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Dietary Iron, 'Mate' Intake and Breast Cancer Risk: A Case-Control Study in Uruguay

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Abstract

Purpose: Albeit iron has been indicated as a tumor associated factor in breast carcinogenesis, the evidence about dietary iron and Breast Cancer (BC) is still inconsistent. The intake of 'mate', a staple infusion from *Ilex Paraguariensis* herb in temperate South America, showed inverse associations with BC risk. Experimental research revealed its antioxidant, hormonal and iron-chelating properties. Since no epidemiologic research has still addressed possible associations of BC with 'mate' and dietary iron, we performed the present study.

Methods: A case-control study was performed on 572 BC cases and 1.707 controls, using a specific questionnaire with a food frequency questionnaire (64 items) including infusions as tea, 'mate' and coffee. Controls were age-frequency matched to cases. Food-derived nutrients were calculated from available databases. Total dietary iron was calculated according to its animal or plant source, additionally adjusted by energy. Odds Ratios (OR) were estimated by logistic regression, adjusting for potential confounders.

Results: Total dietary iron was not associated with BC risk. However, high animal-based and plant-based iron intakes displayed different associations. An Animal/Plant Iron Ratio (APIR) revealed a risk increase among all women (OR=1.82), higher in pre-than in postmenopausal ones (OR=3.39 *vs*. OR=1.67, respectively). High 'mate' intake was inversely associated with BC risk (OR=0.41), even stronger in high than low APIR strata (OR=0.29 *vs* OR=0.59, respectively).

Conclusions: We report a positive association between BC risk and dietary iron, when it is expressed as an APIR. The higher the ratio, the stronger the inverse association of 'mate' intake on BC risk was. Our findings suggest possible benefits for the infusion in a western, meat-based dietary style, perhaps explained in part by iron chelation by 'mate' at the aromatase level, at oxidant-generating processes, or both things combined.

Keywords: Breast cancer; Chelation; *Ilex Paraguariensis*; Iron; Mate

Introduction

Breast cancer (BC) is the leading malignancy among Uruguayan women [1], with the highest incidence rate in South America [2]. The nutritional epidemiology of BC has been extensively studied in Uruguay [3,4]. Few years ago, a study on dietary patterns and ductal BC described a protective pattern based on 'mate' and tea infusions [5]. Later, we reanalyzed the subject and reported significantly reduced BC risks for high 'mate' intakes [6], also studied regarding dietary antioxidants intake [7] and from a hormonal viewpoint [8].

'Mate', a hot infusion made from the herb *Ilex Paraguariensis*, is a staple non-alcoholic beverage in temperate South America. Uruguay has the World's highest per capita 'mate' consumption (9-10 kg/person/year of the herb and ~400 liters/person/year of infusion) and over 80% of its inhabitants are 'mate' consumers [9]. International experts have considered 'mate' drinking as a possible carcinogenic for humans [10,11] but it will be soon reassessed [12]. Research revealed the presence of several antioxidant compounds (polyphenols, flavonols) in the infusion [13,14], showing comparable oxygen radical scavenger activity as ascorbate, glutathione and cysteine [15].

Although Uruguay is a developing country, its typical dietary style is meat-rich: it has not only very high red meat consumption [16], but also the World's highest per capita beef intake [17]. A high intake of red and processed meat has been found a risk factor for several cancer sites, including BC [18,19]. One possible consequence of a western diet, with ~15 mg/day of iron, is that its high levels have been epidemiologically linked to the increased development of tumors in humans [20]. The iron absorbed from the diet can vary from <1% to >50%. On average, adult men and women absorb 6% and 13% of dietary iron, respectively [21].

Systemic iron balance is maintained by careful control of iron intake and recycling. Both heme (only in red meat, fish, poultry) and non-heme (in plant foods, also in meat) dietary iron are largely present in the oxidized state (Fe^{3+}) [22]. Non heme-iron is absorbed ~10%, and heme-iron is absorbed ~30%. Unlike the former, the absorption of the latter is less stringently regulated in response to iron status, dietary inhibitors and enhancers [23]. In addition, heme constitutes 95% of functional iron in the human body, as well as 2/3 of the average person's iron intake in developed countries [24]. Dietary iron can either be stored in enterocytes in the form of ferritin or exit the cell and enter the circulation by the iron exporter protein ferroportin (FPT), which is found in macrophages, liver, breast and brain tissues [25]. Another protein, the hormone hepcidin, known as the master iron regulator, increases in high iron or inflammatory conditions and binds to FPT, degrading it and causing iron to be stored in cells [26]. Processed red meats are rich in added nitrite/nitrate, amines, and in heme-iron. The latter also enhances endogenous N-nitroso compounds formation and has been implicated in the etiology of BC [26-30]. Albeit iron has been indicated as a tumor associated factor in breast carcinogenesis, the evidence about dietary iron and BC is still inconsistent [30-35].

Deregulation in cellular iron homeostasis characterizes a malignant state, particularly by differences in the expression of iron-regulatory proteins, tending to show over expression of ferritin and hepcidin, and reduced FPT activity [22,25,36]. The contributory role of iron in cancers could be mediated by: overproduction of reactive oxygen species and free radicals through Fenton reaction (Fe^{2+} oxidized to Fe^{3+}), induction of oxidative stress-responsive transcriptional factors and pro-inflammatory cytokines, hypoxia signaling, and promotion of DNA synthesis driven by ribonucleotide reductase [36]. As a constituent of the aromatase complex, heme-iron (Fe^{3+}) should be taken into account, since iron overload may enhance estrogen synthesis [37], a key factor in BC development.

In addition to antioxidant and hormonal activity, research revealed iron-chelating properties of 'mate' [38]. After having reported a stronger inverse association for high 'mate' intake in the stratum of high compared to low red meat intake [6], we cannot rule out that it could be in part reflecting the afore mentioned iron-chelating effect: a high iron intake might be followed by a more intense chelation from high 'mate' intakes. According to the findings, this might be expressed as a stronger protection, but it deserves further research. Therefore, our aim was to explore possible epidemiologic associations between dietary iron and 'mate' intake, regarding the risk of BC.

Patients and Methods

In order to perform the present analyses, we combined two databases, already used in epidemiologic studies on BC which were conducted in Uruguay by us during 1996-2004 in the major public hospitals of Montevideo (Pasteur, Maciel, Clinicas, Oncology Institute) and in a private hospital. For this type of study formal consent was not required. The study was conducted after receiving the approval of each Medical Director belonging to the involved hospitals, following an ethical approval in each institution.

As a consequence of the most severe financial crisis in the story of our country which took place in the early 2000s, epidemiologic research on cancer in Uruguay continued with the remaining data bases-as the ones used for the present study-and without funds to update, increase or improve them. It would have been desirable to count on information about cancer stages at the moment of diagnosis as well as on hormonal receptors, for example. However, such data were unavailable as at the time of interviews and they were not routinely requested. Both databases had the same basic structure, allowing us to analyze a total sample of 2279 participants, 572 BC cases and 1707 controls. Each one is briefly described as follows.

Public hospitals

In the study period 480 newly diagnosed, microscopically confirmed BC cases were considered eligible for the study, which was a part of a large multi-site research focused on nutritional epidemiology of cancer. Nineteen patients refused the interview, leaving a final number of 461 cases to be included (response rate 96.0%). In the same time period and hospitals, 1510 hospitalized patients afflicted with diseases unrelated with smoking and drinking and without recent dietary changes were considered eligible for the study. Twenty five patients refused the interview, leaving 1485 controls (response rate 97.7%). Trained social workers interviewed patients in the hospitals between 1-10 days after admittance; no proxy interviews were conducted. Patients admitted in public hospitals belonged to low-to-mid socio-economic strata from the whole country, and they have free access to most medical services.

Private hospital

On the other hand, an independent epidemiologic study focused on BC was carried out in the years 1999-2001. In the study period 116 verified cases of BC and 223 healthy women with a normal mammography [39], performed ≤ 1 year before the interview, were selected as controls (2 controls per case) at a pre-paid medical institution in Montevideo (IMPASA). One control and two cases rejected the interview and three cases were excluded for medical reasons, therefore leading to a final number of 111 cases and 222 controls (response rates: 95.7% and 99.6% respectively). They were age-matched (± 5 years). All participants, inhabitants of the capital city Montevideo and close neighbourhoods, were not hospitalized at the moment of the interview. Women were <85 years old, they underwent routine mammography testing and belonged to mid-to-high socio-economic strata. Interviews were conducted in the hospital and performed face-to-face by a trained nurse, who was blinded concerning major risk factors.

Interviews and questionnaire

Participants asked a structured questionnaire which included: socio-demographic variables; occupation; BC history in 1° and 2° degree relatives; self-reported height and weight 5 years before the interview; smoking and alcohol; history of 'mate', tea and coffee drinking (age at starting and quitting, average daily amount of the infusion drunk); menstrual-reproductive events; and a detailed food frequency questionnaire (FFQ) on 64 items, representative of Uruguayan diet, which asked about food consumption 5 years prior to the interview. The FFQ was not validated, but was tested for reproducibility [40], allowing the estimation of total energy for each subject. All dietary questions of our semi-quantitative questionnaire were open-ended. To calculate energy, we compiled an analysis program using servings/year and kilocalories of each food. In the case of iron intake, since it showed high correlation with energy, we calculated an iron density expressed as daily mg of the mineral/kcal*1000. Local tables of food composition were used in order to estimate energy and nutrients [41]. Proxy interviews were not accepted.

Statistical analysis

Most questionnaire variables were originally continuous and when necessary they were categorized for analysis purposes. In order to analyze the association between exposure levels and the disease, we estimated Odds Ratios (ORs) and 95% confidence intervals (95% CI) for each interest variable, which were calculated by unconditional logistic regression [42]. Potential confounders were included in the multivariate analyses. Most equations included terms for age, residence, education, Body Mass Index (BMI), menopausal status, family history of BC in 1° and 2° degree relatives, smoking status, alcohol status, and total energy intake, intakes of red meat, total fruits, total vegetables, tea and coffee. A term for 'mate' intake was included in the analyses of iron intake. Likelihood-ratio tests were performed in order to explore possible heterogeneities in the stratified analyses. All calculations were done with the software STATA (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=0.66). There were more rural than urban cases (13.1% *vs* 10.7%, respectively), and educational level was significantly higher in cases compared to controls. Some nutritional factors (dietary energy, alcohol status, 'mate' intake) displayed significant differences between cases and controls, although BMI did not.

Table 2 compares mean iron intake between BC cases and controls, either for the whole sample or for each subset of menopausal status. Cases tended to have higher iron intake, and differences are based on animal source and postmenopausal subset. Conversely, plant-based iron displayed non significant higher intake among controls compared to cases, but this occurred only in postmenopausal women.

Table 1: Distribution of cases and controls by selected variables

Variable intake	Categories	Controls	%	Cases	%	Global p-value
Age, years	<40	104	6.1	40	7.0	
	40-49	217	12.7	83	14.5	
	50-59	409	24.0	143	25.0	
	60-69	474	27.8	155	27.1	
	70-79	428	25.1	129	22.5	
	≥ 80	75	4.4	22	3.8	0.66
Residence	Urban	1525	89.3	497	86.9	
	Rural	182	10.7	75	13.1	0.11
Education, years	≤ 6	1230	72.1	359	62.8	
	7-12	355	20.8	142	24.8	
	≥ 13	122	7.1	71	12.4	<0.001
BMI kg/m^2	≤ 24.99	705	41.3	238	41.6	
	25.0-29.99	636	37.3	210	36.7	
	≥ 30.0	366	21.4	124	21.7	0.97
Menopausal status	Premenopause	294	17.2	97	17.0	
	Postmenopause	1413	82.8	475	83.0	0.88
Family History BC	No	1609	94.3	445	77.8	
	Yes	98	5.7	127	22.2	<0.001
Energy (kcal/day)	≤ 1604	459	26.9	110	29.2	
	1605-1954	408	23.9	161	28.1	
	1955-2329	424	24.8	149	26.0	
	≥ 2330	416	24.4	152	26.6	0.003
Alcohol status	Non drinker	1432	83.9	451	78.8	
	Ever drinker	275	16.1	121	21.2	0.006
'Mate' intake (l/day)	Non drinker	257	15.9	108	18.9	
	0.01-0.99	650	38.1	275	48.1	
	1.00	479	28.1	122	21.3	
	≥ 1.1	326	18.8	67	11.7	<0.001
Total participants		1707	100.0	572	100.0	

BMI=Body Mass Index

Table 2: Mean values of dietary iron (mg/day) ± standard error. Global and stratified values by menopausal status

Subset	Iron source	Controls Mean ± SD	Cases Mean ± SD	Difference (p-value)
All	Total	13.6 ± 4.9	14.4 ± 5.0	0.002
	Animal-based	5.2 ± 2.6	5.9 ± 2.4	<0.001
	Plant-based	8.1 ± 3.4	7.8 ± 3.4	0.13
Premenopause	Total	14.0 ± 5.3	14.8 ± 3.9	0.17
	Animal-based	5.8 ± 3.3	6.3 ± 2.3	0.14
	Plant-based	8.0 ± 3.6	8.1 ± 3.2	0.84
Postmenopause	Total	13.5 ± 4.8	14.3 ± 5.2	0.005
	Animal-based	5.1 ± 2.4	5.8 ± 2.5	<0.001
	Plant-based	8.1 ± 3.4	7.8 ± 3.4	0.08

Dietary iron is analyzed in table 3. Crude and adjusted OR's of total iron intake, as well as estimates according to its animal-or plant-based source are presented, also stratified by menopausal status. Globally considered, total iron was not associated to BC risk neither in pre-nor in postmenopausal subsets. Except for a non significant risk increase among premenopausal women, the same applies to animal-based iron. Conversely, plant-based iron displayed inverse associations with BC risk in all the analyses. The adjusted estimates were statistically highly significant for the whole sample and the postmenopausal subset (p_{trend}<0.001 in both cases), but not among premenopausal subset (p_{trend}=0.11).

Regarding the aforementioned trends, we created an animal/plant iron ratio (APIR) and analyzed its associations with BC risk, which are shown in table 4. The three analyses displayed significant positive associations for a high APIR, all of them having significant trends. The OR=1.82 for the whole sample is composed by an OR=3.39 in premenopause and an OR=1.67 in postmenopause. In spite of this difference, a heterogeneity test was not significant (lrtest, p=0.16). In other words, given the proportions of each category, when the animal iron fraction exceeded>85% the one of plant iron, BC risk increased significantly compared to the reference APIR of ≤ 52%.

Table 5 displays the adjusted OR's of BC for 'mate' intake (in liters/day), stratified by dietary APIR. For purpose analysis, APIR was dichotomized into Low/High by the median value (0.6370). Regarding the whole sample, 'mate' drinking was inverse-and significantly associated to BC risk (OR=0.41, p_{trend}<0.001). The association was stronger in the high APIR strata than in the low one (OR=0.29 *vs.* OR=0.59 respectively), but without heterogeneity (lrtest, p=0.14). Considering menopausal status, stratified analyses revealed apparently stronger benefits for high 'mate' intake within a high APIR in the premenopausal than in the postmenopausal subset (OR=0.14 *vs.* OR=0.32, respectively), but without heterogeneity between both sub groups (lrtest, p=0.76).

Discussion

Regarding total iron intake and BC risk, our findings report lack of association (OR=0.94) for the whole sample, which is aligned to results of other authors [31,32]. When total iron was dichotomized into animal (partially heme-iron) and plant-based (non heme-iron), the same applies to animal-based iron (OR=1.03). Conversely, plant-based iron displayed an inverse association with BC risk in all the analyses (OR=0.60).

Different associations between heme-and non-heme iron and BC were already observed [33]. These authors found that non-heme iron intake was significantly lower in cases than in controls. Our study reports something similar for plant-based iron, but with non-significant differences (whole sample p=0.13, premenopausal women p=0.08). Given the low absorption and availability of non-heme iron the major part of dietary iron, then the existing difference in animal-based (partially heme) iron might explain a harmful effect of certain amounts of this mineral.

Given these different associations of iron, we calculated an animal/plant ratio for dietary iron (APIR), which displayed significant risk increases in the whole sample and also for each menopausal status, all of them with significant trends. The inclusion of terms for red meat (as a major iron contributor), fruits and vegetables (as ascorbate and fiber contributors) and energy-adjusted iron (due to iron-energy co linearity), allowed us to reduce the chances of confusion in our results. Although this APIR is not exactly a heme/non-heme ratio, it gives us an indirect idea of proportions for both types. We found a risk increase when the quoted ratio overcomes 0.85 compared to the reference category (≤ 0.52). In other words, a low-risk range for dietary iron could be the one including half or less (≤ 52%, the reference category) of animal-based iron from the total intake. To our knowledge, similar analyses of iron intake and BC were not performed before.

After that, our risk estimations for 'mate' intake (OR=0.41 for the highest *vs.* the lowest quartile, p_{trend}<0.001) were rather similar to those previously reported. The present findings, however, indicate that such effect was stronger among strata of high APIR iron compared to low strata (OR=0.29 *vs.* OR=0.59 respectively). This potential protective effect was found even better in pre than in postmenopausal women (OR=0.14 and OR=0.32, respectively). Estimates for both menopausal stata were statistically significant, but without heterogeneity between them (lrtest, p=0.76).

Table 3: Breast cancer crude and adjusted OR's for total dietary iron and according to animal or plant-based source, stratified by menopausal status

Subset	Dietary Iron	Categories	Controls /cases	OR[a]	95% CI	OR[b]	95% CI
All	**Total iron**	≤ 6.182	568/192	1.00	----	1.00	----
		6.183-7.305	585/175	0.88	0.70-1.12	0.81	0.63-1.05
		≥ 7.306	554/205	1.09	0.87-1.38	0.94	0.72-1.22
	Trend			*p=0.43*		*p=0.62*	
	Animal-based	≤ 2.252	596/165	1.00	----	1.00	----
		2.253-2.999	584/175	1.08	0.85-1.38	0.83	0.61-1.13
		≥ 3.000	527/232	1.59	1.26-2.00	1.03	0.69-1.52
	Trend			*p<0.001*		*p=0.79*	
	Plant-based	≤ 3.407	512/248	1.00	----	1.00	----
		3.408-4.405	580/180	0.64	0.51-0.80	0.68	0.53-0.86
		≥ 4.406	615/144	0.48	0.38-0.61	0.60	0.46-0.79
	Trend			*p<0.001*		*p<0.001*	
Premenopause	**Total iron**	≤ 6.182	95/29	1.00	----	1.00	----
		6.183-7.305	92/34	1.01	0.53-1.96	1.20	0.62-2.33
		≥ 7.306	107/34	0.93	0.49-1.78	0.97	0.49-1.90
	Trend			*p=0.93*		*p=0.90*	
	Animal-based	≤ 2.252	88/22	1.00	----	1.00	----
		2.253-2.999	83/25	1.20	0.63-2.30	1.03	0.44-2.42
		≥ 3.000	123/50	1.63	0.92-2.88	1.61	0.59-4.42
	Trend			*p=0.08*		*p=0.29*	
	Plant-based	≤ 3.407	94/44	1.00	----	1.00	----
		3.408-4.405	95/30	0.67	0.39-1.16	0.76	0.41-1.43
		≥ 4.406	105/23	0.47	0.26-0.83	0.58	0.29-1.14
	Trend			*p=0.009*		*p=0.11*	
Postmenopause	**Total iron**	≤ 6.182	473/163	1.00	----	1.00	----
		6.183-7.305	493/141	0.83	0.64-1.07	0.74	0.56-0.98
		≥ 7.306	447/171	1.11	0.86-1.43	0.93	0.70-1.24
	Trend			*p=0.41*		*p=0.62*	
	Animal-based	≤ 2.252	508/143	1.00	----	1.00	----
		2.253-2.999	501/150	1.06	0.82-1.38	0.79	0.57-1.09
		≥ 3.000	404/182	1.60	1.24-2.07	0.91	0.59-1.40
	Trend			*p<0.001*		*p=0.74*	
	Plant-based	≤ 3.407	418/204	1.00	----	1.00	----
		3.408-4.405	485/150	0.63	0.49-0.81	0.67	0.51-0.87
		≥ 4.406	510/121	0.49	0.37-0.63	0.60	0.45-0.79
	Trend			*p<0.001*		*p<0.001*	

Iron intake expressed as daily mg/kcal*1000
[a]Crude OR[b] Adjusted OR Regression model included: outcome, age, urban years, education years, menopausal status, family history of BC, body mass index, smoking status, alcohol status and intakes of: red meat, fruits, vegetables, 'mate', tea, coffee and energy

Table 4: Breast cancer adjusted OR's for dietary animal/plant iron ratio (APIR)

Subset	APIR Categories	Controls /Cases	OR	95% CI	Trend
All	Low	614/147	1.00	---	
	Mid	589/170	1.07	0.80-1.43	
	High	504/255	1.82	1.30-2.53	p<0.001
Premenopause	Low	93/16	1.00	---	
	Mid	94/32	2.54	1.11-5.79	
	High	107/49	3.39	1.34-8.59	p=0.01
Postmenopause	Low	521/131	1.00	---	
	Mid	495/138	0.94	0.68-1.28	
	High	397/206	1.67	1.17-2.40	p=0.003

Categories: Low ≤ 0.528; Mid 0.529-0.852; High ≥ 0.853
Regression model included: outcome, age, urban years, education years, menopausal status, family history of BC, body mass index, smoking status, alcohol status and intakes of: red meat, fruits, vegetables, 'mate', tea, coffee and energy.
Heterogeneity test (likelihood ratio test) for menopausal status p=0.16

Table 5: Breast cancer adjusted OR's for 'mate' intake stratified by dietary Animal/Plant Iron Ratio (APIR) levels (dichotomized)

		I			II		III		IV		
	APIR	ND			0.01-0.99		1.00		≥ 1.1		
Subsets	strata	n	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	Trend
All	-----	2279	1.00	---	0.97	0.72-1.32	0.55	0.40-0.78	0.41	0.28-0.60	<0.001
All	Low	1140	1.00	---	0.91	0.59-1.41	0.64	0.42-0.99	0.59	0.35-0.99	0.01
	High	1139	1.00	---	0.88	0.56-1.38	0.41	0.25-0.68	0.29	0.16-0.51	<0.001
Premenopause	Low	177	1.00	---	1.54	0.40-5.96	0.64	0.14-2.85	2.30	0.53-10.1	0.47
	High	214	1.00	---	0.82	0.24-2.83	0.32	0.07-1.35	0.14	0.03-0.66	0.001
Postmenopause	Low	962	1.00	---	0.87	0.54-1.39	0.65	0.41-1.03	0.45	0.25-0.82	0.004
	High	925	1.00	---	0.91	0.56-1.49	0.42	0.24-0.74	0.32	0.17-0.61	<0.001

Regression model included: outcome, age, urban years, education years, menopausal status, family history of BC, body mass index, smoking status, alcohol status and intakes of: red meat, fruits, vegetables, tea, coffee and energy.
APIR levels: Low ≤ 0.67370
High ≥ 0.67371
Heterogeneity test (likelihood ratio test): for APIR>p=0.14; for menopausal status>p= 0.14

A previous paper [6] reported a stronger association for high 'mate' intake in the stratum of high red meat intake (OR=0.31, p_{trend}<0.001) compared to that of low red meat intake (OR=0.67, p_{trend}=0.13). Regarding the current results, we might consider that such findings could probably in part reflect the aforementioned iron-chelating effect of 'mate', something that deserves further research. Anyway, in spite of the present findings, the antioxidant, anti-inflammatory and antiproliferative capabilities of 'mate' should be taken into account, and their combination together with chelating capabilities might partially explain our results.

There is considerable epidemiologic support for the benefits of consuming plants (mainly fruits and vegetables) rich in antioxidants, in particular polyphenols, since most polyphenolic compounds (flavones, anthocyanidins, among others) have not only antioxidant properties, but they may also chelate iron [43]. 'Mate' infusion can be included into this combined category, according to recent research [38]. Experimental research performed in the most recent years mainly by Brazilian investigators has expanded the knowledge about *Ilex Paraguariensis* beneficial components and properties which can be related to cancer [44-50].

In addition, anti-aromatase activity of 'mate' is of obvious convenience regarding BC prevention and/or treatment [51]. Iron chelators are investigated as potential new anti-cancer therapies that beyond iron sequestration from rapidly proliferating cancer cells, also affect expression of diverse genes including those involved in cell cycle control [52,53].

Iron was already studied and proposed as a risk factor for rectal cancer in Uruguayan population (OR for the highest tertile=3.18; 95% CI=1.92-5.29) [54]. A recent research on the intake of hot beverages and colorectal cancer risk showed a modest protective effect of high 'mate' consumption but restricted to women [55]. Despite a potential hormonal role for the infusion, dietary iron might be influenced by 'mate'. Tseng et al. [56] found that colorectal adenoma recurrence was inversely associated with iron intake, but they noted that there was very low meat intake in the study population and iron intake was highly correlated with dietary fiber (Pearson r=0.70), which may explain the inverse association. That study suggested potential benefits if dietary iron is derived from plant sources as opposed to meat, or perhaps the benefit is purely supported on the absorption decrease caused by fiber. Ashmore et al. [57] remarked the need to account for the iron source to clarify the relation between its intake and CRC. In this sense, we think that the plant/animal index created in the present research on BC is useful as an attempt of establishing differences between both sources.

As other case-control studies, our work shares limitations and strengths. Among limitations we recognize the lack of validation of the questionnaire, although the instrument was tested for reproducibility and showed good correlations [40]. Another limitation was related to 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 sizes of foods. Besides, although additional pathological information of BC (e.g. hormonal receptors) would have been extremely 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 'mate' intake, dietary iron and those hormonal items.

Besides, control population displayed somehow different profiles: hospitalized participants belonged to the public system and non hospitalized ones to the private system. All of them shared a common condition: absence of any cancer. The latter subgroup (a minor fraction) had also documented absence of breast pathology. Thus, having selected as controls women with normal mammograms and not only without cancer, we reduced at least in part the likelihood of biasing results if benign breast diseases had any association with the analyzed dietary items.

Also to be mentioned as strengths, the study population included subsets proceeding from the whole country, and times of data collection were coincident. Although age matching was not perfect, the distribution was adequate. Finally, a high participation was achieved (~97% of patients), reducing the likelihood of selection bias. Albeit it is not possible to avoid completely any bias, including recall bias, we think that results were not chance findings.

Conclusions

We reported a positive association between BC risk and dietary iron, but only when the latter was expressed as an animal/plant iron ratio. In addition, the higher this ratio, stronger the inverse association of 'mate' intake on BC risk was. Our findings suggest possible benefits for the infusion within a meat-based dietary style as the western one. Whether this hypothetical protection could be partially explained by chelating activity of 'mate' on the iron at the aromatase level, at oxidant-generating processes, or even both things combined, is something that requires further research. Both the plant and the infusion have several favorable components which can operate in a protective synergy against BC development, involving actions beyond dietary iron.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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