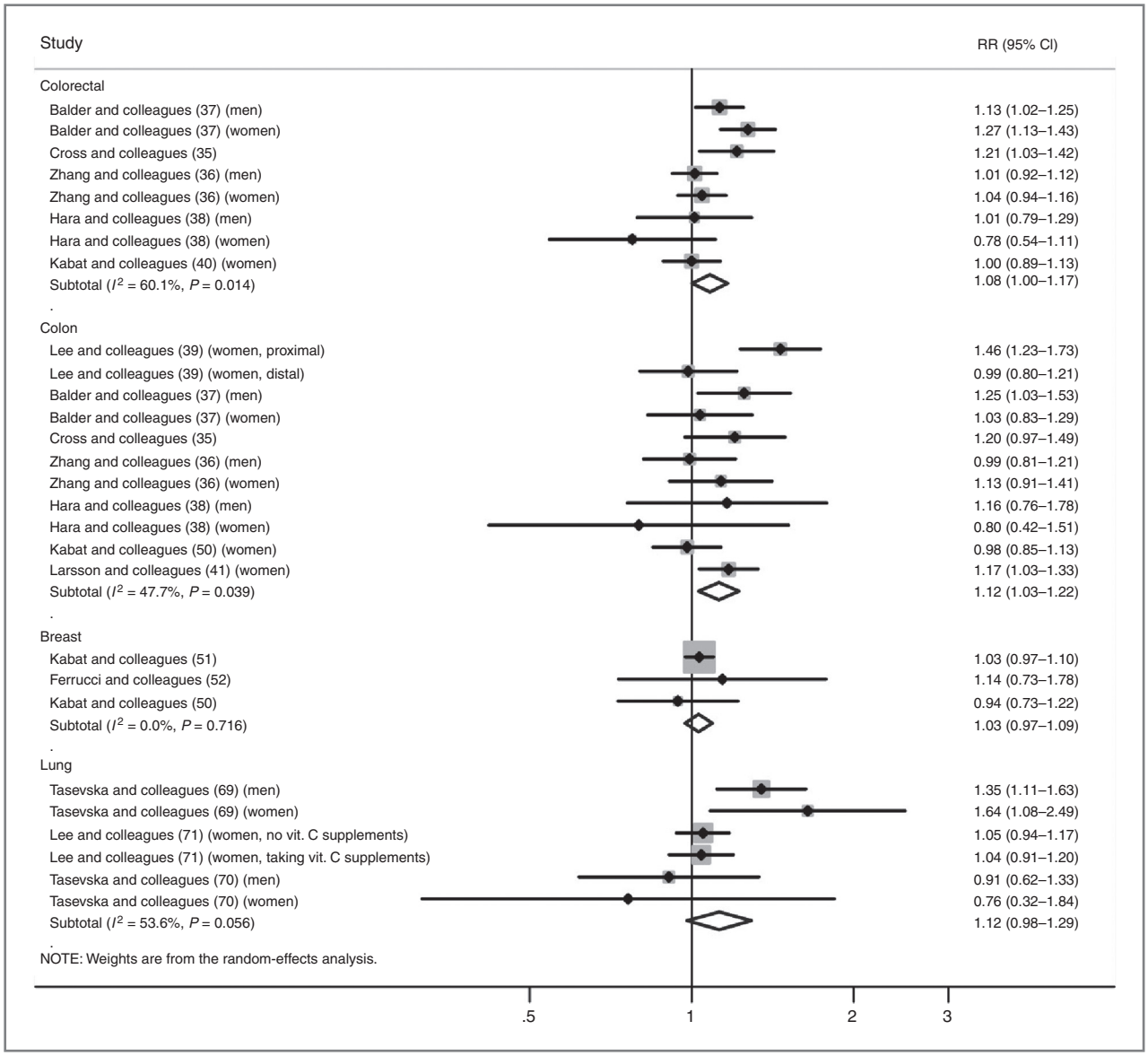

Figure 1. Meta-analysis of prospective studies on the risk of heme iron intake and selected tumor sites. Estimates shown in the figure are RRs for an increase of 1 mg/d in the intake of heme iron. Overall RRs for each cancer site estimated from a random-effects model. *I*-square is the percentage of variation attributable to heterogeneity (i.e., the proportion of between-study heterogeneity that is attributable to variability in the true effect of heme iron rather than sampling variation). *P* value tests the null hypothesis of homogeneity across studies.

studies (Fig. 1), we found a significant increase in risk of colorectal cancer of 8% (RR, 1.08; 95% CI, 1.00–1.17) for 1 mg increase in heme iron intake. Regarding colon cancer, a meta-analysis of 7 studies (including specific RR for colon reported in the 5 studies dealing with colorectal cancer), the corresponding RR was 1.12 (95% CI, 1.03–1.22). Our results are highly consistent with those from previous meta-analysis (18, 19). The latter (19) reported an RR of 1.11 (95% CI, 1.03–1.18) for 1 mg/d heme iron intake associated with colorectal and colon cancer (both outcomes combined) using the same prospective studies included in our meta-analysis.

Regarding body iron status, all studies had a prospective design. Three of 4 studies using serum ferritin as an indicator of high body iron stores showed an inverse relation [RR, 0.48; 95% CI, 0.27–0.88 (ref. 42); RR, 0.4; 95% CI, 0.2–0.9 (ref. 43); RR, 0.40; 95% CI, 0.2–0.8 (ref. 25)]. Overall, associations regarding dietary intake of iron and especially heme iron showed to be positive with colorectal and colon cancer risk. Information concerning iron biomarkers showed an unexpected negative association with risk of developing colorectal cancer.

Biologic plausibility behind the dietary iron–induced carcinogenesis relies first in the prooxidant role of iron, which may influence colorectal carcinogenesis by forming

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ROS (1) that can lead to DNA damage. Second, emerging evidence suggests that heme iron may play a more important role in colorectal carcinogenesis than other forms of iron (18, 47). Heme iron catalyzes the formation of *N*-nitroso compounds and lipid peroxidation end products, which partially explains the promotion effect of red and processed meat on colorectal cancer (18). Bingham and colleagues conducted a human experiment where they exposed male volunteers to high amounts of red meat or heme iron. They found that these individuals produced higher levels of fecal *N*-nitroso compounds than when exposed to the same amounts of white meat or ferrous iron (48, 49).

Breast cancer

From the 10 breast cancer studies gathered in this review (5 prospective and 5 case–control; refs. 50–56), the results obtained by the 2 biggest cohort studies [3,396 cases (ref. 50) and 2,545 cases (ref. 51)] did not show any associations between dietary iron and heme iron intakes and breast cancer risk. Another cohort study, with 1,205 cases, found a statistically significant positive association between dietary iron and breast cancer risk (RR, 1.25; 95% CI, 1.02–1.52; ref. 52). A meta-analysis of 3 prospective studies (Fig. 1) produced a small nonsignificant increase in risk associated with 1 mg of heme iron intake per day (RR, 1.03; 95% CI, 0.97–1.09). Globally, in relation to breast cancer, data obtained from these studies were heterogeneous and inconclusive. Furthermore, we did not find breast cancer studies with iron biomarkers data in the available literature. Despite not having found sufficient epidemiologic evidence on iron intake and breast cancer risk, there is a biologic plausibility behind it (57).

Gastric cancer

Eight studies (4 prospective and 4 case–control) gathered in this review researched the association between iron and gastric cancer risk (4 on dietary iron, 3 on heme iron, and 1 measured iron biomarkers; refs. 58–63). One of the biggest studies researching heme iron and gastric cancer risk (444 cases) was conducted within the European Prospective Investigation into Cancer and Nutrition Study (59) and found a statistically significant association between heme iron intake and gastric cancer risk, showing that subjects in the top quartile of heme iron intake had a 70% higher risk of developing gastric cancer than the lowest consumers (RR, 1.67; 95% CI, 1.20–2.34). A small case–control study with 92 cases (62) showed a statistically significant negative association between dietary iron and gastric cancer risk (OR, 0.41; 95% CI, 0.19–0.89). The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, which measured iron biomarkers in 341 cases, found a non-statistically significant decreased risk between iron deposits, given by serum ferritin, and gastric cancer risk (RR, 0.69; 95% CI, 0.44–1.09; ref. 60). Overall, the evidence is rather heterogeneous and insufficient to lead to any conclusions. Although there is a biologic plausibility between gastric cancer and iron intake (64–67), more studies are needed to better elucidate this possible relation.

Esophageal cancer

Seven studies researched the possible association between iron and esophageal cancer risk (26, 58, 63, 68): 2 case–control studies looked into dietary iron, 2 case–control and 2 cohort studies looked into heme iron, and 1 case–control measured iron biomarkers through toenail iron. The 2 studies on dietary iron showed opposite results, and the 1 with a statistically significant association, with the biggest number of cases ($n = 224$), showed a 50% decreased risk with higher intakes of iron (OR, 0.50; 95% CI, 0.25–0.98; ref. 26). The 2 case–control studies found a statistically significant positive association between heme iron and esophageal cancer (OR, 3.04; 95% CI, 1.20–7.71; ref. 63; and OR, 3.11; 95% CI, 1.46–6.61; ref. 26). Furthermore, 1 case–control study conducted a toenail iron analysis which showed a statistically significant 60% decreased risk of esophageal adenocarcinoma cancer (OR, 0.40; 95% CI, 0.17–0.93; ref. 26), contrasting the hypothesis that higher iron stores are a risk factor for esophageal adenocarcinoma. Overall, heme iron could play a positive role on esophageal adenocarcinoma cancer risk and evidence relating to dietary iron is insufficient. Furthermore, more prospective studies including iron biomarkers are needed to further investigate the relation between body iron stores and esophageal cancer risk.

Lung cancer

We found 4 studies on iron and lung cancer risk (1 case-control study on dietary iron and 3 prospective studies on heme iron; refs. 69–72). The NIH-AARP Diet and Health Study, a prospective study with 6,361 cases (69), showed a statistically significant positive association between heme iron intake and lung cancer risk but only in men (RR, 1.25; 95% CI, 1.07–1.45). The other statistically significant positive association was found in a case–control study with 923 cases using dietary iron as the exposure variable (OR, 1.45; 95% CI, 1.03–2.06; ref. 72). In the Iowa Women's Health Study, using a cohort with 700 cases, a positive association was found between heme iron and lung cancer risk, which became statistically significant with intakes of vitamin C higher than 700 mg (RR, 8.97; 95% CI, 1.29–62.51; ref. 71). In the meta-analysis of the 3 prospective studies on heme iron and lung cancer we estimated an RR of 1.12 (95%CI: 0.98–1.29) associated with an increased intake of 1 mg/d of heme iron. No studies were found concerning body iron status and lung cancer risk. The evidence gathered, although insufficient, seems to suggest a potential association of dietary iron and heme iron and lung cancer risk.

All the studies abovementioned adjusted for tobacco smoking, but none of them adjusted for other possible confounders, such as heterocyclic amines and polycyclic aromatic hydrocarbons. Several mechanisms might explain the positive associations found in the studies

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above mentioned. Redox-active iron has been detected in the epithelial lining fluid of the normal lung (73). In addition, in its nitrosylated form produced under alkaline conditions in the small bowel, heme iron can induce endogenous NOC formation, and, once absorbed, these compounds can have a systematic effect as tissue-specific carcinogens, directly or after metabolic activation (74). Grilling or barbecuing meat, the main source of heme iron, produces heterocyclic amines and polycyclic aromatic hydrocarbons, which are potent lung carcinogens (75, 76) and are also constituents of cured and smoked foods (77, 78). Furthermore, the plausibility behind the results found for the increased cancer risk with high dosage vitamin C supplementation is based on the fact that vitamin C can act as a prooxidant in the presence of redox-active iron (79, 80).

Other tumors

We also gathered information on other cancer types such as endometrial (81, 82), bladder (83), pancreatic (84), prostate (85), and oral cancers (86). This information can be found in Tables 1 and 2 and a summary of evidence in Table 4. As results on these other tumors were rather scarce, we did not describe them in detail.

General overview

Iron has gained, especially in the last decade, a remarkable place in the interest of the epidemiologic study of cancer. In this review, we were able to gather, systematize, and analyze a wide spectrum of information regarding recent findings on dietary iron, total iron, heme iron, and body iron status with cancer risk. The evidence proved to be heterogeneous according to cancer type, although the link between iron and carcinogenesis has been supported from molecular to epidemiologic studies (5). The debate surrounding the possible mechanisms by which dietary iron has a carcinogenic role has been ongoing for a long time. The first evidence considering dietary iron as a potential carcinogenic was provided by an experimental study conducted by Richmond and colleagues in the 1950s, which showed an induction of sarcoma in rats by injecting an iron–dextran complex (9). In the early 1980s, after the Committee on Diet, Nutrition, and Cancer of the National Research Council conducted a comprehensive evaluation of evidence on the role of dietary factors and carcinogenesis, data regarding dietary iron and carcinogenesis were associated more with iron deficiency than iron overload (87). Shortly after this evaluation process, Graf and Eaton proposed a first theory whereby dietary iron could be positively associated with colorectal cancer (88). In the 1990s, it was shown that the growth rate of tumor xenografts could be influenced by levels of dietary iron (89). Since then, results of *in vitro* studies and *in vivo* interventions in laboratory animals have consistently supported this theory (89–95). What is more, evidence surrounding patients with hemochromatosis has proven that the overload iron status, characteristic of this pathology, can also be a risk factor for several cancer types such as liver, colorectal, and breast (96).

In summary, in the last 60 years, a lot has been done, from molecular to epidemiologic research, to disentangle the different pathways in which dietary iron, and heme iron in particular, could play a role on carcinogenesis, as well as the discovery of new molecules involved in the crucial mechanism of iron homeostasis, such as hepcidin (97). These findings have outlined dietary iron as a potential carcinogen, with an increased risk of some cancer types being suggested in individuals with high iron stores (98–102).

Methodological issues

Study design. Globally, two thirds of the studies gathered in this review had a prospective design. There were the same number of case–control studies and prospective studies investigating dietary iron and cancer risk. It is worth indicating that the only 2 statistically significant negative associations were found in the case–control setting. Concerning heme iron research, there were 21 prospective and 3 case–control studies, and regarding body iron status there were 5 prospective and 2 case–control studies.

It is important to mention that results from case–control studies are less adept at showing a causal relationship than cohort studies. Another important limitation is the bias in the recruitment of cases or controls and in the measurement of their exposure, also called *recall bias* (103). Most case–control studies in this review referred to these limitations while discussing their results.

Dietary assessment. There are 2 major limitations concerning dietary assessment. The first one is related to food frequency questionnaires (FFQ). Most of the studies gathered in this review used FFQs (around 90%). It is well-accepted that FFQs are associated with exposure misclassification due to reporting error and imprecise portion size estimation (104). The second limitation lies in the fact that heme iron intake is usually determined indirectly, using 2 possible methods. One method uses the 40% of total iron from meat (20, 39, 105) and the second method uses meat specific proportions: 69% for beef; 39% for pork, ham, bacon, pork-based luncheon meats, and veal; 26% for chicken and fish; and 21% for liver (37). Recently, Cross and colleagues created a heme iron database for meats according to meat type, cooking method, and doneness level (21). Their data showed that heme iron values in different types of meat derived from the same animal showed varying heme iron contents. From the total number of studies researching heme iron intake and cancer risk (25 studies), 6 studies used the 40% of total iron from meat to estimate heme iron and 10 studies used the different animal specific proportions. In 2 studies (81, 82), the authors have used the different meat-specific proportions and also the 40% of total iron from meat as estimators of heme iron intake. Two studies did not

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provide information regarding the estimation of heme iron. Finally, 7 studies used the new NCI heme iron database (21). These later studies used only meat sources to estimate heme iron intake, obtaining lower levels of intake when compared with other studies that have included all food sources.

Another important limitation might have been the failure to take into account supplementation of iron. Only 3 studies in our review have considered total iron that represents the sum of iron from foods and supplements. In populations with low supplementation, results could be valid. Nevertheless, in a population like the United States, results simply could not be interpreted (106). Another important fact is that iron is extensively supplemented, not just voluntarily by intake of vitamin tablets but also through iron fortification in several foods from breakfast cereals to infant formulas to the flour used for baking. In the United States, where levels of supplementation are very high, mild iron deficiency is reported to occur in less than 1% in American men and less than 2% in American women (106).

Biomarkers of iron status. In this review, a small proportion of studies (7 of 56) measured biomarkers for iron status, mainly serum iron, serum ferritin, transferrin saturation, and TIBC. The evidence, especially with serum ferritin, seems to suggest a negative association of high body iron stores on the risk of developing cancer. Some older studies conducted in the late 1980s and early 1990s (not included in this review) supported a model in which increased levels of iron in the body, as measured by serum iron, transferrin saturation, and TIBC, were associated with increased cancer risk (107–109). The main limitation of these earlier studies was not having taken into consideration serum ferritin as a marker of iron status.

It is important to mention that there are several conditions that alter these measures up to 25% (age, gender, day-to-day variations, etc.). So, one single value, in a long-term follow-up study might not precisely reflect the iron stores of the subject over the length of time necessary for tumor initiation. If this alteration was entirely random, then one would expect this variation to bias the study toward null results. Despite these limitations, it has been suggested that human studies should incorporate serum or plasma measurements to overcome the methodologic limitation of dietary assessment (110, 111). Furthermore, there is controversy as to whether diet can dramatically influence body iron stores (43), as experimental studies have reported that dietary iron cannot induce iron overload (112–114). In our review, evidence with heme iron intake suggests a positive association with cancer risk, the opposite of what was found with body iron stores, and this is difficult to explain. One might argue that dietary heme iron acts in promoting the formations of (pre)carcinogens, for example, in the intestine, rather than via increased iron stores. Nonetheless, with the information available in this review, we are not able to explore in more depth this hypothesis.

There are emergent biomarkers that need to be taken into consideration. One of the most important recent discoveries in iron homeostasis is the ferroportin/hepcidin regulatory axis (115). Hepcidin became the leading candidate for the long-sought iron-regulatory hormone (116). Despite the importance of this hormone, no study gathered in this review took it into consideration. It is not our goal to enter in the mechanisms whereby hepcidin acts as an iron regulator, but a review of the past 10 years as the discovery of hepcidin can be found elsewhere (117).

Inflammation is also another relevant topic to debate. Most of the studies that looked into iron biomarkers did not take into consideration the C-reactive protein (CRP) (except refs. 43 and 60). The CRP is an acute-phase protein considered a prognostic marker of inflammation that is known to be associated with body iron stores. Furthermore, this protein is frequently overexpressed in invasive breast carcinomas (118) and it is possible that CRP behaves similarly in other cancer types.

Another possible factor to consider is vitamin C, an important enzyme cofactor that is known to enhance iron absorption, especially the non-heme type (119, 120). Vitamin C can quench ROS produced in the gastric environment, thus limiting free radical–mediated damage in the gastric epithelium (121), and it can scavenge nitrite, inhibiting *in vivo* nitrosation and the production of carcinogenic N-nitroso compounds (122). There were 2 studies that included vitamin C in their analyses. One of them found a positive association between heme iron and gastric cancer in subjects with low levels of vitamin C in plasma (59), whereas the other study found an important increased risk of lung cancer in postmenopausal women with higher intakes of heme iron and high dosage of vitamin C (71).

Strengths and limitations

In this comprehensive review of epidemiologic studies of iron and cancer risk, we were able to cover several measures of iron intake and iron status and several types of cancer. Furthermore, we conducted a meta-analysis of heme iron intake and colorectal and colon cancer risk, as well as breast and lung cancer. We also discussed some methodologic issues found among the studies gathered in the review. Nonetheless, this review presents some limitations. Any literature review faces the same 2 challenges, namely, the quality and completeness of the information included. The information included would be regarded as complete if all information pertinent to the objectives of the study was included, that is to say, no relevant data were excluded. However, we could not overcome the limitations present in each study, such as the type of biomarkers selected, the variables used for the adjustments in the statistical analysis and the methodology used to estimate iron intake.

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Final Remarks

Globally, on the basis of the systematic review and the meta-analysis results, a higher intake of heme iron has shown a tendency toward a positive association with cancer risk. Evidence regarding high levels of biomarkers of iron stores suggests a negative effect toward cancer risk. Prospective studies considering the complex interactions between all aspects related to iron metabolism including information on iron intake, markers of body iron stores, genetic susceptibility, and other related factors are needed to better understand the possible role of iron in human carcinogenesis.

Disclosure of Potential Conflicts of Interest

The funders were independent of the present research and did not influence the manuscript preparation. No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: A. Fonseca-Nunes, P. Jakszyn, A. Agudo
Development of methodology: A. Fonseca-Nunes, P. Jakszyn, A. Agudo
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Fonseca-Nunes, A. Agudo
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A. Fonseca-Nunes, P. Jakszyn, A. Agudo
Writing, review, and/or revision of the manuscript: A. Fonseca-Nunes, P. Jakszyn, A. Agudo
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Fonseca-Nunes, P. Jakszyn
Study supervision: A. Agudo, P. Jakszyn

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