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A case-control study on heme/non-heme iron and breast cancer risk

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Abstract

Background and purpose: Iron metabolism was found to be implicated in Breast Cancer (BC). Although dietary iron showed inconsistencies regarding its possible associations with BC risk, its source might be important. We have reported that an animal/plant ratio of dietary iron was directly associated to this risk. Based on estimates of heme and non-heme iron contents in representative foods, we carried out the present study, with the aim of more accurately reanalyzing dietary iron and its role on BC risk.

Methods: A case-control study was performed on 572 BC cases and 889 controls, using a specific multi-topic questionnaire including a food frequency questionnaire. Controls were age-frequency matched to cases. Food-derived nutrients were calculated from available databases. Total dietary iron was calculated according its heme or non-heme source, additionally adjusted by energy. Odds Ratios (ORs) were estimated by logistic regression, adjusting for potential confounders.

Results: Total iron intake was not associated with BC risk. Heme iron was positively associated among postmenopausal women and for the overall sample. Non-heme iron showed an inverse association among premenopausal women and the overall sample. Regarding heme/non heme ratio, risks tended to increase in all analyzed groups.

Conclusions: Although total dietary iron showed no association with BC risk, heme and non-heme iron actually did and a high heme/non-heme ratio was associated with a risk increase in both menopausal strata. Therefore, the source and the proportions of the available iron might be of importance as a link to breast carcinogenesis. Further studies are needed to clarify this point.

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Introduction

Breast Cancer (BC) is the leading malignancy among Uruguayan women [1], with the highest incidence rate in South America and close to North American figures [2]. The Uruguayan average diet is meat-based, with the World's highest per capita beef intake [3,4]. High intakes of red and processed meat are considered a risk factor for BC [5,6]. Although iron is essential for life, a western diet, with ~15 mg/day of iron might be epidemiologically linked to the increased development of tumors in humans [7]. Adult men absorb 8% and women 17% of dietary iron, on average [8].

Iron balance is achieved by careful control of its intake and recycling. Both heme (in red meat, fish, poultry) and non-heme (in plant foods, also in meat) dietary iron are mostly present as $Fe3^{+}$ (oxidized state) [9]. Non heme-iron is absorbed ~10%, and heme-iron ~30%. The latter consists of 95% of the functional iron in the human body, as well as 2/3 of the average person's iron intake in developed countries [10]. Non-heme iron absorption is less stringently regulated [11].

Dietary iron is stored in enterocytes as ferritin or either exits the cell and enters the circulation through ferroportin (FPT), the iron exporter protein found in macrophages, liver, breast and brain tissues [12]. Besides, the hormone known as hepcidin increases in high iron or inflammatory conditions and binds to FPT, causing iron to be stored in cells [13,14]. Iron has been associated to breast carcinogenesis; nevertheless the evidence about dietary iron and BC is still inconsistent [15-23]. Processed red meats are rich in added nitrite/nitrate, amines, and in heme-iron, which has also been implicated in BC etiology [14,18,24-26]. Several features of heme iron related to BC have been deeply analyzed in a recent study by Roe [27]. Evidence suggests that estrogens and iron are mutually influenced and they may act synergically [14,28]. As a constituent of the aromatase complex, heme-iron should be taken into account, since iron overload may enhance estrogen synthesis [29], a key factor in BC development.

We have previously reported that regarding dietary iron source, an animal/plant ratio was directly associated to BC risk [30]. Based on more accurate estimates of heme and non-heme iron contents in representative foods, we carried out the present study with the aim of more thoroughly analyzing dietary iron and its role on BC risk within a population featured by a western dietary style.

Subjects and methods

In order to perform the present analyses, we combined two databases, already used in epidemiologic studies on BC, which were carried out in Uruguay during 1996-2004 in the main state hospitals in Montevideo (Pasteur, Maciel, Clinicas, Oncology Institute) as well as in a private hospital (Institución Médica de Previsión y Asistencia, [IMPASA]). For this type of study, formal consent was not required. The studies were conducted after being authorized by Hospital Directors, who issued an ethical approval in each participant institution. Both databases, with a similar structure, enabled us to study a total sample of 1461 participants (572 BC cases, 889 controls). Each one of the samples is briefly described as follows.

Public hospitals

As a part of a multi-site epidemiologic research, during the study period, 480 incident BC cases were eligible for the study. Nineteen patients rejected an interview, leaving 461 cases to be included (response rate 96.0%). In the same time period and hospitals, 685 admitted patients afflicted with diseases unrelated to smoking and drinking were eligible for the study. 25 patients rejected the interview, leaving 667 controls (response rate 97.4%). Trained social workers interviewed patients in the hospitals shortly after admittance. No proxy interviews were conducted. Patients admitted in public hospitals were people with low incomes coming from all around the country, having free access to most medical services, as is mandatory by Uruguayan laws.

Private hospital

An epidemiologic study on BC conducted in 1999-2001 at a pre-paid medical institution in Montevideo (IMPASA), derived 116 incident BC cases and 223 controls women having a normal mammography (Breast Imaging Reporting and Data System [BI-RADS] 1) [31] ≤1 year before the interview. One control and two cases refused the interview and three cases were excluded for medical reasons, finally resulting in a data base of 111 cases and 222 controls (response rates: 95.7% and 99.6% respectively). They were age-matched (± 5 years). All participants, inhabitants of Montevideo (the capital city) were not staying at the hospital during the interviews. Women were <85 years old and belonged to mid-to-high socio-economic strata. Interviews were face-to-face conducted in a hospital office by a trained nurse, who was blinded concerning major risk factors.

Interviews and questionnaire

Participants answered a structured questionnaire which included socio-demographic variables; occupation; BC history in relatives of 1^{o}-2^{o} degree; self-reported height and weight 5 years prior to the interview; smoking and alcohol; history of 'mate', tea and coffee drinking; menstrual-reproductive events; and a food frequency questionnaire (FFQ) of 64 items, representative of the Uruguayan diet, focused on food consumption 5 years before the interview. Proxy interviews were not accepted. The FFQ was not validated, even though it was tested for reproducibility [32], allowing individual energy estimation. All dietary questions were open-ended. Local tables of food composition were used for estimating energy and nutrients [33].

We estimated heme iron intake using our FFQ and following previous dietary studies [34-36]. Heme iron was estimated by using its percentage of total iron in the following foods: 69% for beef, 39% for ham, bacon, mortadella, salami, hot dogs, saucisson and sausage, 26% for chicken, 21% for liver, and 26% for fish, eggs and milk. We calculated mean daily heme iron intake by multiplying consumption frequency by amount of total iron and the quoted percentages. Non-heme iron intake was calculated substracting heme iron intake from total iron.

In order to calculate energy, an analysis program was compiled, which made the sum of all individual values, each one obtained after multiplying the number of servings/year by the ratio calories of the serving/100 g of each, divided by 365 days. Most typical or average servings of solid foods are within the range of 100-150 g. Since iron intake showed high correlation with energy, we calculated an iron density expressed as daily mg of the mineral/kcal*1000.

Statistical analysis

Almost all questionnaire variables were originally continuous. When necessary, they were categorized for analysis purposes. Apart from basic descriptive analyses (frequencies, mean values), we calculated Odds Ratios (ORs) and 95% confidence intervals (95% CI) by unconditional logistic regression [37]. Also for analysis purposes and based on the original iron variables, a Heme/Non-Heme (H/NH) ratio was created. Terms for potential confounders were included in the multivariate analyses. Most equations included age, residence, education, Body Mass Index (BMI), menopausal status, family history of BC, smoking status, alcohol status, and intakes for total energy, red meat, total fruits, total vegetables, tea, 'mate' and coffee. Possible heterogeneities in the stratified analyses were explored through likelihood-ratio tests. STATA software was used to make all calculations (Release 10, Stata Corp LP, College Station, TX, 2007).

Results

Table 1 shows the distribution of cases and controls according to selected socio-demographic variables. Although participants were not completely matched, an adequate age distribution was achieved (p = 0.87). There were more rural cases than controls (12.9 % vs. 9.4%, resp.). Most traditional BC risk factors (family history of cancer, reproductive variables) displayed significant or marginal differences between cases and controls. On the other hand, educational level and BMI did not display differences.

Table 1: Distribution of cases and controls

Variables	Categories	Controls (%)	Cases (%)	Total (%)	Global p-value
Age groups	≤ 39	78 (8.8)	40 (7.0)	118 (8.0)	
	40-49	122 (13.7)	83 (14.5)	205 (14.0)	
	50-59	223 (25.1)	143 (25.0)	366 (25.0)	
	60-69	243 (27.3)	155 (27.1)	398 (27.2)	
	70-79	193 (21.7)	129 (22.5)	322 (22.0)	
	80-89	30 (3.4)	22 (3.8)	52 (3.6)	0.87
Health system	Public	667 (75.0)	461 (80.6)	1128 (77.2)	
	Private	222 25.0)	111 (19.4)	333 (22.8)	0.01
Education years	≤ 6	551 (62.0)	359 (62.8)	910 (62.3)	
	7-12	223 (25.1)	142 (24.8)	365 (25.0)	
	≥ 13	115 (12.9)	71 (12.4)	186 (12.7)	0.94
Residence	Urban	805 (90.5)	498 (87.1)	1303 (89.2)	
	Rural	84 (9.4)	74 (12.9)	158 (10.8)	0.03
Body Mass Index	≤ 24.99	389 (43.8)	238 (41.6)	627 (42.9)	
(kg/m2)	25.0-29.99	327 (36.8)	210 (36.7)	537 (36.8)	
	≥ 30.0	173 (19.5)	124 (21.7)	297 (20.3)	0.54
Fam.History of BC	No	811 (91.2)	450 (78.7)	1261 (86.3)	
	Yes	78 (8.8)	122 (21.3)	200 (13.7)	<0.001
Menopausal status	Pre	182 (20.5)	97 (17.0)	279 (19.1)	
	Post	707 (79.5)	475 (83.0)	1182 (80.9)	0.09
Age of menarche	≤ 11	207 (23.3)	138 (24.1)	345 (23.6)	
	12	273 (30.7)	145 (25.3)	418 (28.6)	
	13	175 (19.7)	136 (23.8)	311 (21.3)	
	≥ 14	234 (26.3)	153 (26.7)	387 (26.5)	0.09
Nº of live births	Nulliparous	111 (12.5)	104 (18.2)	215 (14.7)	
	1-2	394 (44.3)	252 (44.1)	646 (44.2)	
	≥ 3	384 (43.2)	216 (37.8)	600 (41.1)	0.006
Age at 1st live birth	≤ 20	281 (36.1)	150 (32.0)	431 (34.6)	
	21-26	304 (39.1)	173 (37.0)	477 (38.3)	
	≥ 27	193 (24.8)	145 (31.0)	338 (27.1)	0.054
Breastfeeding time	≤ 3	283 (31.8)	218 (38.1)	501 (34.3)	
(total months)	4-15	307 (34.5)	168 (29.4)	475 (32.5)	
	≥ 16	299 (33.6)	186 (32.5)	485 (33.2)	0.03
Total patients		889 (100.0)	572 (100.0)	1461 (100.0)	

Some selected lifestyle variables were analyzed and presented in Table 2. Energy, red meat and alcohol intake were directly and significantly associated to BC risk. On the other hand, fruits, vegetables, and the three infusions (coffee, tea and 'mate') were inversely and significantly associated to the risk.

Table 2: Crude Odds Ratios (OR) of selected consumptions linked to lifestyle.

Variable	Categories	Controls/cases	Global p-value	OR* (95% CI)	p-value for trend
Red meat	≤ 112	254/101			
(servings/year)	113-183	256/118			
	184-290	228/138			
	≥ 291	151/215	<0.001	3.58 (2.62-4.88)	<0.001
Fruits	≤ 218	207/159			
(units/year)	219-365	204/159			
	366-844	236/130			
	≥ 845	242/124	0.006	0.67 (0.49-0.90)	0.001
Vegetables	≤ 400	190/173			
(servings/year)	401-620	226/141			
	621-905	245/118			
	≥ 906	228/140	<0.001	0.67 (0.50-0.90)	0.003
Energy	≤ 1625	244/121			
(Kcal/day)	1626-1944	225/140			
	1945-2288	215/150			
	≥ 2289	205/161	0.02	1.58 (1.17-2.14)	0.002
Coffee	Never	607/431			
(Consumption)	Ever	282/141	0.004	0.70 (0.56-0.89)	0.004
Tea	Never	503/386			
(Consumption)	Ever	360/212	0.02	0.77 (0.62-0.95)	0.02
'Mate' intake	None	146/108			
(ml/day)	0.1-999	308/275			
	1000	267/122			
	>1000	168/67	<0.001	0.54 (0.37-0.79)	<0.001
Alcohol	Non drinker	759/451			
Status	Ex –drinker	26/34			
	Curr.drinker	104/87	0.002	1.41 (1.03-1.91)	0.007
Smoking	Non smoker	659/409			
Status	Ex –smoker	59/54			
	Curr.smoker	171/109	0.14	1.03 (0.78-1.34)	0.57

* Crude OR (highest vs. lowest category)

Table 3 compares mean dietary iron intake between cases and controls, in the whole sample and for each menopausal status. Total iron intake was quite similar in cases and controls, however, heme iron was higher among cases and non-heme iron was higher among controls. Cases showed a significantly higher H/NH ratio. Regarding menopausal status, all estimates among pre-menopausal women were very similar. The highly significant differences found in the postmenopausal subset explain the overall results described above.

Table 3: Estimated mean intakes ± standard deviation of heme iron, non-heme iron and heme/non-heme ratio (H/NH). Comparison between cases and controls.

		Total iron (mg/d)	Heme (mg/d)	Non Heme (mg/d)	H/NH ratio (%)
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Overall	All	6.99 ± 0.63	1.72 ± 0.63	5.27 ± 1.52	36.1 ± 18.9
	Controls	7.02 ± 1.46	1.67 ± 0.62	5.36 ± 1.47	34.3 ± 18.1
	Cases	6.93 ± 1.54	1.80 ± 0.63	5.14 ± 1.59	39.0 ± 19.7
	Dif.(p)	0.27	0.0001	0.008	<0.0001
Premenopausal	All	6.97 ± 1.40	1.87 ± 0.64	5.10 ± 1.41	40.3 ± 19.0
	Controls	6.99 ± 1.41	1.86 ± 0.66	5.12 ± 1.43	40.1 ± 19.7
	Cases	6.93 ± 1.37	1.89 ± 0.61	5.04 ± 1.38	40.6 ± 17.8
	Dif.(p)	0.76	0.76	0.66	0.83
Postmenopausal	All	6.99 ± 1.52	1.68 ± 0.62	5.31 ± 1.55	35.2 ± 18.7
	Controls	7.03 ± 1.48	1.61 ± 0.60	5.42 ± 1.48	32.8 ± 17.4
	Cases	6.93 ± 1.58	1.78 ± 0.64	5.16 ± 1.63	38.7 ± 20.0
	Dif.(p)	0.28	<0.0001	0.005	<0.0001

Table 4 shows the adjusted ORs of BC for different types of iron, among the overall sample and by menopausal status. Total iron showed lack of association. Heme iron was positively and significantly associated with BC among postmenopausal women and for the overall sample. Besides, non-heme iron showed a significant inverse association only among premenopausal women; the overall sample was marginally associated. Regarding H/NH ratio, risks tended to increase in all groups, although the trend was significant among postmenopausal women and close to significance among premenopausal ones.

Table 4: Adjusted Odds Ratios (ORs) of BC for dietary iron: total, heme, non-heme and heme/non-heme ratio (H/NH), with global estimations and stratified analyses by menopausal status. Likelihood ratio (Lr) tests for heterogeneity between strata of menopausal status.

		Intake levels of iron (mg/d)				
Iron		**I**	**II**	**III**		
		OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**Trend (p)**	**Lr test (p)**
Total		≤ 6.1	6.2-7.3	≥ 7.4		
(mg/d)	Overall	1.00 (---)	0.87 (0.65-1.17)	1.08 (0.77-1.51)	0.65	
	Premenopausal	1.00 (---)	1.47 (0.67-3.21)	0.93 (0.38-2.24)	0.83	
	Postmenopausal	1.00 (---)	0.79 (0.57-1.09)	1.11 (0.77-1.60)	0.60	0.42
Heme		≤ 1.39	1.40-1.94	≥ 1.95		
(mg/d)	Overall	1.00 (---)	1.12 (0.84-1.49)	1.51 (1.12-2.04)	0.006	
	Premenopausal	1.00 (---)	0.79 (0.35-1.74)	1.12 (0.53-2.35)	0.66	
	Postmenopausal	1.00 (---)	1.16 (0.85-1.58)	1.60 (1.15-2.24)	0.005	0.63
Non		≤ 4.53	4.54-5.66	≥ 5.67		
Heme	Overall	1.00 (---)	0.69 (0.51-0.94)	0.70 (0.47-1.05)	0.07	
(mg/d)	Premenopausal	1.00 (---)	0.48 (0.22-1.03)	0.22 (0.07-0.70)	0.01	
	Postmenopausal	1.00 (---)	0.72 (0.51-1.02)	0.80 (0.52-1.25)	0.30	0.94
H/NH		≤ 25.3%	25.4-41.3%	≥ 41.4%		
ratio	Overall	1.00 (---)	1.15 (0.85-1.56)	1.93 (1.35-2.74)	<0.001	
(%)	Premenopausal	1.00 (---)	1.15 (0.51-2.61)	2.07 (0.84-5.11)	0.09	
	Postmenopausal	1.00 (---)	1.14 (0.82-1.59)	1.99 (1.35-2.95)	0.001	0.62

Regression model including terms for: age (categoric), urban years (continuous), education years (categoric), family history of BC in 1st and 2nd relatives (categoric), menopausal status (binary), alcohol status (categoric), body mass index (categoric), age of first live birth (continuous), breastfeeding time (continuous), dietary energy (categoric), tea intake (binary), 'mate' intake (categoric), fruit intake (categoric), vegetable intake (categoric), vitamin C (continuous) and dietary fibre (continuous).

Table 5 shows adjusted ORs of BC for dietary iron, after performing analyses by strata of alcohol status, 'mate' intake and body mass index. Total iron showed a lack of association in all strata. Heme iron was positively associated with risk among alcohol consumers, low 'mate' consumers and overweight-obese women. Non-heme iron was found to be borderline protective among alcohol abstainers, not significantly protective at any level of 'mate' intake, and significantly inversely associated among normo-weight women. Finally, a high H/NH ratio tended to be directly associated to BC risk in most strata: significant trends were found regardless of the level of alcohol intake, at a low level of 'mate' intake and among overweight-obese women.

Table 5: Adjusted Odds Ratios (ORs) of BC for dietary iron (reference category omitted). Stratified analyses by alcohol status, 'mate' intake and body mass index (BMI).

			Exposure levels of each iron variable		
			II	III	Trend
	Stratified Variable	Categories	OR (95% CI)	OR (95% CI)	(p)
Total iron	Alcohol	Never	0.77 (0.55-1.06)	1.05 (0.73-1.53)	0.76
(mg/d)		Ever	1.59 (0.79-3.21)	1.29 (0.58-2.89)	0.50
	Mate	Low	0.89 (0.61-1.28)	1.18 (0.76-1.83)	0.50
		High	0.89 (0.53-1.50)	1.04 (0.60-1.80)	0.84
	BMI	NW	0.94 (0.58-1.51)	0.93 (0.56-1.57)	0.80
		OW-OB	0.84 (0.57-1.24)	1.30 (0.83-2.04)	0.28
Heme	Alcohol	Never	1.07 (0.78-1.46)	1.34 (0.96-1.87)	0.09
(mg/d)		Ever	1.53 (0.70-3.36)	3.12 (1.45-6.71)	0.003
	Mate	Low	1.08 (0.74-1.58)	1.95 (1.30-2.92)	0.001
		High	1.14 (0.73-1.79)	1.00 (0.62-1.61)	0.99
	BMI	NW	1.14 (0.75-1.73)	1.16 (0.73-1.84)	0.52
		OW-OB	1.16 (0.78-1.72)	1.87 (1.24-2.80)	0.002
Non Heme	Alcohol	Never	0.60 (0.43-0.85)	0.67 (0.43-1.04)	0.058
(mg/d)		Ever	1.28 (0.60-2.70)	0.87 (0.30-2.48)	0.91
	Mate	Low	0.80 (0.54-1.18)	0.78 (0.46-1.33)	0.32
		High	0.54 (0.31-0.92)	0.61 (0.31-1.21)	0.18
	BMI	NW	0.63 (0.38-1.03)	0.51 (0.28-0.94)	0.03
		OW-OB	0.78 (0.52-1.16)	0.93 (0.53-1.63)	0.69
H/NH ratio	Alcohol	Never	1.16 (0.83-1.62)	1.79 (1.20-2.65)	0.004
(%)		Ever	0.93 (0.41-2.11)	2.57 (1.05-6.29)	0.01
	Mate	Low	1.01 (0.67-1.53)	2.55 (1.58-4.13)	<0.001
		High	1.39 (0.87-2.20)	1.07 (0.60-1.91)	0.73
	BMI	NW	1.31 (0.84-2.05)	1.71 (0.98-2.96)	0.057
		OW-OB	1.06 (0.70-1.63)	2.08 (1.29-3.34)	0.001

Regression model including terms for: age (categoric), urban years (continuous), education years (categoric), family history of BC in 1st and 2nd relatives (categoric), menopausal status (binary), alcohol status (categoric), body mass index (categoric), age of first live birth (continuous), breastfeeding time (continuous), dietary energy (categoric), tea intake (binary), 'mate' intake (categoric), fruit intake (categoric), vegetable intake (categoric), vitamin C (continuous) and dietary fibre (continuous).

Abbreviations: NW: Normal Weight (BMI≤ 24.99); OW-OB: Overweight-Obese (BMI≥ 25.0)

Finally, Table 6 shows selected and reordered data from Table 4, with the aim of visually remarking the different degree of associations among iron type and the whole sample, as well as with menopausal strata.

Table 6: Summary of putative breast cancer risk associations for iron intake, derived from data presented in Table 4.
Risk associations for Iron intake

	TOTAL IRON	High Heme	High Non Heme	High Heme/Non Heme
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
All	1.08 (0.77-1.51)	1.51* (1.12-2.04)	0.70 (0.47-1.05)	1.93* (1.35-2.74)
Premenopausal	0.93 (0.38-2.24)	1.12 (0.53-2.35)	0.22* (0.07-0.70)	2.07 (0.84-5.11)
Postmenopausal	1.11 (0.77-1.60)	1.60* (1.15-2.24)	0.80 (0.52-1.25)	1.99* (1.35-2.95)

(*): statistically significant

Discussion

Our findings show a lack of association for total iron intake and BC risk in the whole sample (OR=1.08), among pre- (OR=0.93) and postmenopausal women (OR=1.11). Results are aligned to those of other authors [19,20,1,38]. Nevertheless, when total iron was dichotomized into heme and non-heme, opposite associations were found: Heme iron was directly and non-heme iron was inversely associated (OR=1.51 vs. OR=0.70, respectively) with the risk of BC. Different associations between heme- and non-heme iron and BC were already observed by other authors, who found that non-heme iron intake was significantly lower in cases than in controls [21]. Our study replicated the findings for non-heme iron (p=0.008) but heme iron was simultaneously different (p=0.0001).

Premenopausal women displayed particular features regarding their dietary iron source; whereas high heme iron intake did not increase BC risk, a high non-heme iron intake was inversely associated with the disease. Conversely, postmenopausal women showed a risk increase with high heme iron, but non-heme iron showed a lack of association. The associations can be summarized as follows (Table 6):

The calculated H/NH ratio displayed significant risk increases in the whole sample. Estimates were significant for postmenopausal and marginal for premenopausal women. However, strata were not heterogeneous. Inclusion of fruits and vegetables (as ascorbate and fiber contributors) and energy-adjusted iron (due to iron-energy collinearity) in the regression, allowed us to reduce possible confounding effects. To our knowledge, few comparable analyses of iron intake and BC, taking into account its source, have been conducted to date [25,30]. In those studies, the estimated animal- and plant-based iron as a proxy of heme- and non-heme displayed opposing effects. We reported then a positive association between BC risk and dietary iron, but only when the latter was expressed as an animal/plant iron ratio [30].

Given the low absorption, availability and better regulation of non-heme iron –the major part of dietary iron-, the existing associations with heme-iron might explain a potential damage exerted by certain amounts of it. The contributory role of iron in cancers could be mediated by over production of Reactive Oxygen Species (ROS) and free radicals through Fenton reaction (Fe^{2+} oxidized to Fe^{3+}), as well as participating in inflammation and DNA synthesis [17]. Moreover, since heme-iron is a component of the aromatase complex, an iron overload may enhance estrogen synthesis [29].

Although BC prevails in postmenopausal women, serum circulating estrogen concentrations are lower in post- than in premenopausal women but estrogen alone cannot explain the differences between both subgroups [39]. Whereas estrogen decreases because of the cessation of ovarian functions, iron increases as a result of decreasing menstrual periods. Potential health problems in women could be linked to increased iron storage during menopause, which is normal but not necessarily healthy [40]. A role for iron has been proposed in the pathogenesis of diseases such as diabetes, cancer and osteoporosis, among others [41].

Therefore, concerning the regulation of iron homeostasis, young women could be said to benefit from biology. First, iron losses produced by menstrual bleeding, systematically reduce the iron storage in premenopausal women. Second, these women bear a larger, more active muscle mass compared to postmenopausal ones, since skeletal muscle is a tissue which requires iron for its elevated mitochondrial activity and myoglobin production [42,43]. Together, iron losses together with larger and more active skeletal muscles mean lesser chances to have an iron excess. These differences have already been linked to BC development [14,39,44-46]. The axis iron-estrogen has recently gained force as a factor linked to an increase of BC incidence during the perimenopause [45].

Besides, ovarian proliferating granulosa cells have a requirement for iron, which is delivered by transferrin [47]. Transferrin exists in the follicular fluid at a relatively high level, suggesting an important role in the local regulation of ovarian functions, apart from its iron-binding characteristic [48]. At low doses, transferrin suppresses aromatase activity, attenuating the response of granulosa cells to follicule-stimulating hormone (FSH), therefore reducing estrogen synthesis [47]. However, above some critical transferrin levels, it might act as an anti-apoptotic, thus facilitating carcinogenesis [47].

A western dietary pattern, with high red and processed meat intake as well as the consumption of certain fat types [25], might overcome the naturally limited regulatory capabilities of the human body regarding heme iron homeostasis. Iron fortification of foods like flour should be reanalyzed, taking into account if the prevailing dietary style in a given society is of a western-type. Non-heme iron homeostasis can be regulated but not that for heme iron [49]. Therefore, fortification with ferrous sulphate might implicate several risks.

Concerning alcohol intake strata, we found no association for total iron but a direct one for heme iron in ever drinkers (OR=3.12), whereas non-heme iron lost its inverse association in this stratum. Therefore, alcohol drinking might be disadvantageous regarding both iron types. Results seem aligned with those by Lee [50], who found no overall association of dietary intake of iron or heme iron with BC risk, but reported an association for both among women who consumed ≥20 g/day of

alcohol. Conversely, a more recent cohort study found no association for the dietary intake of iron or heme iron with BC, without evidence of any effect modifications by alcohol [36].

Analyses of iron intake according to BMI strata showed that among overweight/obese participants, total iron was not associated to BC risk, but a significant increase for heme iron (OR=2.57) was found, and non-heme iron lost its negative association. Factors such as BMI, alcohol consumption and iron supplement use are critical determinants of body iron storage in postmenopausal women [14]. Besides, heme-iron is known to induce adipogenesis [51]. Excessive iron fosters oxidative stress and inflammation in obesity [52], whereas metabolic and immune disruptions featuring obesity are linked to perturbations in the hepcidin/ferroportin regulatory axis [53]. In adipose tissue, the enzyme heme oxygenase-1(HO-1) is increased [54]. HO-1, identified as a mediator for ROS-augmented proliferation in BC cells, plays several roles related to carcinogenesis [55,56].

The present study found that heme iron and H/NH ratio showed risk associations among low 'mate' consumers, but lost them among high 'mate' consumers. We had reported inverse associations between tea and 'mate' infusions on BC [57,58], in particular a stronger inverse association for high 'mate' intake in the strata of high red meat intake was described [57]. Despite other plausible explanations (antioxidant, anti-inflammatory and anti-aromatase activities), iron chelation should be considered. In support of this, a study on healthy subjects receiving ferrous sulphate showed that 'mate' infusion reduced by a 76% the absorption of this non-heme iron [59]. We cannot rule out that it could reflect the aforementioned iron-chelating effect; A high iron intake might be followed by a more intense chelation from high 'mate' intakes, a property shown by research [59,60]. According to our findings, this could be expressed as a stronger protection, but it deserves further research.

Therefore, modulating iron absorption could be convenient for individuals who have the habit of a meat-rich diet. Iron-chelating compounds possess anti-cancer activity, an effect largely attributed to ribonucleotide reductase inhibition in proliferating cells [61]. Since sixteen iron regulatory genes were found to be predictive of outcomes in BC, patients bearing tumors with low iron import and/or high iron export experienced more favorable prognoses [62]. Nevertheless, side effects and the toxicity of chelating agents as a cancer therapy are still problems to be solved [63,64]. With the same purpose, some foods and infusions like tea and 'mate' could exert beneficial actions through their polyphenols.

Regarding the potential benefits of tea, 'mate', fruits and vegetables on BC, some questions emerge: Do benefits derive from polyphenols and other antioxidants, or even from their content in chlorophyll? Is non-heme iron actually protective, or is it reflecting other components such as chlorophyll in plants? Chlorophyll's similar molecular structure to hemoglobin, but with magnesium instead of iron [65], might compete with the latter, protecting individuals from its relative excess. A recent meta-analysis showed a significantly inverse association between dietary magnesium and cancer risk [66]. This protection can be summarized as follows: antioxidant activity, mutagen trapping, regulation of detoxification pathways, and the induction of apoptosis in cancer cells [67]. Plants also contain other heme proteins, notably catalase and peroxidases, antioxidant enzymes which can convert ROS and inhibit oxidative DNA damage [68].

The ability of chlorophyll to modulate xenobiotic metabolizing enzymes and to induce apoptosis in cancerous cells could be useful in cancer prevention [67,69]. Chlorophyll can inhibit several cytochrome P450 enzymes [70]. It therefore seems reasonable that clorophyllll may block heme reactivity at different levels (gastrointestinal tract, adipose tissue, mammary gland), therefore partially preventing the formation of cytotoxic heme metabolites [35,71]. Chlorophyll also inhibits the carcinogenicity of compounds like benzo[a] pyrene, present in cooked meat [72]. In the past decade, de Vogel et al. hypothesized that chlorophyll prevented certain heme-induced cytotoxic effects on the epithelial cells on the colon surface, through a "sandwich" of heme with chlorophyll molecules [71], based on their π-π interactions, generating a hydrophobic complex. As a consequence, chlorophyll might inhibit the catalytic activity of heme in the generation of lipid hydroperoxides and the formation of a cytotoxic heme metabolite [73]. We hypothesize that if chlorophyll could block heme at the aromatase level, it might also decrease estrogen biosynthesis. It sounds biologically plausible, due to the place that iron occupies in the active site of the enzyme [74].

Our work shares some of the limitations and strengths that are commonplace in case-control studies. Among the limitations we recognize the lack of validation of the questionnaire, although the instrument was tested for reproducibility and showed good correlations [32]. Another limitation was related to the estimations of iron intake; they might not have been as accurate as desirable because they were based on average serving sizes and not on actual food sizes. Iron supplements were not part of the FFQ. We cannot exclude the possibility of confounding by other dietary factors, such as other constituents of animal foods or the effects of different cooking methods. Besides, although additional pathological information on BC (e.g. hormonal receptors) would have been useful, such data were unavailable since at the time of interviews they were not routinely requested by oncologists. Therefore, we were not able to make deeper analyses in search for interrelationships among dietary iron and those hormonal items.

As strengths of the study, the analyzed population included subsets coming from the whole country, and times of data collection were coincident. Although age matching was not perfect, the distribution was adequate. The potential for selection bias exists in our study, as in any case-control study, but such bias is unlikely to have substantially affected our results due to the overall high participation rates achieved in this study (~97%). Although it is quite difficult to completely avoid any kind of bias, including recall bias, we think that the results of the present study were not chance findings.

Conclusions

Although total iron intake showed no epidemiological association with BC risk, heme iron was positively associated among postmenopausal women and for the overall sample. Conversely, non-heme iron showed inverse associations among premenopausal women and for the overall sample. A high H/NH ratio was associated with a risk increase in both menopausal strata. Therefore, the source and the proportions of the available iron might be of importance for oxidant-generating processes, inflammation, DNA synthesis or for the aromatase complex as a link to breast carcinogenesis, but further epidemiologic and experimental studies are needed to clarify this point.

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