RESEARCH ARTICLE

Mate and Tea Intake, Dietary Antioxidants and Risk of Breast Cancer: a Case-Control Study

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Abstract

Recently, we reported an inverse association between high 'mate' intake (infusion of *Ilex paraguariensis* herb, a staple beverage in temperate South America) and breast cancer (BC) risk. Stronger inverse associations were found in high strata of tea, vegetable, fruit and energy intakes, and in overweight/obese women, suggesting possible roles for 'mate' mainly from its antioxidant contribution. The present study attempted to thoroughly explore possible associations among 'mate' and tea intake, dietary antioxidants and BC risk. Combining two databases of previous studies, 572 BC incident cases and 889 controls were interviewed with a specific questionnaire featuring socio-demographic, reproductive and lifestyle variables, and a food frequency questionnaire (64 items), focusing on 'mate' intake (consumer status, daily intake, age at start, age at quit, duration of habit). Food-derived nutrients were calculated from available databases. Odds ratios (OR) and their 95% confidence intervals were calculated through unconditional logistic regression, adjusting for relevant potential confounders. The highest 'mate' intake was significantly inversely associated with BC risk for both low and high carotenoids (OR=0.40 *vs.* 0.41), vitamin C (OR=0.33 *vs.* 0.50), vitamin E (OR=0.37 *vs.* 0.45), flavonols (OR=0.38 *vs.* 0.48) and reduced glutathione (OR=0.48 *vs.* 0.46) strata. High tea intake showed significant inverse risk associations only with high carotenoids (OR=0.41), vitamin E (OR=0.48) and reduced glutathione (OR=0.43) strata. In conclusion, a strong and inverse association for 'mate' intake and BC was found, independent of dietary antioxidant levels. Also strong inverse associations with tea intake were more evident only at high levels of certain dietary antioxidants.

Keywords: Breast cancer - *Ilex paraguariensis* - mate - tea - infusions - antioxidants

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Introduction

Breast cancer (BC) is the leading malignancy among Uruguayan women, with a national age-adjusted incidence rate of 73.1 per 100.000 (Barrios et al., 2014), the highest one among South American registries (Ferlay et al., 2013). Several studies conducted in Uruguay have thoroughly analyzed the relationship between nutrition and BC, from diet as well as from anthropometry (Ronco et al., 2010a; Ronco and De Stefani, 2012).

Regarding possible associations between hot drinks like tea and coffee and BC risk, the international literature is still inconsistent (Gierach et al., 2012; Jiang et al., 2013; Wu et al., 2013; Gao et al., 2013; Nie et al., 2014; Bhoo-Pathy et al., 2015). Five years ago, our group published a multi-site case-control study focused on 'mate' drinking and the risk of several cancers in population admitted to the public healthcare system, which showed a non significant negative association for high 'mate' intake and BC risk (OR=0.85, 95% CI 0.67-1.09, p for trend=0.31) (De Stefani et al., 2011). It was the first time that findings on this topic were reported, but at that time the employed regression model lacked of terms for menopausal status, dietary energy, menstrual/reproductive history and family history of cancer.

'Mate' is a hot infusion made from the herb ilex paraguariensis, a staple nonalcoholic beverage in temperate South America. Hot 'mate' drinking has been considered as a 2A agent, that is, a possible carcinogenic for humans according to the International Agency for Research on Cancer (IARC, 1991), due to the presence of polycyclic aromatic hydrocarbons (PAH) (IARC, 2010). Nevertheless, although a recent paper reported the presence of 8 PAHs in hot and cold 'mate' infusions, it also highlighted that none of the infusions exceeded the maximum level for certain PAHs suggested by the World Health Organization for drinking water (700 ng/ml) (Thea et al., 2016).

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In addition, the infusion is among a series of products having priority to be reassessed by the quoted Agency (IARC, 2014), probably because basic research has demonstrated the presence of several compounds having antioxidant properties (polyphenols, flavonols), among other ones as chlorogenic acids (Jaiswal et al., 2010) and methylxantines (caffeine, teobromin) (Heck and de Mejia, 2007; Bracesco et al., 2011). Furthermore, 'mate' infusion has shown comparable oxygen radical scavenger activity as ascorbate, glutathione and cysteine (Coppes et al., 2014).

A recent communication (Ronco et al., 2016a) reported significant reduced risks for high intakes of black tea (OR=0.40, p- for trend=0.001) and 'mate' (OR=0.21, p- for trend=0.001) among women coming from our private healthcare system. This study reported also lack of association for coffee consumption (OR=0.72, p-value for trend=0.22). In addition, a more recent paper which analyzed a larger sample (Ronco et al., 2016b), reported again strong inverse associations between the intake of 'mate' (OR=0.40 for >1 liter/day, p- for trend<0.001). The associations were even stronger among high strata of tea drinkers (OR=0.22, p- for trend<0.001) and of fruits/vegetables combined (OR=0.35, p- for trend<0.001). Such results suggested us two concepts: 1. Potential carcinogenic compounds which have been found in 'mate' infusion could be counterbalanced and also overcome by its own antioxidant compounds. 2. Potential protection could be linked to an additional antioxidant load coming from different sources.

Therefore, taking into account that: a) Uruguay has the World's highest per capita 'mate' consumption (9-10 kg/person/year of the herb and ca. 400 liters/person/year of infusion) (Comisión Honoraria de Lucha Contra el Cancer, 1993); and b) Antioxidants, as bioactive substances mainly derived from vegetables and fruits, have been demonstrated as protective agents on BC risk among Uruguayan women (Ronco et al., 1999; 2010b; 2016c) we decided to perform additional analyses on 'mate' and tea intakes and their relationships with selected dietary antioxidants, in order to better know their mutual influence concerning BC risk.

Materials and Methods

Two case-control studies on BC were conducted in Montevideo (where 45% of inhabitants live) by our group: one of them was carried out during 1996-2004 in the major public hospitals (Oncology, Clinicas, Pasteur, Maciel) and the other one was performed in a private hospital (IMPASA, abbreviated name of former Instituto Medico de Previsión, Asistencia y Servicios Afines) in the years 1999-2001. The respective databases, having the same basic structure, allowed us the analysis of a total sample including 1461 participants, 572 cases and 889 controls. We will briefly describe the selection criteria regarding participants from each healthcare system.

Public hospitals

In the study period a total number of 480 newly diagnosed and microscopically confirmed BC were considered eligible for the study. A number of 19 patients refused the interview, leaving a final total of 461 cases which were included in the study (response rate 96.0 %). In the same time period and in the same hospitals, 685 hospitalized patients having diseases not related with smoking, drinking and without recent changes in their diet were considered eligible for this study. Patients proceeded from any part of the country, even from rural areas. Of them, 18 patients refused the interview, leaving a final total of 667 controls (response rate 97.4%). Four trained social workers interviewed cases and controls in the hospitals shortly after admittance and no proxy interviews were conducted.

Private hospital

The chosen medical institution was representative of the pre-paid system in Montevideo, with ca. 15.000 female affiliates (mostly inhabitants at the capital city) and showing a crude rate of BC of 267/100.000 due to its ca. 40 incident cases/year. During the study period 116 histologically verified cases of BC were collected. In the same time period 223 healthy women with a normal control mammography (Birads 1) (Feig, 1999), performed no longer than one year before the interview, were selected as controls (2 controls per case). One control and two cases had rejected the interview and three other cases (0.9%) died during the study period, leading to a final number of 111 cases and 222 controls (response rates of 95.7% and 99.6% respectively). They were matched by age (± 5 years) and residence (Montevideo and surrounding neighbourhoods) and they were not hospitalized at the moment of the interview nor diagnosed with cancer. All women had ages <85, in an attempt to reduce a possible recall bias. Both cases and controls were women undergoing routine mammography testing and belonged to mid-to-high socio-economic strata. All 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

A structured questionnaire was applied to all participants. The questionnaire included the following sections: (1) socio-demographic variables; (2) a section on occupation based on job titles and the duration of each activity; (3) history of cancer in first- and second-degree relatives; (4) self-reported height and weight 5 years before the interview; (5) a tobacco smoking section (including age at starting, age of quitting, and average number of cigarettes smoked per day); (6) a history on alcohol drinking (including type of beverage, age at starting, age of quitting, and average amount of alcohol drunk per day); (7) a history of 'mate', tea and coffee drinking (age at starting, age of quitting, and average amount of the infusion drunk per day); (8) menstrual and reproductive events; and (9) a detailed food-frequency questionnaire (FFQ) on 64 items representative of the diet of the Uruguayan population, which asked about food consumption 5 years prior to diagnosis in cases and prior to the interview in controls. Tea intake was assumed as black tea, since the introduction of other types (green, red)

is very recent in the Uruguayan society. The FFQ was not validated, but was tested for reproducibility, having high correlations (Ronco et al., 2006). Furthermore, the FFQ allowed the intake of total energy and several nutrients for each subject to be estimated. All dietary questions of our semi-quantitative questionnaire were open-ended.

In order to achieve an estimation of selected dietary antioxidants, and due to the lack of local tables of food composition, we used foreign tables regarding carotenoids (Holden et al., 1999), vitamin C and E (Mazzei et al., 1995), flavonoids (Bhagwat et al., 2013) and glutathione (Wierzbicka et al., 1989). For the calculation of antioxidants, we estimated intakes of α-carotene, β-carotene, β-cryptoxanthin, lutein, lycopene and total carotenoids. Regarding flavonoids, we estimated intakes of quercetin, kaempferol, and flavonols as the sum of

Table 1. Distribution of Cases and Controls Concerning Socio-Demographic and Relevant Epidemiological Variables

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

Table 2. Comparison of Selected Nutritional Features between Cases and Controls

Variable	Units	Controls mean ± SE*	Cases mean ± SE*	p-value
Red meat intake	servings/year	281.5 ± 5.2	318.8 ± 6.8	<0.001
Chicken intake	servings/year	69.7 ± 1.7	58.8 ± 2.2	<0.001
Fish intake	servings/year	49.9 ± 1.4	41.7 ± 1.5	<0.001
Milk intake	cups/year	123.6 ± 5.4	145.9 ± 7.2	<0.001
Vegetables intake	servings/year	746.3 ± 14.9	724.2 ± 24.1	0.41
Fruit intake	servings/year	605.2 ± 17.3	533.9 ± 21.5	0.01
Dietary energy	Kcal/day	1964.6 ± 20.2	2081.8 ± 25.3	<0.001
Coffee intake	ml/day	39.2 ± 2.7	33.9 ± 4.2	0.26
Tea intake	ml/day	73.1 ± 3.8	55.3 ± 4.1	0.002
Mate intake	ml/day	871.0 ± 24.9	702.2 ± 24.6	<0.001
Carotenoids	μg/day	13351 ± 289	12853 ± 422	0.33
Vitamin C	mg/day	120.5 ± 2.0	115.9 ± 2.8	0.17
Vitamin E	mg/day	4.40 ± 0.06	4.47 ± 0.11	0.58
Flavonols	mg/day	58.4 ± 10.0	54.7 ± 12.9	0.02
Glutathione	mg/day	49.4 ± 0.6	50.4 ± 0.7	0.31

* SE = Standard Error

Table 3. Odds Ratios (OR) of Estimated Dietary Antioxidants in the Analyzed Sample. Reference Category (I) Omitted

Variable	Model	II		III		IV		Trend
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	(p)
α-carotene	A	0.83	(0.61-1.13)	0.97	(0.71-1.32)	0.77	(0.47-1.27)	0.56
	B	0.92	(0.67-1.26)	0.96	(0.70-1.33)	0.84	(0.49-1.46)	0.66
β-carotene	A	0.97	(0.71-1.32)	0.96	(0.70-1.32)	0.58	(0.39-0.86)	0.03
	B	0.97	(0.71-1.32)	0.96	(0.69-1.32)	0.60	(0.38-0.95)	0.11
Lutein	A	1.02	(0.76-1.39)	0.82	(0.60-1.11)	0.44	(0.29-0.66)	<0.001
	B	1.00	(0.73-1.37)	0.80	(0.58-1.11)	0.42	(0.27-0.67)	0.001
Lycopene	A	0.96	(0.71-1.31)	0.83	(0.61-1.14)	0.82	(0.60-1.13)	0.15
	B	1.00	(0.73-1.37)	0.77	(0.56-1.07)	0.80	(0.56-1.15)	0.11
β-Cryptoxanthin	A	0.99	(0.73-1.35)	1.19	(0.87-1.62)	0.92	(0.65-1.30)	0.91
	B	1.01	(0.74-1.38)	1.26	(0.92-1.73)	1.22	(0.80-1.86)	0.14
Total carots.	A	0.92	(0.68-1.25)	0.67	(0.49-0.93)	0.50	(0.33-0.76)	0.001
	B	0.88	(0.65-1.21)	0.63	(0.44-0.89)	0.45	(0.27-0.75)	0.001
Vitamin C	A	0.81	(0.59-1.11)	0.66	(0.48-0.91)	0.53	(0.38-0.75)	<0.001
	B	0.82	(0.59-1.13)	0.67	(0.47-0.86)	0.53	(0.33-0.84)	0.005
Vitamin E	A	0.85	(0.61-1.19)	0.62	(0.42-0.91)	0.61	(0.38-0.98)	0.02
	B	0.85	(0.60-1.20)	0.69	(0.46-1.03)	0.76	(0.44-1.31)	0.17
Quercetin	A	0.82	(0.60-1.11)	0.62	(0.45-0.86)	0.45	(0.32-0.63)	<0.001
	B	0.86	(0.63-1.18)	0.69	(0.49-0.96)	0.45	(0.36-0.75)	<0.001
Kaempferol	A	1.23	(0.90-1.68)	0.53	(0.38-0.75)	0.74	(0.53-1.02)	0.002
	B	1.28	(0.93-1.76)	0.60	(0.42-0.85)	0.97	(0.62-1.50)	0.09
Flavonols	A	0.79	(0.58-1.07)	0.63	(0.46-0.86)	0.46	(0.33-0.64)	<0.001
	B	0.83	(0.61-1.14)	0.70	(0.50-0.98)	0.53	(0.37-0.78)	0.001
Animal GSHT	A	0.96	(0.68-1.36)	1.51	(1.03-2.22)	1.39	(0.88-2.20)	0.04
	B	1.03	(0.72-1.47)	1.59	(1.08-2.36)	1.57	(0.99-2.50)	0.01
Veget. GSHT	A	0.86	(0.63-1.17)	0.64	(0.46-0.89)	0.62	(0.44-0.86)	0.002
	B	0.81	(0.59-1.12)	0.63	(0.45-0.89)	0.54	(0.36-0.83)	0.002
Fruit GSHT	A	1.00	(0.74-1.35)	0.73	(0.53-1.01)	0.72	(0.50-1.03)	0.03
	B	1.07	(0.78-1.46)	0.83	(0.58-1.19)	0.98	(0.56-1.71)	0.52
Total GSHT	A	0.91	(0.65-1.27)	0.90	(0.62-1.29)	0.64	(0.42-0.99)	0.06
	B	0.97	(0.69-1.37)	1.03	(0.69-1.52)	0.81	(0.48-1.37)	0.60

*Model A: Adjusted for hospital (binary), residence (binary), age (categorized), menopausal status (binary), family history of BC in 1st and 2nd degree (categorized), body mass index (categorized), dietary energy (categorized), smoking status (categorized), alcohol drinking frequency (continuous) and total red meat (continuous); Model B: Id. + vegetables, fruits, mate, tea and coffee (all of these as continuous variables)

Table 4. Odds Ratios (OR) and 95% Confidence Intervals (CI) for 'Mate' Consumption, Showing Results with and without Inclusion of Dietary Antioxidants (AOX)

Variable	Categories	Controls/ Cases	Without AOX OR (95% CI)	With AOX OR (95% CI)
Mate status	Non drinker	146/108	Ref.	Ref.
	Ex–drinker	59/44	0.73 (0.44-1.20)	0.66 (0.39-1.11)
	Current drinker	684/420	0.63 (0.47-0.86)	0.65 (0.47-0.90)
	p for trend		0.004	0.01
Amount (liters/day)	Non drinker	146/108	Ref.	Ref.
	0.01-0.99	262/235	0.82 (0.58-1.17)	0.83 (0.58-1.18)
	1.00	265/122	0.63 (0.46-0.87)	0.64 (0.46-0.89)
	≥1.01	173/68	0.38 (0.25-0.57)	0.41 (0.27-0.63)
	p for trend		<0.001	<0.001
Duration (years)	Non drinker	146/108	Ref.	Ref.
	1-34	273/148	0.62 (0.43-0.90)	0.64 (0.44-0.94)
	35-50	247/161	0.64 (0.45-0.91)	0.67 (0.47-0.95)
	≥51	223/155	0.62 (0.42-0.91)	0.62 (0.42-0.93)
	p for trend		0.01	0.02
Intensity (liters*years)	Non drinker	146/108	Ref.	Ref.
	0.1-24.0	238/165	0.79 (0.55-1.13)	0.78 (0.55-1.13)
	24.1-44.0	246/173	0.70 (0.50-0.99)	0.73 (0.51-1.04)
	≥44.1	259/126	0.46 (0.32-0.67)	0.49 (0.34-0.71)
	p for trend		<0.001	<0.001

Regression models: Without AOX: Adjusted for hospital (binary), residence (binary), age (categorized), menopausal status (binary), family history of BC in 1st and 2nd degree (categorized), body mass index (categorized), dietary energy (categorized), smoking status (categorized), alcohol drinking frequency (continuous), total red meat (continuous), total vegetables (continuous), total fruits (continuous), tea (continuous) and coffee (continuous). With AOX: Id. + total carotenoids (continuous), vitamin C (categorized), vitamin E (categorized), total flavonols (continuous) and total reduced Glutathione (continuous)

both. In order to calculate daily nutrients, or energy, we compiled an analysis program which 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 individual foodstuff, divided by the 365 days of the year. Most typical or average servings of solid foods were found to be within the range of 100-150 grams.

Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated by unconditional logistic regression (Breslow and Day, 1980). Potential confounders were included in the multivariate analysis. All equations included terms for hospital, residence, age, education, age at menarche, body mass index, number of childbirths, menopausal status, family history of BC in first and second degree relatives, smoking status, alcohol intake, total energy intake, and intakes of red meat, total fruits, total vegetables, tea and coffee. Additional analyses required the inclusion 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, StataCorp LP, College Station, TX, 2007).

Results

The distribution of cases and controls according to sociodemographic and reproductive factors is shown on Table 1. Although participants were not completely matched, an adequate age distribution was achieved (p- value=0.87). More cases proceeded from rural areas than controls (12.93 vs. 9.45 % respect.), but there were similarities regarding educational level (p = 0.94) and body mass index (p = 0.54). Family history of BC, number of live births and breastfeeding time displayed significant differences and the age at first live birth was close to significance.

Table 2 compares the mean values with standard deviations of 15 selected items concerning the case/control status of study participants. Cases showed higher intake of

Table 5. Odds Ratios (OR) of Mate Intake (quartiles) and 95% Confidence Intervals (CI), Stratified for Categories of Selected Dietary Antioxidants (Low/High Intake according to Median Values) and of Menopausal Status. Reference category for Mate Intake are Non-drinkers omitted in Table

Variable	Strata	Mate Intake (liters/day) II 0.01-0.99		III 1.00		IV ≥1.01		Trend
		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	(p)
Crude OR	----	1.12	(0.81-1.53)	0.83	(0.61-1.12)	0.53	(0.37-0.77)	<0.001
Adjusted OR	----	0.84	(0.59-1.20)	0.65	(0.47-0.90)	0.38	(0.25-0.58)	<0.001
α-carotene	Low	1.15	(0.66-2.00)	0.89	(0.52-1.54)	0.60	(0.31-1.16)	0.04
	High	0.65	(0.39-1.07)	0.48	(0.30-0.74)	0.30	(0.17-0.55)	<0.001
β-carotene	Low	0.80	(0.48-1.32)	0.81	(0.49-1.34)	0.49	(0.25-0.93)	0.07
	High	1.01	(0.59-1.71)	0.53	(0.33-0.83)	0.37	(0.21-0.65)	<0.001
Lutein	Low	0.97	(0.59-1.57)	0.82	(0.51-1.34)	0.54	(0.30-0.99)	0.04
	High	0.90	(0.51-1.56)	0.57	(0.35-0.92)	0.37	(0.20-0.69)	<0.001
Lycopene	Low	1.09	(0.65-1.82)	0.70	(0.43-1.12)	0.46	(0.25-0.83)	0.002
	High	0.64	(0.38-1.08)	0.64	(0.40-1.04)	0.35	(0.19-0.65)	0.003
β-Cryptoxanthin	Low	0.89	(0.52-1.50)	0.62	(0.37-1.04)	0.34	(0.17-0.68)	<0.001
	High	0.79	(0.47-1.33)	0.68	(0.43-1.07)	0.47	(0.27-0.81)	0.006
Total carots.	Low	0.84	(0.51-1.39)	0.70	(0.42-1.15)	0.40	(0.21-0.78)	0.006
	High	0.96	(0.56-1.65)	0.62	(0.39-0.98)	0.41	(0.23-0.73)	<0.001
Vitamin C	Low	0.75	(0.45-1.25)	0.55	(0.33-0.90)	0.33	(0.17-0.64)	<0.001
	High	0.87	(0.52-1.47)	0.74	(0.46-1.18)	0.50	(0.29-0.87)	0.01
Vitamin E	Low	0.87	(0.51-1.46)	0.85	(0.50-1.43)	0.37	(0.19-0.74)	0.01
	High	0.85	(0.50-1.46)	0.52	(0.33-0.81)	0.45	(0.26-0.78)	<0.001
Quercetin	Low	0.73	(0.44-1.20)	0.73	(0.46-1.16)	0.38	(0.20-0.73)	0.01
	High	1.02	(0.60-1.75)	0.58	(0.35-0.95)	0.49	(0.27-0.89)	0.001
Kaempferol	Low	0.89	(0.53-1.48)	0.80	(0.48-1.32)	0.57	(0.31-1.06)	0.07
	High	0.91	(0.53-1.55)	0.63	(0.40-1.01)	0.33	(0.18-0.61)	<0.001
Flavonols	Low	0.73	(0.45-1.21)	0.75	(0.47-1.19)	0.38	(0.20-0.73)	0.01
	High	1.00	(0.59-1.70)	0.57	(0.35-0.94)	0.48	(0.27-0.86)	0.001
Animal GSHT	Low	0.71	(0.44-1.13)	0.56	(0.35-0.88)	0.62	(0.34-1.14)	0.03
	High	1.12	(0.63-2.00)	0.81	(0.47-1.38)	0.38	(0.20-0.70)	<0.001
Veget. GSHT	Low	0.66	(0.39-1.11)	0.68	(0.41-1.13)	0.45	(0.23-0.88)	0.05
	High	1.14	(0.68-1.91)	0.61	(0.39-0.96)	0.42	(0.24-0.73)	<0.001
Fruit GSHT	Low	1.05	(0.61-1.78)	0.85	(0.50-1.44)	0.51	(0.27-0.99)	0.02
	High	0.82	(0.49-1.38)	0.59	(0.38-0.92)	0.42	(0.24-0.74)	0.001
Total GSHT	Low	0.74	(0.45-1.22)	0.71	(0.43-1.15)	0.48	(0.25-0.94)	0.04
	High	1.16	(0.67-2.01)	0.68	(0.42-1.10)	0.46	(0.26-0.82)	0.001
Menop.status*	Pre-	1.00	(0.38-2.64)	1.05	(0.42-2.63)	0.77	(0.28-2.14)	0.62
	Post-	0.85	(0.58-1.24)	0.62	(0.43-0.88)	0.34	(0.22-0.55)	<0.001

Regression model: Adjusted for hospital (binary), residence (binary), age (categorized), menopausal status (binary), family history of BC in 1st and 2nd degree (categorized), body mass index (categorized), dietary energy (categorized), smoking status (categorized), alcohol drinking frequency (continuous), total red meat (continuous), total vegetables (continuous), total fruits (continuous), tea (continuous) and coffee (continuous).
*Analyses performed excluding dietary antioxidants

Table 6. Odds Ratios (OR) of Tea intake (tertiles) and 95% Confidence Intervals (CI), stratified for categories of selected dietary antioxidants (low/high intake according to median values) and of menopausal status. Non drinkers constitute the reference category for tea intake (omitted in Table).

		Tea Intake (ml/day)				
Variable	Strata	II 1-250		III ≥ 251		Trend
		OR	(95% CI)	OR	(95% CI)	(p)
Crude OR	----	0.84	(0.67-1.50)	0.46	(0.28-1.27)	0.11
Adjusted OR	----	0.92	(0.71-1.21)	0.48	(0.27-0.84)	0.05
α-carotene	Low	1.02	(0.70-1.50)	0.34	(0.09-1.27)	0.11
	High	0.83	(0.55-1.24)	0.47	(0.24-0.92)	0.04
β-carotene	Low	0.93	(0.64-1.35)	0.30	(0.10-0.92)	0.15
	High	0.93	(0.62-1.40)	0.51	(0.25-1.03)	0.12
Lutein	Low	1.07	(0.73-1.56)	1.07	(0.38-2.98)	0.73
	High	0.77	(0.51-1.14)	0.34	(0.17-0.71)	0.007
Lycopene	Low	1.02	(0.69-1.49)	0.59	(0.27-1.30)	0.44
	High	0.78	(0.53-1.15)	0.40	(0.17-0.93)	0.04
β-Cryptoxanthin	Low	1.05	(0.72-1.52)	0.68	(0.23-1.96)	0.88
	High	0.89	(0.60-1.33)	0.40	(0.20-0.90)	0.03
Total carots.	Low	1.03	(0.71-1.49)	0.56	(0.18-1.71)	0.69
	High	0.85	(0.57-1.28)	0.41	(0.20-0.83)	0.03
Vitamin C	Low	0.80	(0.55-1.17)	0.50	(0.22-1.12)	0.08
	High	1.11	(0.75-1.63)	0.51	(0.23-1.13)	0.45
Vitamin E	Low	0.86	(0.59-1.25)	0.51	(0.16-1.62)	0.22
	High	0.95	(0.64-1.42)	0.48	(0.24-0.94)	0.09
Quercetin	Low	0.82	(0.56-1.21)	0.70	(0.16-2.99)	0.30
	High	1.03	(0.69-1.52)	0.49	(0.24-0.97)	0.17
Kaempferol	Low	1.22	(0.61-2.46)	----	n/a	0.57
	High	1.36	(0.90-2.06)	0.83	(0.43-1.61)	0.96
Flavonols	Low	0.77	(0.52-1.14)	0.68	(0.16-2.89)	0.18
	High	1.09	(0.74-1.60)	0.51	(0.25-1.02)	0.26
Animal GSHT	Low	1.10	(0.75-1.61)	0.50	(0.22-1.16)	0.48
	High	0.73	(0.49-1.07)	0.45	(0.21-0.99)	0.05
Veget. GSHT	Low	0.89	(0.61-1.31)	0.60	(0.24-1.46)	0.30
	High	0.95	(0.64-1.41)	0.38	(0.18-0.81)	0.06
Fruit GSHT	Low	1.24	(0.87-1.78)	0.84	(0.26-2.68)	0.40
	High	0.66	(0.44-1.01)	0.35	(0.18-0.69)	0.002
Total GSHT	Low	0.90	(0.62-1.31)	0.62	(0.25-1.57)	0.33
	High	0.93	(0.63-1.37)	0.43	(0.21-0.91)	0.09
Menop. Status*	Pre-	0.74	(0.39-1.42)	0.33	(0.06-1.89)	0.17
	Post-	0.94	(0.70-1.25)	0.50	(0.28-0.91)	0.09

Regression model: Adjusted for hospital (binary), residence (binary), age (categorized), menopausal status (binary), family history of BC in 1st and 2nd degree (categorized), body mass index (categorized), dietary energy (categorized), smoking status (categorized), alcohol drinking frequency (continuous), total red meat (continuous), total vegetables (continuous), total fruits (continuous), 'mate' (continuous) and coffee (continuous). n/a = not available data to perform the analysis due to the low number of registries; *Analyses performed excluding dietary antioxidants.

red meat, milk but lesser intake of white meat and fruits. Among hot infusions, controls displayed significantly higher mean daily intakes than cases, for tea (73 vs. 55 ml/day resp.) as well as for 'mate' (871 vs. 702 ml/day resp.). Most variables showed statistically significant differences between cases and controls, however, only differences for flavonols reached significance among antioxidants.

The ORs of BC for the calculated dietary antioxidants are presented in Table 3. Certain of these bioactive substances showed significant negative risk associations: β-carotene, lutein, total carotenoids, vitamin C, quercetin, flavonols and vegetable reduced glutathione. The found associations remained significant even after including vegetables and fruits in the regression model. In addition, almost all estimations to these items displayed significant linear trends.

Table 4 is focused on the particular features of 'mate' intake. Adjusted ORs and their 95% CI display a favorable situation for high exposure to this intake, compared to the reference categories of no intake. The results were rather similar for both regression models, including terms for antioxidants or not: Current consumers showed a significant risk reduction of BC (OR=0.63 and OR=0.65). A daily intake higher than 1 liter of the infusion was strongly protective (OR=0.38 and OR=0.41). Duration of the habit suggested the benefit of long-term 'mate' consumption (OR=0.62 for both models) and intensity of consumption (liters*years) also showed a strong inverse association for high consumers compared to non drinkers (OR=0.46 and OR=0.49). The continuous risk of daily 'mate' intake was OR=0.74 (95%CI 0.65-0.83, not shown in the table).

Table 5 shows the adjusted ORs for 'mate' intake, stratified for selected dietary antioxidants levels. High 'mate' intakes displayed significant risk reductions at any level of almost every studied antioxidant. Compared to the basic adjusted estimate (OR=0.38), an even stronger, although slightly inverse association was found for high strata of α-carotene (OR=0.30), lycopene (OR=0.35) and kaempferol (OR=0.33) consumers. In addition, the ORs

Table 7. Continuous ORs for 'Mate' Intake according to Tea Strata. Comparisons with and without Inclusion of Dietary AOX in the Regression Model

Antioxidants	Tea intake	OR (95% CI)	Trend (p)
No	Non drinkers	0.82 (0.70-0.97)	0.02
No	1-250 ml/day	0.70 (0.57-0.85)	0.001
No	≥ 251 ml/day	0.27 (0.12-0.62)	0.002
Yes	Non drinkers	0.83 (0.70-0.98)	0.03
Yes	1-250 ml/day	0.73 (0.59-0.90)	0.004
Yes	≥ 251 ml/day	0.16 (0.04-0.58)	0.005

Regression models: Without AOX: Adjusted for hospital (binary), residence (binary), urban years (continuous), rural years (continuous), age (categorized), menopausal status (binary), family history of BC in 1st and 2nd degree (categorized), body mass index (categorized), dietary energy (categorized), smoking status (categorized), alcohol drinking frequency (continuous), total red meat (continuous), total vegetables (continuous), total fruits (continuous) and coffee (continuous). With AOX: Id. + total carotenoids (continuous), vitamin C (categorized), vitamin E (categorized), total flavonols (continuous) and total reduced Glutathione (continuous).

for 'mate' intake also displayed highly significant trends at high dietary levels of all 15 antioxidants. Finally, regarding menopausal status, high 'mate' intake was significantly associated only among postmenopausal women (OR=0.34, p-value for trend<0.001). Nevertheless, likelihood ratio tests for heterogeneity were not significant for any of the analyzed strata (data not shown).

The risk estimates for tea intake, stratified for selected dietary antioxidants levels, are presented in Table 6. High tea intakes displayed significant risk reductions at high levels of certain dietary antioxidants, mainly carotenoids and glutathione. Compared to the basic adjusted estimate (OR=0.48), a stronger inverse association was found only among high consumers of lutein (OR=0.34), lycopene (OR=0.40), β-cryptoxanthin (OR=0.40), total carotenoids (OR=0.41), vegetable glutathione (OR=0.38), fruit glutathione (OR=0.35) and total glutathione (OR=0.43). Finally, regarding menopausal status, high tea intake was significantly associated only among postmenopausal women (OR=0.50), but without statistically significant trend (p- value = 0.09). Likelihood ratio tests for heterogeneity were not significant for any of the analyzed strata (data not shown).

Finally, Table 7 shows continuous ORs for 'mate' intake according strata of tea intake and the estimations were performed comparing models excluding or including dietary antioxidants. According to these results, 'mate' was significantly and negatively associated with BC risk in all stratified analyses, with or without dietary antioxidants: Among tea abstainers (OR=0.83 vs. OR=0.82), among low tea consumers (OR=0.73 vs. OR=0.70), as well as among high tea consumers (OR=0.16 vs. OR=0.27).

Discussion

We have found inverse associations of 'mate' and tea intake and the risk of BC, considered from the viewpoint of 15 selected dietary antioxidants levels. High 'mate' intakes displayed significant risk reductions at any level of most of them. Compared to the basic adjusted estimate (OR=0.38), slightly stronger, inverse associations were found for high strata of α-carotene (OR=0.30), lycopene (OR=0.35) and kaempferol (OR=0.33). In addition, the ORs for 'mate' intake displayed highly significant trends at high levels of most of the 15 antioxidants. This represents a remarkable finding, since the analyses of certain dietary antioxidants revealed a putative protective effect even after adjusting for vegetables and fruits: such was the case for β-carotene, lutein, total carotenoids, vitamin C, quercetin, flavonols and vegetable-derived reduced glutathione, showing also significant linear trends.

Concerning 'mate' intake, its protective effect appears as strong in several analyses, having remained after exhaustive adjustments. Although tea intake could be also considered protective within the studied population (adjusted OR=0.48, 95% CI 0.27-0.84), it remained protective only among high consumption strata of certain carotenoids and plant-derived glutathione, as shown in Table 6. Anyway, our analyses suggest the existence of a very favorable combination regarding BC risk, when high 'mate' intake is associated to high tea intake, even stronger within a dietary style providing high levels of antioxidants. This was shown in Table 7 and led us to make some considerations.

A recent preliminary communication based only on data corresponding to women from the private healthcare system (Ronco et al., 2016a) had led us to rather similar findings: the ORs for the subset of high 'mate' and high tea consumers was 0.14 (95% CI 0.05-0.38). We should particularly take into account that women from the private system had a lesser 'mate' intake than those from the public hospitals, but at the same time they were more intense consumers of tea, vegetables and fruits (Ronco et al., 2016b), therefore, it can be assumed that also their dietary antioxidants levels were higher indeed.

Some carcinogens like Dimethylbenz[a]anthracene (DMBA) and polycyclic aromatic hydrocarbons (PAH) like Benzo(a)pyrene (BaP) (IARC, 2010), are present in barbequed meat, tobacco smoke and overheated cooking oil, among other sources (Tiwari et al., 2014). They are indirect-acting carcinogens requiring metabolic activation to yield its ultimate carcinogenic form (Badal and Delgada, 2014), in particular an oxidation by CYP enzymes (Szaefer et al., 2014). The quoted components could be partially responsible of the association of 'mate' with cancer in organs which have no direct contact with the beverage, such as the nephro-urinary system (De Stefani et al., 1991; 1998; 2011), among other sites.

The protective effects of 'mate' described in the present study were found stronger among strata of tea drinkers and at any level of dietary antioxidants. According to recent reviews, although high polyphenols contents of different tea types have been described (Wang et al., 2015), lack of association tends to prevail in the literature regarding tea intake and the risk of BC (Gao et al., 2013; Wu et al., 2013).

Despite the lack of statistical heterogeneity regarding menopausal status, the evidence suggests a more protective effect for 'mate' intake somehow linked to time -although not in a time-dependent way-, perhaps enhancing existing biological differences between BC in younger and in older women. BC has already shown differences in both subgroups: we recognize that at least

from a dietary viewpoint, premenopausal women are in a disadvantageous situation compared to postmenopausal ones, mainly due to a relative lack of protective items (Ronco and De Stefani 2013a; Ronco et al., 2012; 2016c). Combining food and nutrients patterns, the latter communication (Ronco et al., 2016c) reported lack of association for Carotenoids, Fruit-based, Prudent and Total fruits dietary patterns among premenopausal women, whereas these patterns showed a protective effect among postmenopausal ones. Along the years we have been constantly observing similar facts: antioxidants -analyzed independently or grouped as patterns— displayed a risk reduction mainly in postmenopausal women than in premenopausal ones (Ronco et al., 1999; 2010; 2016c). And we found that the same applies to hot infusions, taking into account our previous paper (Ronco et al., 2016b) and the present one. Since 'mate' intake was not taken into account in the quoted previous studies focused on nutrition, the facts suggest us that regarding BC risk, those other dietary items with antioxidant capabilities apparently do not work either in benefit of younger women.

The leaves of ilex paraguariensis contain xanthines (mainly caffeine), flavonoid glycosides (as rutin), caffeoylquinic acid derivatives (chlorogenic acids) and a significant amount of triterpenoid saponins (around 10% of total dry weight) including ursolic acid (UA) (Puangpraphant et al., 2011). The natural pentacyclic triterpenoid compounds (UA, its isomer oleanolic acid and several closely related derivatives), exhibited biological and pharmacological properties, such as anti-HIV, hepatoprotective, anti-inflammatory, cytotoxic or anti-microbial activities, which have been summarized in some reviews (Liu 1995; Yogeeswari 2005). UA has multiple intracellular and extracellular targets that play role in apoptosis, metastasis, angiogenesis and inflammatory processes (Kashyap et al., 2016). Mate saponins have potent chemopreventive properties: they specifically upregulate the p53 cascade (Puangpraphant et al., 2013).

'Mate' is one of the best sources of chlorogenic acids in nature. Chlorogenic or caffeoylquinic acids are esters of caffeic and quinic acids. Pharmacological properties of these catechols include antioxidant, hepatoprotective, antibacterial, antihistaminic, chemopreventive, and other biological effects (Lima et al., 2016). Lee and Zhu (2006) showed that chlorogenic acids and other catechol-containing dietary polyphenols can inhibit the methylation of synthetic DNA substrates in vitro and can inhibit the methylation of the promoter region of the RAS gene in human BC cells; both are normally hypermethylated in neoplastic cells. Besides, Noratto et al. (2009) in their study, showed the chemopreventive potential of dietary chlorogenic and neochlorogenic acids.

The conversion of androgens into estrogens that takes place mainly in adipocytes and also in selected tissues (i.e. mammary gland, ovaries, brain) is controlled by a unique enzyme called aromatase. Therefore, aromatase has been the target for the design of inhibitor agents in the treatment of estrogen-dependent cancers especially postmenopausal BC (Chumsri et al., 2011). Among natural products, the herb Ilex paraguariensis can be considered an excellent source of UA (Gnoatto 2008), also showing a dose-dependent inhibition capability, as powerful as some phytoestrogens. Anti-aromatase feature of UA and derivatives extracted from different plants has also been reported: in particular oleanolic acid and UA from Urtica diocica L. (Urticaceae) roots were already reported as responsible of aromatase inhibition and this might explain in part the anti-tumour property of this plant (Liu 1995), both having obtained similar enzymatic inhibition. Experimental data indicate that 'mate' components like oleanolic acid and UA, as well as theaflavins from black tea exert an aromatase-inhibitory activity (Way et al., 2004), but green tea catechins do not (Satoh et al., 2002). Moreover, theaflavins have antioxidant, immune enhancing and anti-inflammatory capabilities (Butt et al., 2014). Interestingly, UA has shown an additional estrogenic inhibition potential: the suppression of estrogen receptors alpha (ERα) through down-regulation of estrogen-responsive genes' expression in response to exposure to estradiol (Kim et al., 2014).

Due to the homology between the androgen androstenedione -the main aromatase substrate- and UA, configuration of the latter was seen as appropriate to recognize active site of enzyme and to block aromatisation (Gnoatto et al., 2008). Interestingly, squalene is considered as the common precursor for biosynthesis of both natural steroid and triterpenoid systems which can explain the similitude of their structures (Price et al., 1987). A recent review on squalene, cancer and aging (Ronco and De Stefani, 2013b) mentioned the powerful antioxidant capability of this triterpene and its common chemical structure with carotenoids, vitamin E, and other endogenous antioxidants as glutathione. Although squalene is a half part of olive oil's minor components -all of which account for only 2% of the weight-, it is considered as relevant contributor to the anticarcinogenic capabilities of the quoted food (Newmark, 1999).

Twenty years ago, the influence of UA was demonstrated as capable of arresting the proliferation of estrogen-dependent MCF-7 human BC cells, showing both cytostatic and cytotoxic activity (Es-Saady et al., 1995). Further in vitro experimental research has confirmed its capabilities against BC (Subbaramaiah et al., 2000; Novotný et al., 2001; Kassi et al., 2009; Allouche et al., 2010; Yeh et al., 2010; De Angel et al., 2010; Bishayee et al., 2011; Wang et al., 2012; Chakravarti et al., 2012; Tan et al., 2013). The inhibition of Nuclear factor-kappa B (NF-kB), a key link between inflammation and carcinogenesis, has been shown for UA (Shishodia et al., 2003; Yoon et al., 2007), which exceeds by far the BC issue. In vivo studies, nevertheless, were not able to confirm those findings, according to a review on triterpenoids and BC (Bishayee et al., 2011).

Ilex paraguariensis extracts revealed a dose-dependent potential anti-inflammatory activity, with a relevant decrease of nitric oxide (NO) production even in the presence of low concentrated extracts (Souza et al., 2015). Interestingly, at Uruguay's antipodes, the large-leaved Ilex Kudingcha -another species of genus Ilex- has been described in China as a plant whose constituents share several items with green tea and also with Ilex paraguariensis from South America (Li et al., 2011; 2013),

regarding its components (triterpenoids, phenolic acids, flavonoids, among others) and its properties (antioxidant, hypoglycemic, and anti-tumor effects, vascular protection, regulation of lipid metabolism, among others). Despite the quoted similarities, lack of caffeine in Kudingcha species was remarked by those Chinese authors as a potential advantage for its traditional long-term consumption.

The interest variables of the present study (tea, 'mate' and dietary antioxidants) are probably at the same time mutually interacting and also combining anti-estrogenic, antioxidant and anti-inflammatory activity. Indeed, the idea of a synergistic action emerges straightforward after analyzing the complete results. In support of this assumption is the fall of adjusted continuous estimates for daily 'mate' intake (OR=0.74) among high tea consumers (OR=0.27) and also when dietary antioxidants were included in the adjustment (OR=0.16). According to our results, also stronger anti-aromatase capabilities could be probably built when UA and oleanolic acid (from high 'mate' intake) and theaflavins (from high tea intake) are derived from a combined consumption.

At the light of updated specialized literature (Okoh et al., 2011), an attempt of separating possible protective actions in antioxidant on one side and in hormonal on the other side seems to be nonsense. Estrogens undergo oxidative metabolism and physiologically achievable concentrations of the hormones or their metabolites have been shown to generate reactive oxygen species (ROS) which are implicated in carcinogenic conversion and growth of cancer cells through induction of DNA synthesis, increased phosphorylation of kinases, and activated transcription factors (Roy and Liehr, 1990; Roy et al., 2007). Besides, it has been shown that mitochondria are significant targets of estrogen (Felty et al., 2005a;b). In addition, estrogen-induced oxidative DNA damage through ROS has been extensively reviewed (Roy and Liehr, 1999; Cavalieri et al., 2000; Roy and Singh, 2004).

As other case-control studies, our work has limitations and strengths. Among the limitations we recognize the lack of validation of the questionnaire, although the instrument was tested for reproducibility. Data about antioxidants contents in the analyzed foods were taken from foreign tables: this constitutes a limitation, since it allows the chance of reflecting possible differences regarding composition of local foods. Also, the control population displayed different profiles: hospitalized participants were recruited from the public system and non hospitalized ones from the private system. All of them shared a common condition, which was the absence of any cancer. However, the latter subgroup had also documented absence of any breast pathology. Therefore, having selected as controls women with normal mammograms and not only without cancer, if benign breast diseases had any association with the analyzed dietary items we reduced at least in part the possibility of biasing results due to this. Also to be mentioned as strength, the study population includes subsets of both existing healthcare systems, proceeding from the capital city as well as the rest of the country, and times of data collection were coincident. Although age matching was not perfect for the public hospitals subset, the whole resulting distribution was reasonable. Finally, a high participation was achieved (globally 97.1% of patients under the proposed age limits), 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.

In conclusion, after analyzing a population sample of Uruguayan women who belonged to both healthcare systems existing in the country, we found evidence of protective effects of 'mate' drinking on the risk of BC at both low or high levels of some dietary antioxidants, and in addition, a protective effect was reported for such antioxidants. Also, tea intake was protective mainly at high levels of certain antioxidants. Their inverse associations were usually stronger at high levels of dietary antioxidants. We propose that stronger anti-aromatase and antioxidant capabilities could be probably built when combined high 'mate' and black tea intake takes place. In the light of the findings, further studies are needed in order to better know about 'mate' intake and its hormonal associations, in particular receptors' status.

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