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Dietary Iron Sources and Colorectal Cancer Risk: A Role for Sex

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ABSTRACT

Background and purpose: As in many countries, Colorectal Cancer (CRC) incidence and mortality in Uruguay show increasing trends among men but relative stability among women. Dietary iron has shown inconsistencies regarding the CRC risk. Based on iron contents in representative foods, we carried out the present study, in order to accurately analyzing dietary iron and its role in CRC risk.

Subjects/methods: A case-control study was performed on 611 CRC incident cases and 2394 controls, using a specific multi-topic questionnaire including a food frequency questionnaire. The sample included 1937 men and 1068 women. Controls were matched by sex and age (± 5 years) to cases. Food-derived nutrients were calculated from available databases. Dietary iron was calculated according to its heme or non-heme source, additionally adjusted by energy. Odds Ratios (OR) was calculated through unconditional logistic regression, adjusting for potential confounders. Animal/plant and heme/non-heme (H/NH) ratios were created for analysis purposes.

Results: Total iron intake was inversely associated with CRC risk among men (OR=0.65 for 3rd vs. 1st tertile). Heme-iron was inversely associated among women (OR=0.47). Plant-based and non-heme-iron showed an inverse association among men (OR=0.62 and OR=0.60, respectively). Animal-based iron lacked risk association, suggesting opposite trends between sexes. The Animal/Plant iron ratio was directly associated with CRC risk among men (OR=1.77) and inversely associated among women (OR=0.51). The same occurred to the H/NH ratio, whose risks increased among men (OR=1.53) but decreased among women (OR=0.53).

Conclusion: Dietary iron showed different associations with CRC risk, regarding iron source and sex. The available iron type, due to its wide hormonal, red-ox, and metabolic interactions, might play also different roles linked to colorectal carcinogenesis. Nevertheless, the different associations observed for each sex demand further studies to clarify this point.

Keywords: Aromatase, Chelation, Colorectal cancer, Estrogens, Heme, *Ilex paraguariensis*, Iron, Non-heme

INTRODUCTION

Colorectal cancer (CRC) is the most frequent malignancy in the Uruguayan population, taking into account both sexes combined [1]. The age-adjusted incidence and mortality rates locate Uruguayan men at top of the list in America and very high in the world's ranking [2]. However, mortality trends change annually in +0.3% among men but a -0.5% among women through 1990-2017 [1].

Processed and red meats are considered as major risk factors for CRC [3,4] and base their implication in colorectal carcinogenesis on some of their own or added components like fats, Heterocyclic Amines (HCA), nitrosodimethylamine and heme-iron [3,5,6]. Although Uruguay is a developing country, its average diet is meat-based, with the world's highest per capita beef intake [7]. Meat and its role in the CRC risk were thoroughly analyzed in Uruguayan studies

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[8-14].

Total iron intake was reported as a risk factor for rectal cancer in Uruguay [9]. Reports on iron intake and CRC showed some inconsistency [15,16], but heme-iron is a major participant in the meat-induced promotion of CRC without additive or synergistic effects of HCA and endogenous N-nitroso compounds [17,18]. Heme-iron potentially affects homeostasis and colonic epithelial cell renewal and promotes the formation of mutagenic and carcinogenic agents, also linked to the development of adenomas [19]. The gut microbiota seems to influence the activation of enterocyte genes involved in the initiation and progression of colorectal carcinogenesis [20-22]. Iron supplements beyond certain limits were found as a risk factor for CRC [23]. Recently, a case-control study found different associations of iron types and CRC risk, depending on the source [24]: the iron intakes from red meat and heme-iron were positively associated, iron from white meat and plants were inversely associated, and no significant association was found for total dietary iron, non-heme-iron, and iron from meat.

Iron is essential for many biological processes. Heme-iron is absorbed ~30% and non-heme-iron ~10% [25], therefore most dietary iron is excreted and the human colon contains large amounts [26]. Because humans lack a mechanism for controlled iron excretion, regulatory systems controlling iron absorption, systemic transport and cellular uptake and storage [27], enable the body to reduce pathogenesis [28,29], depending on the organ, tissue or cell type affected [30]. Iron accumulation during lifespan poses a disadvantage for men because women can balance dietary iron excesses with their menses (periodical iron losses) during the reproductive years. Assuming similar dietary styles in both sexes, different body iron levels can be expected close to age 50.

Higher CRC incidence rates among men than women raised a possibility that estrogen and/or progesterone may confer protection against CRC [31]; however, the evidence remains inconclusive [32]. Estrogen acts on non-reproductive, secretory and absorptive tissues (e.g. colon, respiratory tract) expressing Estrogen Receptors (ERs), modulating the electrolyte and fluid balance. The colonic epithelium expresses both ERα and ERβ: in the crypts of the proximal colon, ERα is expressed more highly at the base of the crypt while ERβ expression prevails in its mid-section and the lumen surface cells [33].

Recently important ERβ features were described, linking them to colorectal carcinogenesis [34]: Erβ -the predominant ERs expressed in both normal and malignant colonic epithelium co-exist with limited or no expression of ERα in the colon, and are responsible for tumor-suppressive functions in CRC. Estrogen signaling has an anti-tumorigenic role in the colonic mucosa, through selective activation of pro-apoptotic ERβ-mediated signaling, inhibition of inflammatory signals and modulation of the tumor microenvironment and different immune surveillance mechanisms [34,35].

Hormone Replacement Therapy (HRT) reduces postmenopausal CRC incidence [36,37]. Nevertheless, although estrogen was initially protective, once CRC had developed, exogenous estrogens augmented the growth. This could be explained by ERβ expression, which is selectively lost during tumor progression through methylation-dependent gene silencing [38]. Aromatase is usually overexpressed in colon carcinoma, more than in normal tissues of both sexes [39]. Since aromatase has a place for heme-iron in its molecular structure, women may have a higher demand of it at the colorectal level, to build more aromatases, which in turn synthesize more estrogens needed by women.

Besides, there is a staple beverage in temperate South America known as “mate”, an infusion made from the herb *Ilex paraguariensis*. Uruguayans are the world’s highest consumers (~400 L/person/year of infusion) [40]. Although “mate” drinking was classified in 1991 by the International Agency for Research on Cancer as 2A [41], due to the presence of several pro-carcinogenic substances [42,43], it will be reassessed because it contains several antioxidant and anti-carcinogenic compounds (e.g. polyphenols, chlorogenic acids) [44,45].

Saponins from “mate” leave prevent colorectal carcinogenesis by suppressing inflammation and promoting apoptosis [46]. “Mate” is a rich source of oleanolic acid and ursolic acid (UA) [47]. UA has several intra- and extra-cellular targets playing a role in apoptosis, metastasis, angiogenesis and inflammation [48,49]. These “mate” components and theaflavins from black tea exert an aromatase-inhibitory activity [50]. UA can suppress ERα through down-regulation of estrogen-responsive genes expression in response to exposure to estradiol [51], showing a dose-dependent inhibition capability, comparable to phytoestrogens [47]. Moreover, “mate” iron-chelating capabilities were already demonstrated [52-55]. Our previous study on CRC showed an inverse association of “mate” intake among women, but lack of association among men [56].

There is strong evidence for a role of inflammation, oxidative stress, and metabolic dysfunction as underlying, interactive mechanisms in CRC [57]. Dietary iron and its metabolism are linked to several items, as the intake of processed meats, red meats, alcoholic drinks, and smoking [26,58,59], as well as to hormonal [60,61] and microbiota [20-22] features. Interestingly, the identified risk factors do not make equivalent contributions to CRC development in men and women [62].

The aforementioned epidemiologic links among iron, red/processed meat, “mate” infusion and CRC, justified doing additional studies following the recommended

identification of the iron source to clarify the relationship between its intake and CRC [63]. Therefore, we conducted a case-control study on dietary iron and CRC risk, applying a similar methodology as in previous studies [64-66]. To our knowledge, this is the first Latin American epidemiologic study focusing on dietary iron sources and CRC risk.

PATIENTS AND METHODS

Selection of cases and controls

During 1992-2004, all the newly diagnosed, microscopically confirmed CRC cases were collected from the major public hospitals in Montevideo (Oncología, Clínicas, Maciel, Pasteur), which catch a large fraction of patients from the public healthcare system for diagnosis and/or treatment of cancer. From the initial 625 patients, only 14 (2.3%) refused the interview (response rate 97.7%), finally leaving 611 cases. The former version of International Diseases Code for Oncology was used to classify lesions as colon (153.0 to 153.9) or rectum (154.0 to 154.9).

In the same period and hospitals, 2.460 patients afflicted with non-neoplastic diseases not related to tobacco smoking or alcohol drinking and without recent dietary changes were considered as eligible for the study. Sixty-six (66, 2.7%) of them refused the interview, leaving a final number of 2.394 controls (response rate 97.3%). These controls had the following diseases: skin diseases (357 patients, 14.9%), eye disorders (349, 14.6%), ear disorders (309, 12.9%), abdominal hernia (258, 10.8%), fractures (184, 7.7%), hydatid cysts (151, 6.3%), lipoma (101, 4.2%), osteoarticular diseases (100, 4.2%), varicose veins (91, 3.8%), injuries (92, 3.9%), urinary stones (73, 3.1%), goiter (62, 2.6%) and other acute diseases (267, 11.1%).

Interviews and questionnaire

Two trained social workers, unaware of the study objectives, worked at the hospitals in two phases: First, they looked for newly diagnosed cancer patients, working with the collaboration of Medical Records personnel. Second, they contacted patients who were eligible to be matched by the age-frequencies of the cases. After looking for their will to cooperate with the study, all the participants were face-to-face interviewed in the hospitals. Proxy interviews were not accepted in our study.

A structured questionnaire was applied to all participants. It included the following sections: socio-demographic variables; history of cancer in first- and second-degree relatives; self-reported height and weight 5 years before the interview; menstrual and reproductive events; tobacco smoking (average number of cigarettes/day); alcohol drinking (average amount of alcohol/day and beverage type); "mate", tea and coffee drinking (daily intake). The age at starting and quitting was asked for these 5 habits.

Finally, we included a detailed semi-quantitative food–frequency questionnaire (FFQ) on 64 items representative of the Uruguayan diet, which asked about food consumption 5 years before diagnosis in cases and before to the interview in controls. The FFQ was not validated but was tested for reproducibility, having high correlations [67]. It allowed the estimation of individual total energy intake. All dietary questions were open-ended. Each amount was converted to times/year. To obtain nutritional information about foods, we used foreign tables coming from a neighboring country with similar habits [68].

Estimation of iron and nutrients intake

We estimated heme-iron intake using our FFQ and following previous studies [16,69,70], 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, fish, eggs and milk and 21% for the liver. Mean daily heme-iron intake was calculated by multiplying consumption frequency by the amount of total iron and the quoted percentages. Estimations were made irrespective of the cooking method and doneness of meats since so accurate data [71] were not available at the time of the study design. Non-heme-iron intake was calculated subtracting heme-iron from total iron. Animal-based iron was calculated by addition of estimations from all animal foods; plant-based iron derived from subtracting animal-based iron from total iron. For the present study, we estimated the non-heme component of animal iron, by using the formula: (animal iron) – (heme-iron) [65].

For analysis purposes, based on the original iron variables, an Animal/Plant Iron Ratio (APIR) and a Heme/Non-Heme Ratio (H/NH) were created. To calculate energy and daily nutrients, an analysis program was compiled: it made the sum of all individual values, each one obtained after multiplying the number of servings/year by the ratio nutrient content or 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 a high correlation with energy, we calculated an iron density expressed as daily mg of iron/1000 KCal.

STATISTICAL ANALYSIS

Descriptive statistics, means, frequencies and percentages were used to show the distribution of patients' features. Most questionnaire variables were originally continuous. They were categorized into tertiles or quartiles or dichotomized for analysis purposes. Odds Ratios (ORs) and 95% confidence intervals (95% CI) were calculated by unconditional logistic regression [72]. Potential confounders were included in the multivariate analyses. All equations included terms for age, sex, education, years of urban residence, history of cancer in 1^{st}-2^{nd} degree relatives, body mass index, smoking status and intakes of alcohol, total energy, red meat, processed meat, total plant foods, infusions (tea, "mate", coffee), dietary calcium and total HCA. The best regression models included continuous and

categorized variables. Menopausal status was included for analyses in women. Likelihood-ratio tests were performed to explore possible heterogeneities in the stratified analyses. All calculations were done with STATA software (Release 10, StataCorp LP, College Station, TX, 2007).

RESULTS

Table 1 shows the distribution of general features among cases and controls. Although there was not a perfect matching, distribution of age groups was adequate (p=0.42). Neither urban/rural status nor residence displayed significant differences (p=0.53 and p=0.23, respectively). Whereas "mate" intake was highly prevalent (~86% ever consumers), tea (~19%) and coffee (~15%) were less frequently consumed. All infusions tended to be more consumed by the control population than by cancer cases, in spite of statistical differences. Finally, dietary energy showed highly significant differences (p<0.001).

Table 1. Main features of the studied sample (n=3005). Distribution of cases and controls.

Variables	Categories	Controls	%	Cases	%	Global p-value	OR	95% CI
Age groups	<40	47	2.0	12	2.0	0.42	---	---
	40-49	211	8.8	53	8.7			
	50-59	442	18.5	100	16.4			
	60-69	818	34.2	194	31.7			
	70-79	730	30.5	208	34.0			
	80-89	146	6.1	44	7.2			
Sex	Men	1576	65.8	361	59.1	0.002	---	---
	Women	818	34.2	250	40.9			
Education years	≤ 3	1021	42.6	280	45.8	0.14	0.74	0.55-1.00
	4-6	1067	44.6	269	44.0			
	≥ 7	306	12.8	62	10.2			
Urban/rural status	Urban	1940	81.0	508	83.1	0.23	0.87	0.68-1.10
	Rural	454	19.0	103	16.9			
Residence regions	Montevideo	1259	52.6	307	50.3	0.53	1.07	0.86-1.33
	Canelones	555	23.2	153	25.0			
	Other counties	580	24.2	151	24.7			
Body mass index (kg/m^2)	≤ 24.99	1108	46.3	287	47.0	0.26	0.81	0.61-1.08
	25.0-29.99	944	39.4	252	41.2			
	≥ 30.0	342	14.3	72	11.8			
FHC in siblings	No	2070	86.5	517	84.6	0.24	1.16	0.91-1.49
	Yes	324	13.5	94	15.4			
FHC in parents	No	2019	84.3	467	76.4	<0.001	1.66	1.34-2.06
	Yes	375	15.7	144	23.6			
Tea status	Never	1828	76.4	517	84.6	<0.001	0.59	0.46-0.75
	Ex drinker	11	0.5	2	0.3			
	Current	555	23.2	92	15.1			
'Mate' status	Never	312	13.0	92	15.1	0.10	0.86	0.65-1.15

	Ex drinker	160	6.7	52	8.5			
	Current	1922	80.3	467	76.4			
Coffee status	Never	1956	81.8	531	86.9	<0.001	0.67	0.46-0.97
	Ex drinker	20	0.8	13	2.1			
	Current	417	17.4	67	11.0			
Red meat intake (serv/year)	≤ 260	849	35.5	148	24.2	<0.001	1.72	1.17-2.37
	261-377	813	34.0	243	39.8			
	≥ 378	732	30.5	220	36.0			
Dietary energy (kcal/day)	≤ 1745	648	27.1	101	16.5	<0.001	2.23	1.71-2.91
	1746-2158	599	25.0	150	24.6			
	2159-2618	591	24.7	167	27.3			
	≥ 2619	566	23.2	193	31.6			
Alcohol status	Never	1102	46.0	316	51.7	0.04	0.81	0.67-0.98
	Ex drinker	297	12.4	64	10.5			
	Current	995	41.6	231	37.8			
Smoking status	Never	910	38.0	262	42.9	0.08	0.79	0.64-0.98
	Ex-smoker	672	28.1	164	26.8			
	Current	812	33.9	185	30.3			
Tumor site	Colon men	----		161	44.6	<0.001	----	----
	Rectum men	----		200	55.4			
	Colon women	----		158	63.2			
	Rectum women	----		92	36.8			
Total patients		2.394	100.0	611	100.0			

Abbreviations: FHC: Family History of Cancer in 1st Degree Relatives

The mean values of iron intake and other selected dietary items are presented in **Table 2**, with two comparisons, between cases/controls and men/women. Most iron variables displayed significant differences in both comparisons. Cases had higher intakes of animal-based and heme-iron, while their plant and non-heme-iron intakes were lower. Regarding comparisons by sex, men showed higher intakes in the quoted four sources, they showed higher intake of energy, red meat and processed meat, while women had a higher intake of white meat, vegetables and pulses.

Table 2. Mean values of iron and selected dietary items ± standard deviation. Comparisons between cases/controls and men/women. Iron values calculated in mg/1000 kcal/day.

Variables	Units	Controls Mean ± SD	Cases Mean ± SD	Diff. (p-value)	Men Mean ± SD	Women Mean ± SD	Diff. (p-value)
Energy	Kcal/d	2170.1 ± 669.7	2404.6 ± 753.2	<0.001	2279.3 ± 685.4	2106.1 ± 695.4	<0.001
Red meat	Serv/year	349.2 ± 188.4	406.7 ± 208.1	<0.001	383.1 ± 200.3	320.6 ± 174.9	<0.001
Proc. meat	Serv/year	138.9 ± 157.0	149.1 ± 166.0	0.15	154.2 ± 160.8	116.8 ± 107.7	<0.001
White meat	Serv/year	90.1 ± 76.0	97.7 ± 79.8	0.03	84.0 ± 73.8	105.3 ± 80.5	<0.001
Total veg.	Serv/year	450.3 ± 327.3	449.2 ± 351.2	0.94	422.7 ± 310.9	499.8 ± 362.6	<0.001
Total fruits	Serv/year	462.7 ± 364.7	471.4 ± 440.8	0.60	464.6 ± 378.0	464.3 ± 351.8	0.98
Total pulse	Serv/year	38.6 ± 52.3	32.8 ± 54.8	0.01	35.2 ± 51.6	41.4 ± 54.9	0.002
Total fibre	g/d	16.1 ± 6.5	16.8 ± 8.3	0.02	16.3 ± 7.0	16.1 ± 6.7	0.32
Calcium	mg/d	616.3 ± 316.2	633.8 ± 323.1	0.22	614.5 ± 319.7	629.7 ± 313.7	0.21
Total iron	mg/10^3 Kcal	7.18 ± 1.50	7.07 ± 1.43	0.10	7.42 ± 1.50	6.69 ± 1.32	<0.001
Animal iron	mg/10^3 Kcal	2.69 ± 0.96	2.83 ± 1.00	0.001	2.76 ± 0.96	2.64 ± 0.98	0.001
Plant iron	mg/10^3 Kcal	4.49 ± 1.48	4.24 ± 1.39	<0.001	4.66 ± 1.54	4.05 ± 1.22	<0.001
A/P ratio	%	71.0 ± 49.9	80.1 ± 71.9	<0.001	71.2 ± 55.0	75.8 ± 55.4	0.03
Heme iron	mg/10^3 Kcal	1.67 ± 0.67	1.75 ± 0.70	0.005	1.73 ± 0.66	1.61 ± 0.69	<0.001
NH iron	mg/10^3 Kcal	5.51 ± 1.40	5.32 ± 1.31	0.002	5.69 ± 145	5.08 ± 1.15	<0.001
H/NH ratio	%	32.7 ± 16.9	35.3 ± 18.3	<0.001	32.9 ± 17.1	33.7 ± 17.4	0.22
A. NH iron	mg/10^3 Kcal	1.02 ± 0.34	1.08 ± 0.36	<0.001	1.04 ± 0.35	1.03 ± 0.34	0.51

Abbreviations: A/P ratio: Animal/Plant Iron Ratio; H/NH ratio: Heme/Non-Heme-Iron Ratio; A. NH: Animal Non-Heme-Iron; mg/10^3 Kcal: Milligrams/1000 Kilocalories per Day

Table 3 shows the adjusted ORs of CRC for all iron variables, including estimates for each sex. Considering the whole sample, none of the eight iron variables were associated to CRC risk, neither comparing the highest vs. lowest tertile, nor the p-values for trend for each one of the analyzed variables. A significant inverse association was found for total dietary iron among men (OR=0.65, p_{trend}=0.005), but not among women. Animal-based iron displayed inverse associations between sexes, but both were non-significant: a positive one among men and a negative one among women. Conversely, plant-based iron was significantly associated reducing the risk among men (OR=0.62, p_{trend}=0.003), and marginally increasing the risk among women (OR=1.56, p_{trend}=0.07). Heme-iron was not associated among men, but marginally inversely associated among women (OR=0.47, p_{trend}=0.06). Estimates of non-heme-iron were different: they displayed a highly significant association among men (OR=0.60, p_{trend}=0.001), but they were not significantly associated among women, tending to a risk increase. The animal non-heme-iron did not show a risk association. Finally, the calculated ratios displayed risk associations among men and protective associations among women. Both estimations were significant for the latter

subset. Regarding the iron types, all likelihood ratio tests for heterogeneity between sexes were significant.

Table 3. Adjusted odds ratios (OR) of CRC for dietary iron: total, animal-based, plant-based, animal/plant (A/P) ratio, heme, non-heme, heme/non-heme ratio (H/NH) and animal non-heme. Estimates for the whole sample and for each sex. Likelihood ratio Test for heterogeneity between sexes.

Iron variables	Set	I		II		III		Trend (p)	LR test (p)
		OR	95% CI	OR	95% CI	OR	95% CI		
Total	All	1.00	---	1.05	0.83-1.32	0.85	0.66-1.09	0.20	0.03
	M	1.00		1.08	0.79-1.47	0.65*	0.47-0.90	0.005	
	W	1.00		0.99	0.68-1.44	1.27	0.82-1.97	0.34	
Animal	All	1.00	---	1.06	0.82-1.37	0.98	0.68-1.42	0.95	0.002
	M	1.00		1.17	0.82-1.66	1.27	0.79-2.02	0.32	
	W	1.00		0.94	0.61-1.44	0.61	0.31-1.18	0.19	
Plant	All	1.00	---	1.00	0.80-1.25	0.87	0.68-1.11	0.26	<0.001
	M	1.00		1.11	0.83-1.50	0.62*	0.45-0.85	0.003	
	W	1.00		0.90	0.63-1.30	1.56*	1.02-2.36	0.07	
A/P ratio	All	1.00	---	1.13	0.88-1.45	1.07	0.79-1.45	0.69	<0.001
	M	1.00		1.62*	1.16-2.28	1.77*	1.19-2.63	0.006	
	W	1.00		0.72	0.48-1.08	0.51*	0.30-0.86	0.01	
Heme	All	1.00	---	1.03	0.79-1.34	0.73	0.50-1.07	0.13	0.003
	M	1.00		1.14	0.80-1.62	0.94	0.58-1.54	0.81	
	W	1.00		0.96	0.63-1.47	0.47*	0.24-0.94	0.06	
Non-heme	All	1.00	---	0.97	0.78-1.21	0.82	0.65-1.04	0.11	<0.001
	M	1.00		1.05	0.78-1.40	0.60*	0.44-0.82	0.001	
	W	1.00		0.91	0.64-1.30	1.36	0.90-2.05	0.23	
H/NH ratio	All	1.00	---	1.09	0.85-1.41	0.94	0.68-1.31	0.71	<0.001
	M	1.00		1.55*	1.10-2.19	1.53	0.99-2.35	0.06	
	W	1.00		0.71	0.47-1.08	0.53*	0.30-0.92	0.02	
Animal NH	All	1.00	---	1.11	0.87-1.42	1.05	0.77-1.42	0.76	0.002
	M	1.00		1.27	0.91-1.77	1.36	0.91-2.02	0.14	
	W	1.00		1.02	0.68-1.52	0.73	0.43-1.23	0.26	

Regression model including terms for cancer (binary, as dependent variable), age (categorical), education years (categorical), urban years of residence (continuous), family history of cancer in 1st and 2nd degree relatives (binary no/yes), body mass index (continuous), energy as kilocalories (categorical), cigarette amount (continuous), alcohol status (categorical), total plant foods (vegetables+fruits+legumes) (continuous), tea intake (binary never/ever), coffee intake (binary never/ever), "mate" intake (categorical), dietary calcium (continuous), red meat (continuous), processed meat (continuous) and total heterocyclic amines (continuous) as independent variables. Menopausal status was included in the analyses of women

Abbreviations: M: Men; W: Women; A/P ratio: Animal/Plant Iron Ratio; H/NH ratio: Heme/Non-Heme-Iron Ratio; Animal NH: Animal Non-Heme-Iron; LR test: Likelihood Ratio Test for Heterogeneity

Significant ORs appear in bold letter with an asterisk

Table 4 shows the continuous ORs as estimates derived from stratified analysis of "mate" intake and by sex. Considering the differences between "mate" intake (12% non-drinkers, 88% ever drinkers), and despite the significance level, the Table displays two different risk trends, each one for each sex in the Ever drinkers column: while the ORs tended to a slight increase among men, they tended to a slight, but stronger, decrease among women. Ever drinkers improved the significance of trends compared to those presented in **Table 3**. Of 16 calculated trends for ever-drinkers, there are 8 significant and 3 marginally significant ones.

Table 4. Continuous odds ratios (ORs) of CRC for dietary iron: total, animal-based, plant-based, animal/plant (A/P) ratio, heme, non-heme, heme/non-heme ratio (H/NH) and animal non-heme. Estimates derived from stratified analysis by 'mate' intake and by sex.

Iron variables	Set	Never drinkers N=404			Ever drinkers N=2601		
		OR	95% CI	Trend (p)	OR	95% CI	Trend (p)
Total	M	0.65	0.39-1.09	0.10	0.82*	0.69-0.97	0.02
	W	1.62	0.95-2.77	0.08	1.12	0.89-1.41	0.34
Animal	M	0.83	0.40-1.75	0.63	1.19	0.93-1.53	0.17
	W	1.41	0.63-3.15	0.40	0.70*	0.50-0.99	0.04
Plant	M	0.68	0.42-1.10	0.11	0.80*	0.68-0.94	0.008
	W	1.44	0.85-2.44	0.18	1.23	0.99-1.54	0.07
A/P ratio	M	1.19	0.64-2.19	0.59	1.33*	1.08-1.64	0.008
	W	0.55	0.29-1.07	0.07	0.72*	0.55-0.96	0.02
Heme	M	0.67	0.31-1.47	0.31	1.02	0.79-1.32	0.87
	W	1.05	0.48-2.32	0.90	0.66*	0.47-0.94	0.02
Non-Heme	M	0.71	0.45-1.11	0.13	0.79*	0.67-0.93	0.004
	W	1.40	0.83-2.35	0.20	1.15	0.93-1.43	0.21
H/NH ratio	M	1.27	0.65-2.48	0.48	1.22	0.98-1.53	0.08
	W	0.65	0.33-1.29	0.22	0.71*	0.53-0.96	0.02
Animal NH	M	1.37	0.74-2.51	0.31	1.16	0.94-1.44	0.16
	W	1.35	0.70-2.57	0.37	0.77	0.58-1.01	0.06

Regression model including terms for cancer (binary, as dependent variable), age (categorical), education years (categorical), urban years of residence (continuous), family history of cancer in 1st and 2nd degree relatives (binary no/yes), body mass index (continuous), energy as kilocalories (categorical), cigarette amount (continuous), alcohol status (categorical), total plant foods (vegetables+fruits+legumes) (continuous), tea intake (binary never/ever), coffee intake (binary never/ever), "mate" intake (categorical), dietary calcium (continuous), red meat (continuous), processed meat (continuous) and total heterocyclic amines (continuous) as independent variables. Menopausal status was included in the analyses of women'

Abbreviations: M: Men; W: Women; A/P ratio: Animal/Plant Iron Ratio; H/NH ratio: Heme/Non-Heme-Iron Ratio; Animal NH: Animal Non-Heme-Iron

Significant ORs appear in bold letter with an asterisk

Table 5 displays the estimates derived from stratified analysis of tumor site and by sex, as continuous ORs. Regarding colon cancer, significant risk reductions were found for heme-iron, APIR and H/NH ratio and only among women. A direct and marginally significant association (p_{trend}=0.07) for plant iron was also found among women. Rectal cancer, conversely, displayed all significant risk associations among men: Total, plant-based and non-heme-iron was inversely associated, whereas APIR and H/NH ratios were directly associated. Except for total iron, all

likelihood ratio tests for heterogeneity between sexes were significant for both tumor sites.

Table 5. Continuous odds ratios (ORs) of CRC for dietary iron: total, animal-based, plant-based, animal/plant (A/P) ratio, heme, non-heme, heme/non-heme ratio (H/NH) and animal non-heme. Estimates derived from stratified analysis by tumor site and by sex. Likelihood ratio Test for heterogeneity between sexes.

Iron variables	Set	Colon N=319				Rectum N=292			
		OR	95% CI	Trend (p)	LR test (p)	OR	95% CI	Trend (p)	LR test (p)
Total	M	0.89	0.72-1.11	0.30	0.27	0.74*	0.60-0.90	0.003	0.11
	W	1.17	0.91-1.51	0.23		1.19	0.86-1.65	0.29	
Animal	M	1.04	0.75-1.44	0.80	0.04	1.20	0.89-1.61	0.24	0.02
	W	0.72	0.49-1.06	0.09		1.03	0.64-1.66	0.90	
Plant	M	0.89	0.72-1.10	0.29	0.001	0.72*	0.60-0.88	0.001	0.004
	W	1.26	0.98-1.62	0.07		1.26	0.92-1.73	0.14	
A/P ratio	M	1.18	0.90-1.55	0.24	0.001	1.41*	1.10-1.81	0.006	0.006
	W	0.66*	0.48-0.90	0.008		0.80	0.54-1.18	0.27	
Heme	M	0.90	0.64-1.26	0.54	0.06	1.05	0.77-1.43	0.77	0.02
	W	0.63*	0.42-0.93	0.02		0.93	0.57-1.52	0.77	
Non-Heme	M	0.86	0.70-1.06	0.15	0.004	0.73*	0.60-0.88	0.001	0.004
	W	1.17	0.92-1.49	0.21		1.22	0.90-1.66	0.19	
H/NH ratio	M	1.02	0.76-1.37	0.87	0.01	1.40*	1.07-1.83	0.01	0.007
	W	0.66*	0.47-0.91	0.01		0.80	0.53-1.22	0.31	
Animal NH	M	1.07	0.81-1.41	0.63	0.04	1.21	0.94-1.56	0.14	0.04
	W	0.85	0.63-1.15	0.29		0.93	0.64-1.36	0.71	

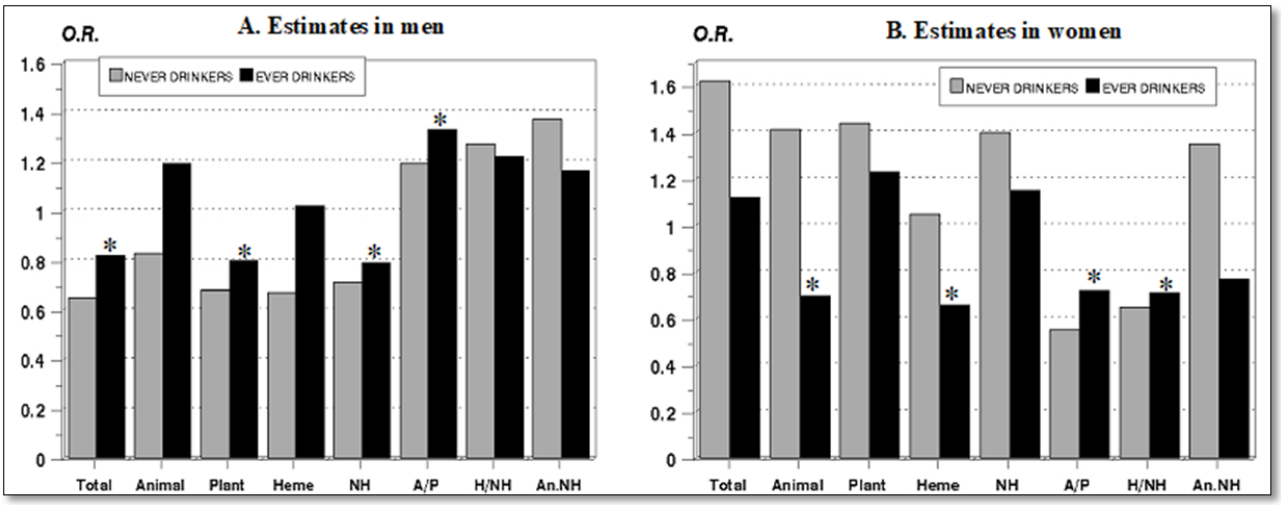
Regression model including terms for cancer (binary, as dependent variable), age (categorical), education years (categorical), urban years of residence (continuous), family history of cancer in 1st and 2nd degree relatives (binary no/yes), body mass index (continuous), energy as kilocalories (categorical), cigarette amount (continuous), alcohol status (categorical), total plant foods (vegetables+fruits+legumes) (continuous), tea intake (binary never/ever), coffee intake (binary never/ever), "mate" intake (categorical), dietary calcium (continuous), red meat (continuous), processed meat (continuous) and total heterocyclic amines (continuous) as independent variables. Menopausal status was included in the analyses of women

Abbreviations: M: Men; W: Women; A/P ratio: Animal/Plant Iron Ratio; H/NH ratio: Heme/Non-Heme-Iron Ratio; Animal NH: Animal Non-Heme-Iron; LR test: Likelihood Ratio Test for Heterogeneity

Significant ORs appear in bold letter with an asterisk

Figure 1 displays a graphic representation of the data shown in **Table 4**. Stratified by never/ever "mate" drinking, the continuous ORs for each iron type reveals different associations for each sex. Whereas the ORs tend to increase slightly among drinker men, the ORs tend to decrease among drinker women. The quoted trends also reflect changes in drinkers according to different iron types: among men, the inverse associations of plant and non-heme-iron tend to be stronger, whereas, among women, inverse risk associations emerge of animal and heme-iron.

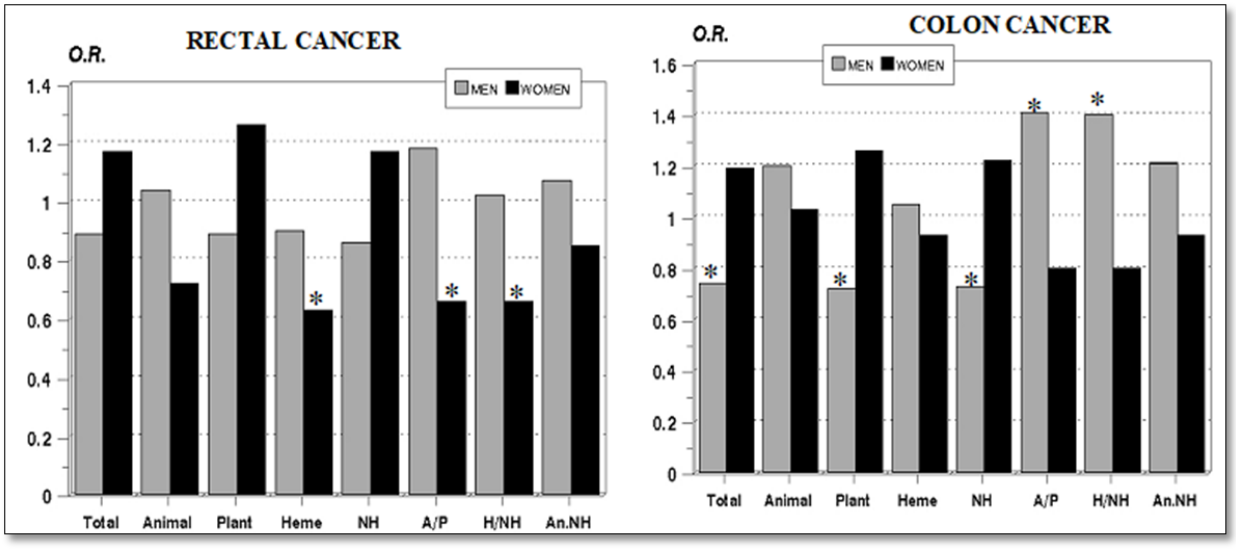
Figure 1. Continuous odds ratios (ORs) of CRC for dietary iron: total, animal-based, plant-based, animal/plant (A/P) ratio, heme, non-heme, heme/non-heme ratio (H/NH), and animal non-heme. Estimates derived from stratified analysis 'mate' intake and by sex. Graphic expression of analyses reported in **Table 4**.



** = statistically significant trends*

Figure 2 shows a graphic representation of the data shown in **Table 5**. Stratified by tumor sub-site and by sex, the continuous ORs for each dietary iron display different associations for each sex. On one hand, the risk associations derived from the intakes of certain iron types among women are supported by stronger effects in the colon but not in the rectum. On the other hand, the risk associations found among men are supported by stronger effects in the rectum but not in colon.

Figure 2. Continuous Odds Ratios (ORs) of CRC for dietary iron: total, animal-based, plant-based, animal/plant (A/P) ratio, heme, non-heme, heme/non-heme ratio (H/NH) and animal non-heme. Estimates derived from stratified analysis for tumor subsites (colon or rectum) and by sex. Graphic expression of analyses reported in **Table 5**.



** = statistically significant trends*

DISCUSSION

Concerning the associations between CRC risk and iron intake, we found significant heterogeneity between sexes. Total iron, plant-based and non-heme-iron showed inverse associations with CRC risk among men (OR=0.65, OR=0.62 and OR=0.60, respectively for 3rd vs. 1st tertile). Heme-iron was inversely associated among women (OR=0.47). Animal-based iron lacked risk association, suggesting opposite trends between sexes. Regarding APIR and H/NH ratio, both were positively associated with CRC risk among men

(OR=1.77 and OR=1.53, respectively) and inversely associated among women (OR=0.51 and OR=0.53, respectively).

Previous findings on total dietary iron and CRC risk are inconsistent and controversial. Some case-control studies showed increased risks with high intake of total iron [9,73,74], but others did not [24,75]. Most prospective studies showed a non-significant relationship between dietary iron and CRC incidence [76]. The controversial results might be partially explained by the different dietary styles and their iron intake among different populations.

Regarding stratified analysis by sex, the present study shows some similarities with a recent case-control study [24]: they found positive associations of heme-iron, iron from meat and iron from red meat and CRC risk among males but not in females. A straightforward explanation for the inverse associations we found between heme-iron and CRC risk among women is hard to find, since heme, but not non-heme-iron, is responsible for intestinal N-nitrosation arising from red meat [77]. The dietary patterns of each sex, usually featured by higher meat/lower vegetable intakes among men compared to women, were recognized as different [78]. According to these authors, different combinations of food groups or nutrients might have also different effects on health outcomes.

Concerning red meat, a recent Uruguayan study showed elevated risks among men, but not among women [14]. Those differences by sex resulted in a significant heterogeneity. Heme-iron could partially explain the differences found in the former study [16]. As women need more iron due to menstrual losses, and heme-iron is more easily absorbed than non-heme-iron, more iron from heme is absorbed in women, and less heme is available during lifetime up to menopause to form cytotoxic factors in the colorectum [16]. Non-heme-iron can react with dissolved oxygen or with peroxides to give Reactive Oxygen Species (ROS) [79]. Besides, a possible role for zinc could be considered. Because zinc and heme-iron food sources are similar (e.g. meats), combined effects of prooxidant iron and antioxidant zinc may attenuate associations between cancer and consumption of those foods [15]. Iron probably exerts different effects on different cancer sites and in women, among whom iron-induced carcinogenesis likely involves a complex interplay with reproductive/hormonal factors [80,81].

As most dietary iron is excreted rather than absorbed, the human colon contains large amounts of iron, however, non-heme-iron might prevail as the remaining iron in women's colorectum. Despite a higher presence of chlorophyll as an iron chelator in several foods containing non-heme-iron, increasing dietary iron was experimentally shown to increase the number of colonic free radicals, the amount of subsequent lipid peroxidation, and the number of aberrant crypt foci recognized as a pre-malignant change [82]. Dietary chlorophylls might act as interceptor molecules of food-borne carcinogens and mutagens [83]. Several epidemiological studies have demonstrated that a magnesium-rich diet, including dark green leafy vegetables (rich in chlorophyll), may reduce the colon cancer occurrence [84]. Magnesium deficiency has therefore been proposed as a risk factor for some human cancers.

Recently, heme-iron intake was positively associated with CRC and colon adenoma risk in a prospective cohort study [18,19]. Heme-iron from meat plays a role promoting experimental CRC, associated with enhanced luminal lipoperoxidation and leading to the subsequent formation of α-β-unsaturated aldehydes (alkenals), such as 4-hydroxynonenal (HNE) from Ω-6 fatty acids [85,86]. A defective mucosal barrier in response to heme exposure, facilitates access to the mucosa for both deleterious luminal heme-induced compounds and opportunistic pathogens, able to promote changes in permeability [87,88], inflammation [89] and genotoxicity [90,91], which are correlated with luminal heme and lipoperoxidation markers and closely associated with a shift in the gut microbiome [92]. Limiting heme-iron bioavailability can prevent these changes [93]. Trapping of luminal heme-induced aldehydes normalized cellular genotoxicity, permeability and ROS formation [59,94,95]. HNE from heme-induced lipoperoxidation selects adenomatous polyposis coli (Apc, a frequently mutated gene in colorectal carcinogenesis)-mutated cells and enhances cancer promotion [96]. The reduction of gut microbiota by antibiotics, preventing a heme-induced lipoperoxidation, suggests a role of the microbiota in the heme-induced formation of aldehydes [97].

Nitrites are harmful because they: a) allow an endogenous intestinal nitrosation; b) can react with hemoglobin and myoglobin to form N-nitroso compounds, and; c) can nitrosylate heme-iron. Cooking red meat causes the release from myoglobin of nitrosyl heme, formed by nitrites, with the production of free nitrosyl-heme [20]. Free nitrosyl-heme from processed meat can be more toxic than native heme (presented as hemoprotein) from fresh meat because the former has a greater ability to induce nitrosamine synthesis and to increase the formation of mucin depleted foci (MDF, precancerous lesions with defective mucus production) [98]. MDF may explain why processed meat is associated with a higher CRC risk than is fresh red meat.

In addition to an elevated breast cancer risk, nuns were also more likely to develop colon cancer, suggesting that lifetime exposure to high endogenous estrogens levels may lead to a greater CRC incidence [99]. Recent research found reported that reproductive factors- all surrogate markers for lifetime estrogen exposure- are linked with colorectal tumorigenesis, suggesting that a greater lifetime endogenous estrogen exposure may increase CRC risk in postmenopausal women. [100] Aromatase activity was reported in human colon epithelial and carcinoma tissue (in several cell lines)

[101,102]. Newer results also suggested that aromatase was frequently overexpressed in human colon adenocarcinoma [39]. These authors consider that circulating testosterone is reasonably postulated as a major precursor substrate of local estradiol production by aromatase in colon carcinoma. Since heme-iron is a component of the aromatase complex, iron overload may enhance estrogen synthesis [103].

Experimental models indicate genomic actions mediated by ER-estrogen binding. During development, part of CRC shifts towards an increasingly estrogenic genotype by down- or up-regulating specific steroid enzymes. Estrogen signaling has an anti-tumorigenic role in the colonic mucosa, through selective activation of pro-apoptotic signaling mediated by ERβ, inhibition of inflammatory signals and modulation of the tumor microenvironment and different immune surveillance mechanisms [34]. Indeed, ERβ (the most abundant colonic ER), was identified as a tumor suppressor in CRC and selectively lost its expression by methylation-dependent gene silencing during tumor progression [31,37]. This absence of ERβ expression is associated with disrupted tight-junction formation and abnormal colonic architecture.

Large doses of exogenous estrogens reduced the hepatic insulin and IGF-1 production, probably attenuating their cancer-promoting effects [104]. HRT in women was protective of the CRC risk [37]. Although initially protective, exogenous estrogens augment the growth once CRC has developed. ERβ functions as a dominant regulator when both receptors are co-expressed and promotes apoptotic and anti-proliferative effects [62]. These authors suggested that the estrogen anti-secretory effect is gender-specific. A selective ERα antagonism decreases inflammation in cancer cells, inhibits proliferation and promotes apoptosis in human CRC cells [105]. According to the literature, inhibition of ERα enhancement of ERβ activity seems logical to be taken into account for CRC [106,107]. ERβ mRNA levels were reduced in animal and human studies models of colitis, supporting a protective effect of ERβ [108] and suggesting that the regulation of colonic epithelial permeability might be ERβ-mediated. Other researchers found that ERβ levels were significantly reduced in CRC of men ($p<0.001$) and women ($p<0.04$) compared with normal colonic mucosa; this reduction in ERβ level was greater in men vs. women ($p<0.04$) [109]. Also, hepcidin levels are lower in women than in men, and premenopausal women have lower serum hepcidin concentrations than postmenopausal ones [61]. While the observation of higher CRC incidence rates among men than women suggested that estrogen and/or progesterone may protect against CRC, the evidence remains inconclusive [32].

Polycyclic Aromatic Hydrocarbons (PAHs) are environmental contaminants because of their toxic, carcinogenic and putative estrogenic or anti-estrogenic properties in the human body. Human exposure to PAHs mainly occurs through oral uptake of charcoal-broiled, grilled and smoked meats [110] and through ingestion of poorly cleaned vegetables. Several PAH metabolites structurally resemble steroidal hormones that bind the human ERs. Human intestinal microbiota can also bioactivate PAHs, tending to estrogenic metabolites. Whereas colon digests of PAH compounds displayed estrogenicity, stomach and small intestine digestions of benzo(a)pyrene showed no estrogenic effects [111]. In our opinion, women might have an enhanced transformation of PAH (mainly derived from meat) to the estrogen biosynthesis, compared to men. Those estrogens could bind preferentially to ERβ.

Intestinal microbiota genes sets can produce estrogen-metabolizing enzymes [112,113]. The gut microbiota deconjugates estrogens into their active forms, through β-glucuronidase secretion, increasing their intestinal reabsorption and enabling them to bind to ERs [114,115]. A diminished deconjugation due to dysbiosis results in reduced circulating estrogens. Besides, the gut microbiome is influenced by estrogens, which modulate inflammatory pathways and decrease the concentration of pathogenic bacteria [116,117]. Male and female microbiota respond differently to diet: the latter may be more susceptible to dietary manipulation [118,119].

The gut microbiota composition is susceptible to the quality and quantity of ingested carbohydrates [120]. A western diet (high in meat, fat and sugar) can cause dysbiosis by increasing certain strains and decreasing others as Bifidobacteria. Conversely, vegetarians and individuals consuming a high proportion of fruits and vegetables and a low proportion of meat increase the Prevotella. Nevertheless, supplementary iron induced decreased levels of Bifidobacteriaceae and Lactobacillaceae, while it caused higher levels of Prevotella [93]. A vegetarian dietary style, therefore, could partially influence the gut microbiota similar to supplementary iron does. Although our results in women subset could be linked to these facts, the picture is complex.

Most polyphenols found in antioxidant-rich plant foods also may chelate iron. Observations suggest that when subjects have a regular diet low in plant-based foods, pro-carcinogenic compounds of “mate” infusion could overcome its potential antioxidant compounds. Other “mate” components, as ferrozine and chlorogenic acid, can also contribute with chelation [53,54]. Recent research on healthy subjects receiving ferrous sulfate showed that “mate” infusion reduced ~76% its absorption [52].

Coffee components as caffeic acid, chlorogenic acid and tocotrienols have a preferential binding to ERβ, which has anti-proliferative action [121-123]. Also, caffeine reduces the ERα expression, possibly explaining an inverse association of coffee intake and CRC found only among men

[56]. Dietary iron might be also influenced by the infusion. Colorectal adenoma recurrence has been inversely associated with iron intake, but there was very low meat intake in the study population and iron intake was highly correlated with dietary fiber, which may explain the inverse association [124]. That study suggested potential benefits if dietary iron is derived from plants as opposed to meat, or perhaps the benefit is purely supported on the absorption decrease caused by fiber.

Data in **Figure 1** suggest different risk associations for each sex. The ORs increase slightly among drinker men but decrease among drinker women. Nevertheless, the quoted trends also reflect different effects of "mate" drinking according to different iron types: the inverse associations of plant and non-heme-iron tend to be stronger among men, whereas among women emerge inverse associations of animal and heme-iron. The differential effects of the infusion on CRC risk in each sex add complexity to the global picture, probably linked to the antioxidant, anti-estrogenic and iron-chelating properties of "mate".

Given the different meat, plants, and iron intakes reported by each sex, the scenario appears advantageous for women, despite their lesser "mate" intake compared to men. A CRC risk reduction for heme-iron among women remains only in their "mate" drinker's subset. Also, the inverse association with heme-iron is slightly stronger than animal iron's, which reflects the associations seen with non-heme-iron. Therefore, the antioxidant capabilities of the infusion could be highlighted in front of iron intake.

Our work shares some limitations and strengths, as other case-control studies. Among the limitations, we recognize the lack of validation of the questionnaire, although the instrument was tested for reproducibility and showed high correlations [67]. The validation was projected to be done but was never performed due to budgetary cuts in 2002-reflecting a severe national economy crisis-. Epidemiologic research on cancer in Uruguay continued with the remaining databases-like the one used for the present study-, without additional funds.

Another limitation was related to iron intake estimations: while based on average serving sizes but not on actual food sizes, they might not be highly accurate. Recall bias could be a problem in the present study, by leading to misclassification. We cannot exclude neither the possibility of confounding by unmeasured factors like physical activity, closely related to the CRC risk nor the possibility of confounding by dietary factors, such as other constituents of animal foods or the effects of cooking methods, which can influence the contents of iron types. The total iron concentration increases with cooking and with the doneness level heme-iron is degraded at higher temperatures, however, different results have been reported [71]. The present study did not ask iron from supplements, therefore it was not part of the exposure.

As the strengths of the study, the analyzed population included subsets coming from the whole country, and times of data collection were coincident. The age distribution was adequate; distribution by urban/rural status and country region gave homogeneity to the sample. The potential for selection bias does exist, as in any case-control study, but it is unlikely to have substantially affected our results due to the high participation achieved (~97%). Since the data collection was performed before 2005, no effect from wheat flour fortification with ferrous sulfate (legally established in 2005 in 30 mg/kg of flour) is expected in our study. Although it is unlikely to completely avoid any kind of bias, we think that the results of the present study were not chance findings.

CONCLUSION

In conclusion, our study shows certain associations between dietary iron and CRC risk. This applies for total iron and also for heme and non-heme subtypes, suggesting different, even opposite, effects for each sex. Further epidemiologic and mechanistic research is needed to disentangle complex nutritional and biochemical interrelationships linked to the disease.

ETHICS APPROVAL

The study was conducted after receiving the approval of each Medical Director of the participant hospitals, following an ethical approval from each institution. For this type of studies and during the years when interviews were performed, patients have not given an informed consent, since it was not mandatory for interviewers to request it. The study was always accepted under the obvious condition of confidentiality for individual data assured for the interviews.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Registro Nacional de Cáncer de Uruguay Situacion epidemiologica del Uruguay en relacion al cancer. Incidencia del cancer en 2011-2015 y tendencia de la mortalidad por cancer 1990-2017. In: http://www.comisioncancer.org.uy/uc_513_1.html

2. Bray F, Ferlay F, Soerjomataram I, Siegel RL, Torre LA, et al. (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer Clin 68: 394-424.

3. Gunter MJ, Alhomoud S, Arnold M, Brenner H, Burn J, et al. (2019) Meeting report from the joint IARC-NCI international cancer seminar series: A focus on colorectal cancer. Ann Oncol 30: 510-519.

4. Bouvard V, Loomis D, Guyton KZ, Grosse Y, El Ghissassi F, et al. (2015) Carcinogenicity of

consumption of red and processed meat. Lancet Oncol 16: 1599-1600.

5. World Cancer Research Fund/American Institute for Cancer Research (2007) Food, nutrition, physical activity and the prevention of cancer: A global perspective Washington DC: AICR.
6. Fonseca-Nunes A, Jakszyn P, Agudo A (2014) Iron and cancer risk - A systematic review and meta-analysis of the epidemiological evidence. Cancer Epidemiol Biomark Prev 23: 12-31.
7. http://www.fao.org/faostat/en/#data/CL
8. De Stefani E, Deneo-Pellegrini H, Mendilaharsu M, Ronco AL (1997) Meat intake, heterocyclic amines and risk of colorectal cancer: A case-control study in Uruguay. Int J Oncol 10: 573-580.
9. Deneo-Pellegrini H, De Stefani E, Boffetta P, Ronco A, Mendilaharsu M (1999) Dietary iron and cancer or the rectum: A case-control study in Uruguay. Eur J Cancer Prev 8: 501-508.
10. Deneo-Pellegrini H, Boffetta P, De Stefani E, Ronco AL, Correa P, et al. (2005) Meat consumption and risk of colorectal cancer: A case-control study in Uruguay. Cancer Ther 2005: 193-200.
11. De Stefani E, Deneo-Pellegrini H, Ronco AL, Correa P, Boffetta P, et al. (2011) Dietary patterns and risk of colorectal cancer: A factor analysis in Uruguay. Asian Pac J Cancer Prev 12: 753-759.
12. De Stefani E, Ronco AL, Boffetta P, Deneo-Pellegrini H, Correa P, et al. (2012) Nutrient-derived dietary patterns and risk of colorectal cancer: A factor analysis in Uruguay. Asian Pac J Cancer Prev 13: 231-235.
13. De Stefani E, Boffetta P, Ronco AL, Deneo-Pellegrini H, Correa P, et al. (2012) Processed meat consumption and risk of cancer: A multisite case-control study in Uruguay. Br J Cancer 107: 1584-1588.
14. De Stefani E, Boffetta P, Ronco AL, Deneo-Pellegrini H, Mendilaharsu M, et al. (2016) Meat consumption and risk of colorectal cancer: A case-control study in Uruguay emphasizing the role of gender. Cancer Res Oncol 2: CROOA-2-015.
15. Lee DH, Anderson KE, Harnack LJ, Folsom AR, Jacobs DR (2004) Heme iron, zinc, alcohol consumption and colon cancer: Iowa Women's Health Study. J Natl Cancer Inst 96: 403-407.
16. Balder HF, de Vogel J, Jansen MCJ, Weijenberg MP, van den Brandt PA, et al. (2006) Heme and chlorophyll intake and risk of colorectal cancer in the Netherlands Cohort Study. Cancer Epidemiol Biomarkers Prev 15: 717-725.
17. Bastide NM, Pierre FH, Corpet DE (2011) Heme iron from meat and risk of colorectal cancer: A meta-analysis and a review of the mechanisms involved. Cancer Prev Res (Phila) 4: 177-184.
18. Bastide NM, Chenni F, Audebert M, Santarelli RL, Taché S, et al. (2015) A central role for heme iron in colon carcinogenesis associated with red meat intake. Cancer Res 75: 870-879.
19. Bastide N, Morois S, Cadeau C, Kangas S, Serafini M, et al. (2016) Heme iron intake, dietary antioxidant capacity and risk of colorectal adenomas in a large cohort study of French women. Cancer Epidemiol Biomarkers Prev 25: 640-647.
20. Sasso A, Latella G (2018) Role of heme iron in the association between red meat consumption and colorectal cancer. Nutr Cancer 70: 1173-1183.
21. Yilmaz B, Li H (2018) Gut microbiota and iron: the crucial actors in health and disease. Pharmaceuticals 11: 98.
22. Buret AG, Motta JP, Allain T, Ferraz J, Lawrence J (2019) Pathobiont release from dysbiotic gut microbiota biofilms in intestinal inflammatory diseases: A role for iron? J Biomed Sci 26: 1.
23. Ashmore JH, Rogers CJ, Kelleher SL, Lesko SM, Hartman TJ (2016) Dietary iron and colorectal cancer risk: A review of human population studies. Crit Rev Food Sci Nutr 56: 1012-1020.
24. Luo H, Zhang NQ, Huang J, Zhang X, Feng XL, et al. (2019) Dietary intakes of different forms and sources of iron and colorectal cancer risk: A case-control study in China. Br J Nutr 121: 735-747.
25. Hooda J, Shah A, Zhang L (2014) Heme, an essential nutrient from dietary proteins, critically impacts diverse physiological and pathological processes. Nutrients 6: 1080-1102.
26. Wallace DF (2016) The regulation of iron absorption and homeostasis. Clin Biochem Rev 37: 51-62.
27. Manz DH, Blanchette NL, Paul BT, Torti FM, Torti SV (2016) Iron and cancer: Recent insights. Ann N Y Acad Sci 1368: 149-161.
28. Coffey R, Ganz T (2017) Iron homeostasis-an anthropocentric perspective. J Biol Chem 292: 12727-12734.
29. Neves J, Haider T, Gassmann M, Muckenthaler MU (2019) Iron homeostasis in the lungs - A balance between health and disease. Pharmaceuticals 12: 5.
30. Wen CP, Lee JH, Tai YP, Wen C, Wu SB, et al. (2014) High serum iron is associated with increased cancer risk. Cancer Res 74: 6589-6597.

31. O'Mahony F, Thomas W, Harvey BJ (2009) Novel female sex-dependent actions of estrogen in the intestine. J Physiol 587: 5039-5044.

32. Keum NN, Giovannucci EL (2017) Epidemiology of colorectal cancer. In: Loda M, et al. (eds.), Pathology and Epidemiology of Cancer © Springer International Publishing Switzerland, Chapter 21, pp: 391-407.

33. Cho NL, Javid SH, Carothers AM, Redston M, Bertagnolli MM (2007) Estrogen receptors α and β are inhibitory modifiers of Apc-dependent tumorigenesis in the proximal colon of Min/+ mice. Cancer Res 67: 2366-2372.

34. Caiazza F, Ryan EJ, Doherty G, Winter DC, Sheahan K (2015) Estrogen receptors and their implications in colorectal carcinogenesis. Front Oncol 5: 19.

35. Niv Y (2015) Estrogen receptor β expression and colorectal cancer: A systematic review and meta-analysis. Eur J Gastroenterol Hepatol 27: 1438-1442.

36. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, Hubbell FA, Ascensao J, et al. (2004) Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 350: 991-1004.

37. Foster PA (2013) Estrogen and colorectal cancer: Mechanisms and controversies. Int J Colorectal Dis 28: 737-749.

38. Foley EF, Jazaeri AA, Shupnik MA, Jazaeri O, Rice LW (2000) Selective loss of estrogen receptor β in malignant human colon. Cancer Res 60: 245-248.

39. Sato R, Suzuki T, Katayose Y, Miura K, Shiiba K, et al. (2012) Aromatase in colon carcinoma. Anticancer Res 32: 3069-3076.

40. Comision Honoraria de Lucha Contra el Cancer (1993) Knowledge, believes, attitudes and practices related to cancer: population survey. Technical co-operation PNUD/BID. Comision Honoraria de Lucha Contra el Cancer, Montevideo, Uruguay (in Spanish).

41. International Agency for Research on Cancer (1991) Coffee, tea, mate, methylxanthines and methylglyoxal: IARC Monogr Eval Carcinog Risks Hum 51: 273-287.

42. Kamangar F, Schantz MM, Abnet CC, Fagundes RB, Dawsey SM (2008) High levels of carcinogenic polycyclic aromatic hydrocarbons in mate drinks. Cancer Epidemiol Biomarkers Prev 17: 1262-1268.

43. Thea AE, Ferreira D, Brumovsky LA, Schmalko ME (2016) Polycyclic aromatic hydrocarbons (PAHs) in yerba mate (*Ilex paraguariensis* St. Hil) traditional infusions (mate and terere). Food Control 60: 215-220.

44. De Mejia EG, Song YS, Heck CI, Ramirez-Mares MV (2010) Yerba mate tea (*Ilex paraguariensis*): Phenolics, antioxidant capacity and in vitro inhibition of colon cancer cell proliferation. J Funct Foods 2: 23-34.

45. Zapaterini JR, Bidinotto LT, Rodrigues MAM, Barbisan LF (2010) Chemopreventive effects of mate against mouse mammary and colon carcinogenesis. Hum Exp Toxicol 29: 175-185.

46. Puangpraphant S, Berhow MA, Gonzalez de Mejia E (2011) Mate (*Ilex paraguariensis* St. Hilaire) saponins induce caspase-3-dependent apoptosis in human colon cancer cells in vitro. Food Chem 125: 1171-1178.

47. Gnoatto SCB, Dassonville-Klimpt A, Da Nascimento S, Galéra P, Boumediene K, et al. (2008) Evaluation of ursolic acid isolated from *Ilex paraguariensis* and derivatives on aromatase inhibition. Eur J Med Chem 43: 1865-1877.

48. Kashyap D, Tuli HS, Sharma AK (2016) Ursolic acid (UA): A metabolite with promising therapeutic potential. Life Sci 146: 201-213.

49. Limami Y, Pinon A, Leger DY, Mousseau Y, Cook-Moreau J, et al. (2011) HT-29 colorectal cancer cells undergoing apoptosis over express COX-2 to delay ursolic acid-induced cell death. Biochimie 93: 749-757.

50. Way TD, Lee HH, Kao MC, Lin JK (2004) Black tea polyphenol theaflavins inhibit aromatase activity and attenuate tamoxifen resistance in HER2/neu-transfected human breast cancer cells through tyrosine kinase suppression. Eur J Cancer 40: 2165-2174.

51. Kim HI, Quan FS, Kim JE, Lee NR, Kim HJ, et al. (2014) Inhibition of estrogen signaling through depletion of estrogen receptor alpha by ursolic acid and betulinic acid from *Prunella vulgaris* var. *lilacina*. Biochem Biophys Res Commun 451: 282-287.

52. Colpo AC, Rosa H, Lima ME, Pazzini CE, de Camargo VB, et al. (2016) Yerba mate (*Ilex paraguariensis* St. Hill.)-based beverages: How successive extraction influences the extract composition and its capacity to chelate iron and scavenge free radicals? Food Chem 209: 185-195.

53. Huang WY, Lee PC, Hsu JC, Lin YR, Chen HJ, et al. (2014) Effects of water quality on dissolution of yerba mate extract powders. Sci World J 768742.

54. Salkic A, Zeljkovic SC (2015) Preliminary investigation of bioactivity of green tea (*Camellia sinensis*), rooibos (*Asphalatus linearis*) and yerba mate (*Ilex paraguariensis*). J Herbs Spices Med Plants 21: 259-266.

55. Rempe CS (2016) Metabolomics approaches to decipher the antibacterial mechanisms of yerba mate (*Ilex paraguariensis*) against *Staphylococcus aureus* and *Salmonella enterica* serovar *typhimurium*. PhD diss.,

University of Tennessee. Available at: http://trace.tennessee.edu/utk_graddiss/3957

56. Ronco AL, De Stefani E, Lasalvia-Galante E, Mendoza B, Vázquez A, et al. (2017) Hot infusions and risk of colorectal cancer in Uruguay: A case-control study. Eur J Clin Nutr 71: 1429-1436.

57. Murphy N, Moreno V, Hughes DJ, Vodicka L, Vodicka P, et al. (2019) Lifestyle and dietary environmental factors in colorectal cancer susceptibility. Mol Aspects Med pii: S0098-2997(19)30033-0.

58. Vieira AR, Abar L, Chan DSM, Vingeliene E, Polemitti E, et al. (2017) Foods and beverages and colorectal cancer risk: A systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Ann Oncol 28: 1788-1802.

59. Martin OCB, Olier M, Ellero-Simatos S, Naud N, Dupuy J, et al. (2019) Heme-iron reshapes colonic luminal environment: Impact on mucosal homeostasis and microbiome through aldehyde formation. Microbiome 7: 72.

60. Hou Y, Zhang S, Wang L, Li J, Qu G, et al. (2012) Estrogen regulates iron homeostasis through governing hepatic hepcidin expression via an estrogen response element. Gene 511: 398-403.

61. Ikeda Y, Tajima S, Izawa-Ishizawa Y, Kihira Y, Ishizawa K, et al. (2012) Estrogen regulates hepcidin expression via GPR30-BMP6-dependent signaling in hepatocytes. PloS One 7: e40465.

62. Haziman AA, Ravinderan S, Thangavelu T, Thomas W (2019) A novel role for estrogen-induced signaling in the colorectal cancer gender bias. Ir J Med Sci 188: 389-395.

63. Ashmore JH, Lesko SM, Miller PE, Cross AJ, Muscat JE, et al. (2013) Association of dietary and supplemental iron and colorectal cancer in a population-based study. Eur J Cancer Prev 22: 506-511

64. Ronco AL, Calderon JM, Espinosa E (2017) Dietary iron, 'mate' intake and breast cancer risk: A case-control study in Uruguay. J Breast Cancer Res Adv 1.

65. Ronco AL, Espinosa E, Calderon JM (2018) A case-control study on heme/non-heme iron and breast cancer risk. Ann Clin Nutr 3: 1011.

66. Ronco AL, Lasalvia-Galante E, Calderon JM, Espinosa E (2019) Dietary iron source and lung cancer risk: A case-control study in Uruguayan men. Multidiscip Cancer Invest 3: 20-36.

67. Ronco AL, De Stefani E, Boffetta P, Deneo-Pellegrini H, Acosta G, et al. (2006) Food patterns and risk of breast cancer: A factor analysis study in Uruguay. Int J Cancer 119: 1672-1678.

68. Mazzei ME, Puchulu MR, Rochaix MA (1995) Table of food chemical composition. Cenexa y Feiden Publishers, 2nd Edn., Buenos Aires (in Spanish).

69. Kabat GC, Miller AB, Jain M, Rohan TE (2007) A cohort study of dietary iron and heme iron intake and risk of colorectal cancer in women. Br J Cancer 97: 118-122.

70. Zhang W, Iso H, Ohira T, Date OC, Tanabe N, et al. (2012) Associations of dietary iron intake with mortality from cardiovascular disease: The JACC study. J Epidemiol 22: 484-493.

71. Cross AJ, Harnly JM, Ferrucci LM, Risch A, Mayne ST, et al. (2012) Developing a heme iron database for meats according to meat type, cooking method and doneness level. Food Nutr Sci 3: 905-913.

72. Breslow NE, Day NE (1980) Statistical methods in cancer research: The analysis of case-control studies. IARC Sci Publ 1: 5-338.

73. Levi F, Pasche C, Lucchini F, La Vecchia C (2000) Selected micronutrients and colorectal cancer. A case-control study from the canton of Vaud, Switzerland. Eur J Cancer 36: 2115-2119.

74. Senesse P, Meance S, Cottet V, Faivre J, Boutron-Ruault MC (2004) High dietary iron and copper and risk of colorectal cancer: A case-control study in Burgundy, France. Nutr Cancer 49: 66-71.

75. Van Lee L, Heyworth J, McNaughton S, Iacopetta B, Clayforth C, et al. (2011) Selected dietary micronutrients and the risk of right- and left-sided colorectal cancers: A case-control study in Western Australia. Ann Epidemiol 21: 170-177.

76. Key TJ, Appleby PN, Masset G, Brunner EJ, Cade JE, et al. (2012) Vitamins, minerals, essential fatty acids and colorectal cancer risk in the United Kingdom dietary cohort consortium. Int J Cancer 131: E320-325.

77. Cross AJ, Pollock JR, Bingham SA (2003) Heme, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. Cancer Res 63: 2358-2360.

78. Northstone K (2012) Dietary patterns: The importance of sex differences. Br J Nutr 108: 393-394.

79. Bechaux J, De la Pomélie D, Théron L, Santé-Lhoutellier V, Gatellier P (2018) Iron-catalysed chemistry in the gastrointestinal tract: Mechanisms, kinetics and consequences. A review. Food Chem 268: 27-39.

80. Kabat GC, Rohan TE (2007) Does excess iron play a role in breast carcinogenesis? An unresolved hypothesis. Cancer Causes Control 18: 1047-1053.

81. Miller EM (2014) Iron status and reproduction in US women: National Health and Nutrition Examination Survey, 1999-2006. PLoS One 9: e112216.

82. Roe T (2015) The role of iron and heme in breast cancer. Doctoral thesis, School of Cancer Sciences, Univ. of Birmingham. Available at: https://etheses.bham.ac.uk/id/eprint/6233/1/Roe15MD.pdf

83. Dashwood R, Yamane S, Larsen R (1996) Study of the forces stabilizing complexes between chlorophylls and heterocyclic amine mutagens. Environ Mol Mutag 27: 211-218.

84. Blaszczyk U, Duda-Chodak A (2013) Magnesium: Its role in nutrition and carcinogenesis. Rocz Panstw Zakl Hig 64: 165-171.

85. Wang Y, Zhu M, Mei J, Luo S, Leng T, et al. (2019) Comparison of furans formation and volatile aldehydes profiles of four different vegetable oils during thermal oxidation. J Food Sci 84: 1966-1978.

86. Guillen MD, Uriarte PS (2012) Aldehydes contained in edible oils of a very different nature after prolonged heating at frying temperature: Presence of toxic oxygenated α, β unsaturated aldehydes. Food Chem 131: 915-926.

87. Hansen SL, Ashwell MS, Moeser AJ, Fry RS, Knutson MD, et al. (2010) High dietary iron reduces transporters involved in iron and manganese metabolism and increases intestinal permeability in calves. J Dairy Sci 93: 656-665.

88. Cindric M, Cipak A, Zapletal E, Jaganjac M, Milkovic L, et al. (2013) Stobadine attenuates impairment of an intestinal barrier model caused by 4-hydroxynonenal. Toxicol Vitr 27: 426-432.

89. Lee SE, Park YS (2013) Role of lipid peroxidation-derived α, β-unsaturated aldehydes in vascular dysfunction. Oxid Med Cell Longev 629028.

90. Glei M, Klenow S, Sauer J, Wegewitz U, Richter K, et al. (2006) Hemoglobin and hemin induce DNA damage in human colon tumor cells HT29 clone 19A and in primary human colonocytes. Mutat Res 594: 162-171.

91. Knoll N, Ruhe C, Veeriah S, Sauer J, Glei M, et al. (2005) Genotoxicity of 4-hydroxy-2-nonenal in human colon tumor cells is associated with cellular levels of glutathione and the modulation of glutathione S-transferase A4 expression by butyrate. Toxicol Sci 86: 27-35.

92. Fang S, Zhuo Z, Yu X, Wang H, Feng J (2018) Oral administration of liquid iron preparation containing excess iron induces intestine and liver injury, impairs intestinal barrier function and alters the gut microbiota in rats. J Trace Elem Med Biol 47: 12-20.

93. Kortman GAM, Dutilh BE, Maathuis AJH, Engelke UF, Boekhorst J, et al. (2016) Microbial metabolism shifts towards an adverse profile with supplementary iron in the TIM-2 in vitro model of the human colon. Front Microbiol 6: 1481.

94. Pierre F, Tache S, Petit CR, Van der Meer R, Corpet DE (2003) Meat and cancer: Hemoglobin and hemin in a low-calcium diet promote colorectal carcinogenesis at the aberrant crypt stage in rats. Carcinogenesis 24: 1683-1690.

95. Pierre FHF, Martin OCB, Santarelli RL, Taché S, Naud N, et al. (2013) Calcium and α-tocopherol suppress cured-meat promotion of chemically induced colon carcinogenesis in rats and reduce associated biomarkers in human volunteers. Am J Clin Nutr 98: 1255-1262.

96. Pierre F, Tache S, Guéraud F, Rerole AL, Jourdan MLL, et al. (2007) Apc mutation induces resistance of colonic cells to lipoperoxide-triggered apoptosis induced by fecal water from heme-fed rats. Carcinogenesis 28: 321-327.

97. Martin OCB, Lin C, Naud N, Tache S, Raymond-Letron I, et al. (2015) Antibiotic suppression of intestinal microbiota reduces heme-induced lipoperoxidation associated with colon carcinogenesis in rats. Nutr Cancer 67: 119-125.

98. Pierre FH, Santarelli RL, Allam O, Tache S, Naud N, et al. (2010) Freeze-dried ham promotes azoxymethane-induced mucin-depleted foci and aberrant crypt foci in rat colon. Nutr Cancer 62: 567-573.

99. Fraumeni JF Jr, Lloyd JW, Smith EM, Wagoner JK (1969) Cancer mortality among nuns: Role of marital status in etiology of neoplastic disease in women. J Natl Cancer Inst 42: 455-468.

100. Zervoudakis A, Strickler HD, Park Y, Xue X, Hollenbeck A, et al. (2011) Reproductive history and risk of colorectal cancer in post-menopausal women. J Natl Cancer Inst 103: 826-834.

101. English MA, Kane KF, Cruickshank N, Langman MJ, Stewart PM, et al. (1999) Loss of estrogen inactivation in colonic cancer. J Clin Endocrinol Metab 84: 2080-2085.

102. Fiorelli G, Picariello L, Martineti V, Tonelli F, Brandi ML (1999) Estrogen synthesis in human colon cancer epithelial cells. J Steroid Biochem Mol Biol 71: 223-230.

103. Gantt SL, Denisov IG, Grinkova YV, Sligar SG (2009) The critical iron-oxygen intermediate in human aromatase. Biochem Biophys Res Commun 387: 169-173.

104. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, et al. (2008) Insulin, insulin-like growth factor-I, endogenous estradiol and risk of colorectal cancer in post-menopausal women. Cancer Res 68: 329-337.

105. Fan W, Gao X, Ding C, Lv Y, Shen T, et al. (2019) Estrogen receptors participate in carcinogenesis signaling pathways by directly regulating NOD-like receptors. Biochem Biophys Res Comm 511: 468-475.

106. Williams C, Dileo A, Niv Y, Gustaffson JA (2016) Estrogen receptor beta as target for colorectal cancer prevention. Cancer Lett 372: 48-56.

107. Saleiro D, Murillo G, Benya RV, Bissonnette M, Hart J, et al. (2012) Estrogen receptor-b protects against colitis-associated neoplasia in mice. Int J Cancer 131: 2553-2561.

108. Looijer-van Langen M, Hotte N, Dieleman LA, Albert E, Mulder C, et al. (2011) Estrogen receptor-b signaling modulates epithelial barrier function. Am J Physiol Gastrointest Liver Physiol 300: G621-626.

109. Nüssler NC, Reinbacher K, Shanny N, Schirmeier A, Glannemann M, et al. (2008) Sex-specific differences in the expression levels of estrogen receptor subtypes in colorectal cancer. Gender Med 5: 209-217.

110. Van Maanen JMS, Moonen EJC, Maas LM, Kleinjans JCS, van Schooten FJ (1994) Formation of aromatic DNA adducts in white blood cells in relation to urinary excretion of 1-hydroxypyrene during consumption of grilled meat. Carcinogenesis 15: 2263-2268.

111. Van de Wiele T, Vanhaecke L, Boeckaert C, Peru K, Headley J, et al. (2005) Human colon microbiota transforms polycyclic aromatic hydrocarbons to estrogenic metabolites. Environ Health Perspect 113: 6-10.

112. Flores R, Shi J, Fuhrman B, Xu X, Veenstra TD, et al. (2012) Fecal microbial determinants of fecal and systemic estrogens and estrogen metabolites: A cross sectional study. J Transl Med 10: 253.

113. Kwa M, Plottel CS, Blaser MJ, Adams S (2016) The intestinal microbiome and estrogen receptor-positive female breast cancer. J Natl Cancer Inst 108: djw029.

114. Plottel CS, Blaser MJ (2011) Microbiome and malignancy. Cell Host Microb 10: 324-335.

115. Chen KL, Madak-Erdogan Z (2016) Estrogen and microbiota cross-talk: Should we pay attention? Trends Endocr Metab 27: 752-755.

116. Baker JM, Al-Nakkash L, Herbst-Kralovetz MM (2017) Estrogen-gut microbiome axis: Physiological and clinical implications. Maturitas 103: 45-53.

117. Blasco-Baque V, Serino M, Vergnes JN, Riant E, Loubieres P, et al. (2013) High-fat diet induces periodontitis in mice through lipopolysaccharides (LPS) receptor signaling: Protective action of estrogens. PLoS One 7: e48220.

118. Kim YS, Unno T, Kim BY, Park MS (2019) Sex Differences in gut microbiota. World J Mens Health 37: e15.

119. Vemuri R, Sylvia KE, Klein SL, Forster SC, Plebanski M, et al. (2019) The microgenderome revealed: Sex differences in bidirectional interactions between the microbiota, hormones, immunity and disease susceptibility. Semin Immunopathol 41: 265-275.

120. Duda-Chodak A, Tarko T, Satora P, Sroka P (2015) Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: A review. Eur J Nutr 54: 325-341.

121. Li G, Ma D, Zhang Y, Zheng W, Wang P (2012) Coffee consumption and risk of colorectal cancer: A meta-analysis of observational studies. Publ Health Nutr 16: 346-357.

122. Schmit SL, Rennert HS, Rennert G, Gruber SB (2016) Coffee consumption and the risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 25: 634-639.

123. Kiyama R (2019) Estrogenic activity of coffee constituents. Nutrients 11: 1401.

124. Tseng M, Sandler RS, Greenberg ER, Mandel JS, Haile RW, et al. (1997) Dietary iron and recurrence of colorectal adenomas. Cancer Epidemiol Biomarkers Prev 6: 1029-1032.