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ORIGINAL ARTICLE

Hot infusions and risk of colorectal cancer in Uruguay: a case–control study

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BACKGROUND/OBJECTIVES: The evidence of possible roles for the most common hot infusions intake (tea and coffee) in the risk of colorectal cancer (CRC) needs additional data. Regarding 'mate' intake (infusion of *Ilex paraguariensis* herb), a previous multi-site study reported lack of association for its highest intake on CRC risk. The present study was conducted to better understand the associations between the intake of this and other infusions and CRC risk.

SUBJECTS/METHODS: Patients (611 CRC incident cases and 2394 controls, all belonging to public hospitals) were interviewed through a questionnaire, including socio-demographic, reproductive and lifestyle variables, and a food-frequency questionnaire of 64 items, analyzing tea, 'mate' and coffee intake (consumer status, daily intake, age at start and at quit). Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated through unconditional logistic regression, adjusting for relevant potential confounders.

RESULTS: Tea and coffee intake displayed significant and inverse associations with CRC risk, mainly among men (OR = 0.54, 95% CI 0.38–0.76 for tea and OR = 0.59, 95% CI 0.41–0.85 for coffee). Mate intake showed a significant inverse association among women (OR = 0.50, 95% CI 0.33–0.77), with a marginal heterogeneity between sexes ($P = 0.07$). Concerning age strata, tea intake displayed inverse associations in all ages, whereas 'mate' and coffee intake showed stronger inverse associations for age $\geqslant 70$, suggesting a gradient along time.

CONCLUSIONS: We found evidence of different significant inverse associations for tea, 'mate' and coffee intake and CRC risk. To our knowledge, this is the first epidemiologic study reporting inverse results on 'mate' intake and CRC, which are explained by a stronger association among women.

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INTRODUCTION

Colorectal cancer (CRC) is highly frequent among the Uruguayan population (third among men and second among women), with national age-adjusted incidence rates of 38.1 and 27.3 per 100 000, for men and women, respectively.[1] Uruguay has the highest CRC incidence among South American registries and is also high in the top world ranking of mortality.[2] Furthermore, trends of incidence/mortality rates in the last 20 years suggest stability among women and a modest but sustained increase among men.[1,3] This fact raises the question about possible roles played by the biology of each sex, assuming that environmental risk factors are shared indistinctly by the whole community.

Among those factors, the Uruguayan population has the world's highest per capita meat intake.[4] Red meat intake has been thoroughly studied and recognized as a risk factor for CRC in Uruguay,[5–7] as representative of typical Western dietary styles. This is aligned with the international literature.[8] Indeed, meeting the World Cancer Research Fund/American Institute for Cancer Research recommendations, including less red and processed meat intake substantially reduced CRC incidence.[9]

'Mate' is the name of a hot infusion made from the herb *Ilex paraguariensis*, which is a staple non-alcoholic beverage in temperate South America, and Uruguayans are the world's highest 'mate' consumers (9–10 kg/person/year of the herb and ca. 400 l/person/year of infusion).[10] Recently, a Working Group of the International Agency for Research on Cancer (IARC) announced the future publication of a Monograph evaluating the carcinogenicity of drinking coffee, mate and very hot beverages.[11] They concluded that there is limited evidence in humans for the carcinogenicity of drinking very hot beverages, and inadequate evidence in humans for the carcinogenicity of drinking mate that is not very hot.

In 1991 IARC classified coffee drinking as 2B (possibly carcinogenic to humans) and hot 'mate' drinking as 2A (probably carcinogenic to humans).[12] Because of antioxidant and other effects, overall coffee drinking was recently evaluated as unclassifiable as to its carcinogenicity to humans (group 3). Besides, hot 'mate' infusion appears within a long list of products, which have priority to be reassessed by the IARC, as it has been extensively studied and basic research has demonstrated the presence of several compounds, which have antioxidant properties (polyphenols and flavonoids), among other ones as chlorogenic acids.[13]

Recent epidemiological research has reported protective effects for high intake of 'mate' and tea infusions on the risk of breast cancer.[14,15] Results suggested a protection from the antioxidant

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contribution of 'mate' and also led the authors to propose a hormonal influence. The quoted articles also reported a modest protective effect for tea (black type) on breast cancer risk, and high consumers of both infusions improved the estimates, compared to non-drinkers.[14]

Taking into account (a) some results derived from experimental research regarding possible effects of 'mate', tea and coffee infusions on carcinogenesis;[16–19] (b) the suggested effects found in our epidemiological research on breast cancer; (c) the high impact of CRC in our country showing different evolution trends for each sex; and (d) the still insufficient epidemiological evidence linking the intake of 'mate', tea and coffee infusions and CRC risk, we decided to conduct a case–control study to explore possible associations between the quoted infusions and the risk of the disease.

SUBJECTS AND METHODS

Selection of cases

In the time period 1992–2004, all the newly diagnosed and microscopically confirmed cases of cancer of the colon and rectum were collected from the four major public hospitals in Montevideo (Oncología, Clínicas, Maciel and Pasteur). The initial number was 625 patients; only 14 (2.3%) refused the interview (response rate 97.7%), leaving a final number of 611 cases.

Selection of controls

In the same time period and in the same hospitals, 2460 patients afflicted with non-neoplastic diseases not related with tobacco smoking or alcohol drinking and without recent changes in their diets were considered as eligible for the study. Sixty-six (2.7%) of them refused the interview, leaving a final number of 2394 controls (response rate 97.3%). These controls presented the following conditions: 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%); acute appendicitis (60, 2.5%); and other acute diseases (207, 8.6%).

Interviews and questionnaire

Two trained social workers who were unaware of the study objectives, worked at the hospitals in two consecutive phases: first, they looked for newly diagnosed and admitted cancer patients, working with the collaboration of medical records personnel. Second, the interviewers proceeded to contact patients who were eligible to be matched as much as possible by the age frequencies of cancer patients. After looking for their will to cooperate with the study, all the participants (cases and controls) were face-to-face interviewed in the hospitals. Proxy interviews were not accepted.

A structured questionnaire was applied to all participants. It 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 (consumer status, daily intake, age at start and at quitting); (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 before diagnosis in cases and before the interview in controls. The FFQ was not validated, but was tested for reproducibility, having high correlations.[20] Furthermore, the FFQ allowed the total energy intake of each subject to be estimated.

All dietary questions of our semiquantitative questionnaire were open-ended and each amount was converted to times/year. To obtain nutritional information of foods, we used foreign tables coming from a neighboring country with similar habits.[21] To calculate 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 calories of the serving/100 g of each individual food, divided by 365 days. Most typical or average servings of solid foods are within the range of 100–150 g.

Regarding tea infusion, black tea has been the all-time second most traditional type of infusion among the Uruguayan population; green tea entered the market very recently. Therefore, our assessment of the infusion takes black tea into account as representative of the whole intake. The study was conducted after receiving the approval of each Medical Director belonging to the involved hospitals, following an ethical approval in each institution.

Statistical analysis

Most questionnaire variables were originally continuous and when necessary they were categorized into tertiles or quartiles, as well as further dichotomized for analysis purposes. Aside from basic descriptive analyses (frequencies and mean values) made to give necessary information to the reader, odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated by unconditional logistic regression.[22] Potential confounders were included in the multivariate analyses. All equations included terms for hospital, residence, age, education, body mass index, history of cancer in first- and second-degree relatives, smoking status, alcohol intake, total energy intake, and intakes of red meat, total fruits and total vegetables. The best regression models included mostly categorized variables. A term for menopausal status was included for analyses in the female subset. Likelihood ratio tests were performed to explore possible heterogeneities in the stratified analyses. All calculations were done with the software STATA (Release 10, StataCorp LP, College Station, TX, USA).

RESULTS

The distribution of general features among cases and controls is shown in Table 1. Although there was not a perfect matching, distribution of age groups was adequate ($P = 0.42$). Neither residence nor urban/rural status displayed significant differences ($P = 0.53$ and 0.23, respectively). Whereas 'mate' intake was highly prevalent (~86% ever consumers), tea and coffee were much less frequently consumed (~19% and ~ 15%, respectively). In addition, all infusions tended to be more consumed by the control population than by cancer cases, despite statistical differences. Besides, whereas tea with milk showed no differences, coffee with milk revealed a significantly higher intake among cancer cases than controls ($P < 0.001$). Finally, dietary energy showed highly significant differences ($P < 0.001$).

Table 2 shows ORs, adjusted by age and sex, for each infusion and comparing ever drinkers vs non-drinkers. The three infusions showed significant inverse associations for drinkers (OR = 0.57, 0.73 and 0.68 for tea, 'mate' and coffee, respectively). Besides, tea with milk suggests a lack of association and coffee with milk a positive association.

Table 3 displays the adjusted ORs (using a complete regression model) for each infusion and stratified by sex. Tea intake was inversely associated to CRC risk (OR = 0.54, 95% CI 0.38–0.76 among men and OR = 0.73, 95% CI 0.50–1.08 among women). Concerning 'mate' intake, global estimations showed a lack of association among men (OR = 0.91) and a significant inverse association among women (OR = 0.58, 95% CI 0.33–0.77). Coffee consumption also displayed a global inverse and significant association, but estimations remained similar only among men (OR = 0.59, 95% CI 0.41–0.85). A borderline heterogeneity between sexes was found for coffee ($P = 0.052$) and 'mate' intake ($P = 0.07$).

Stratified and adjusted ORs of CRC for high intakes of each infusion are shown in Table 4. High tea intake improved its risk reduction among overweight/obese subjects, in non-smokers and in those having high intake of vegetables, fruits and calories. High 'mate' intake improved risk reduction among overweight/obese subjects, but also among high fruit and calorie consumers, in subjects with a family history of cancer and in ever drinkers of alcohol. Finally, high coffee intake showed stronger risk reductions among strata of overweight/obese people, alcohol ever drinkers, high vegetable consumers and subjects with a family history of

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

Variables	*Categories*	*Controls, n (%)*	*Cases, n (%)*	*Global P-value*	*OR (95% CI)*
Age groups	< 40	47 (2.0)	12 (2.0)		
	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)	0.42	—
Sex	Men	1576 (65.8)	361 (59.1)		
	Women	818 (34.2)	250 (40.9)	0.002	—
Education years	⩽3	1021 (42.6)	280 (45.8)		
	4–6	1067 (44.6)	269 (44.0)		
	⩾7	306 (12.8)	62 (10.2)	0.14	0.74 (0.55–1.00)
Urban/rural status	Urban	1940 (81.0)	508 (83.1)		
	Rural	454 (19.0)	103 (16.9)	0.23	0.87 (0.68–1.10)
Residence	Montevideo	1259 (52.6)	307 (50.3)		
Regions	Canelones	555 (23.2)	153 (25.0)		
	Other counties	580 (24.2)	151 (24.7)	0.53	1.07 (0.86–1.33)
Body mass index (kg/m^2)	⩽24.99	1108 (46.3)	287 (47.0)		
	25.0–29.99	944 (39.4)	252 (41.2)		
	⩾30.0	342 (14.3)	72 (11.8)	0.26	0.81 (0.61–1.08)
FHC in siblings	No	2070 (86.5)	517 (84.6)		
	Yes	324 (13.5)	94 (15.4)	0.24	1.16 (0.91–1.49)
FHC in parents	No	2019 (84.3)	467 (76.4)		
	Yes	375 (15.7)	144 (23.6)	< 0.001	1.66 (1.34–2.06)
Tea status	Never	1828 (76.4)	517 (84.6)		
	Ex drinker	11 (0.5)	2 (0.3)		
	Current	555 (23.2)	92 (15.1)	< 0.001	0.59 (0.46–0.75)
Mate status	Never	312 (13.0)	92 (15.1)		
	Ex drinker	160 (6.7)	52 (8.5)		
	Current	1922 (80.3)	467 (76.4)	0.10	0.86 (0.65–1.15)
Coffee status	Never	1956 (81.8)	531 (86.9)		
	Ex drinker	20 (0.8)	13 (2.1)		
	Current	417 (17.4)	67 (11.0)	< 0.001	0.67 (0.46–0.97)
Tea with milk	Never	1945 (81.2)	506 (82.8)		
	Ex drinker	5 (0.2)	5 (0.8)		
	Current	444 (18.6)	100 (16.4)	0.03	1.16 (0.88–1.52)
Coffee with milk	Never	1579 (66.0)	371 (60.7)		
	Ex drinker	37 (1.5)	32 (5.2)		
	Current	778 (32.5)	208 (34.0)	< 0.001	0.94 (0.72–1.24)
Red meat intake (servings/year)	⩽260	849 (35.5)	148 (24.2)		
	261–377	813 (34.0)	243 (39.8)		
	⩾378	732 (30.5)	220 (36.0)	< 0.001	1.72 (1.17–2.37)
Dietary energy (kcal)	⩽1745	648 (27.1)	101 (16.5)		
	1746–2158	599 (25.0)	150 (24.6)		
	2159–2618	591 (24.7)	167 (27.3)		
	⩾2619	566 (23.2)	193 (31.6)	< 0.001	2.23 (1.71–2.91)
Alcohol status	Never	1102 (46.0)	316 (51.7)		
	Ex drinker	297 (12.4)	64 (10.5)		
	Current	995 (41.6)	231 (37.8)	0.04	0.81 (0.67–0.98)
Smoking status	Never	910 (38.0)	262 (42.9)		
	Ex smoker	672 (28.1)	164 (26.8)		
	Current	812 (33.9)	185 (30.3)	0.08	0.79 (0.64–0.98)
Total patients		2394 (100.0)	611 (100.0)		

Abbreviations: CI, confidence interval; FHC, family history of cancer in first-degree relatives; OR, odds ratio.

cancer. Among the high coffee drinkers, although estimates were not significant, an improvement is also suggested for consumers of high calories.

The ORs by large age groups are shown in Table 5. Within the youngest subset, only tea drinkers showed a marginally inverse risk association (OR = 066, 95% CI 0.41–1.05); coffee and 'mate' intakes were not associated. Among the middle age group (ages 60–69) again only tea intake revealed a significant inverse association (OR = 0.62, 95% CI 0.40–0.96). The oldest subset (ages ⩾70) showed significant inverse associations for intakes of 'mate' (OR = 0.60, 95% CI 0.40–0.91) and coffee (OR = 0.52, 95% CI 0.32–0.84) infusions, whereas tea consumption was marginally significant (OR = 0.67, 95% CI 0.45–1.01).

DISCUSSION

Our results give evidence for an inverse association of tea, 'mate' and coffee infusions regarding CRC risk. This finding was more evident among the oldest subset (age ⩾70), where high intakes of all infusions were significantly (for 'mate' and coffee) or marginally (for tea) associated. The three infusions were either inversely associated to CRC risk or having no association, but no positive risk associations were found for any. Tea intake seemed to show strongest association among the whole study population. Stratified analyses displayed the strongest inverse associations among smokers, in high red meat consumers and in high vegetables/fruits consumers, whereas the association was evident along all ages.

Besides, 'mate' infusion also displayed inverse associations, mainly among women (OR = 0.50). Concerning tea and coffee intake, inverse associations were observed mainly among men (OR = 0.54 and 0.59, respectively), although with a marginally significant heterogeneity between sexes. In addition, its consumption appears significantly and inversely associated among several strata of analyzed items (e.g. high fruit, red meat and energy intake, among non-smokers).

Tea intake and its associations with CRC have been widely studied in the literature;[23,24] however, observations from epidemiologic studies are inconsistent regarding the role of black and green teas as risk factors for CRC.[23,25–27] Furthermore, in the last years studies have emphasized the analysis of green tea and its components, where catechins emerge as most relevant.[28–30] Black tea has been also widely studied.[31–33] Theaflavin-2, a major component of black tea extract, induces apoptosis of human colon cancer cells and suppresses the expression of inducible nitric oxide synthase.[34] Moreover, epicatechingallate, a polyphenol from tea catechins induces cell death via p53 activation and stimulation of p38 and JNK in human colon cancer SW480 cells.[35]

Concerning 'mate' infusion, 5 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 public hospitals.[36] The study showed a lack of association for high 'mate' intake and CRC risk (OR = 1.22, 95% CI 0.92–1.63, *P* for trend = 0.17); it was the first report on this topic. The inclusion of terms for family history of cancer, body mass index, energy from diet, red meat intake, tea and coffee, suggests that a better regression model was found for the present report.

Recent communications[14,15] reported significant reduced breast cancer risks for high intakes of 'mate' infusion. The initial paper[14] reported even stronger associations among high consumers of tea and of fruits/vegetables. Such results suggested the authors that procarcinogenic compounds found in 'mate' infusion could be counterbalanced and also overcome by its own antioxidant compounds and perhaps also due to an additional antioxidant load coming from other, different sources. Later, the inverse association of 'mate' was found more remarkable in the presence of high dietary antioxidant intake.[15] Although results supported a protection from the own antioxidant contribution of 'mate', the evidence still suggests combined anti-estrogenic–antioxidant effects for the infusion.

Some components of 'mate' infusion have revealed potent properties against cancer, especially against colon cancer.[16,37–41] The leaves of *I. paraguariensis* herb have chlorogenic acids and methylxanthines (caffeine and teobromin),[42,43] and are also an excellent source of triterpenoid saponins (~10% of total dry weight) including ursolic acid.[40] Ursolic acid has multiple intracellular and extracellular targets that have role in apoptosis, metastasis, angiogenesis and inflammatory processes.[44,45] 'Mate' saponins have potent chemopreventive properties: they specifically upregulate the p53 cascade,[41] inhibit colon cancer cell proliferation by inducing apoptosis through activating caspase-3

Table 2. ORs and 95% CIs of colorectal cancer for intake of all infusions, adjusted for age and sex

Whole sample (n = *3005*)			
Variables	*Categories*	*OR (95% CI)*	*Cases/controls*
Tea (cups/year)	ND	1.00 (—)	517/1828
	Drinkers	0.57 (0.45–0.73)	94/567
Trend		< 0.001	
Mate (l/day)	ND	1.00 (—)	92/312
	0.1–0.9	0.69 (0.51–0.92)	140/665
	1.00	0.97 (0.73–1.28)	217/780
	⩾ 1.01	0.93 (0.69–1.24)	162/637
Trend		0.40	
	Drinkers	0.86 (0.67–1.11)	519/2082
Trend		0.25	
Coffee (cups/year)	ND	1.00 (—)	531/1956
	Drinkers	0.68 (0.53–0.88)	80/438
Trend		0.007	
TWM (cups/year)	ND	1.00 (—)	506/1945
	Drinkers	0.84 (0.67–1.07)	105/449
Trend		0.16	
CWM (cups/year)	ND	1.00 (—)	371/1579
	Drinkers	1.26 (1.05–1.51)	240/815
Trend		0.015	

Abbreviations: CI, confidence interval; CWM, coffee with milk; ND, non-drinkers; OR, odds ratio; TWM, tea with milk.

Table 3. Adjusted[a] ORs and 95% CIs of colorectal cancer for intake of all infusions and stratified by sex

Variables	*Categories*	*All* (n = *3005*)	*Men* (n = *1937*)	*Women* (n = *1068*)	*LR test* (P)
		OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*	
Tea (cups/year)	ND	Ref. (—)	Ref. (—)	Ref. (—)	
	Drinkers	0.63 (0.49–0.81)	0.54 (0.38–0.76)	0.73 (0.50–1.08)	
Trend		< 0.001	0.001	0.12	0.15
Mate (l/day)	ND	Ref. (—)	Ref. (—)	Ref. (—)	
	Drinkers	0.73 (0.56–0.95)	0.91 (0.63–1.31)	0.50 (0.33–0.77)	
Trend		0.02	0.61	0.001	0.07
Coffee (cups/year)	ND	Ref. (—)	Ref. (—)	Ref. (—)	
	Drinkers	0.76 (0.58–0.99)	0.59 (0.41–0.85)	1.10 (0.70–1.74)	
Trend		0.047	0.005	0.67	0.052
TWM (cups/year)	ND	Ref. (—)	Ref. (—)	Ref. (—)	
	Drinkers	0.83 (0.65–1.06)	0.68 (0.47–0.98)	0.95 (0.66–1.36)	
Trend		0.13	0.04	0.78	0.10
CWM (cups/year)	ND	Ref. (—)	Ref. (—)	Ref. (—)	
	Drinkers	1.14 (0.94–1.38)	1.13 (0.88–1.45)	1.24 (0.89–1.72)	
Trend		0.19	0.33	0.21	0.51

Abbreviations: CI, confidence interval; CWM, coffee with milk; LR test, likelihood ratio test for heterogeneity between sexes; ND, non-drinker; OR, odds ratio; Ref., reference; TWM, tea with milk. [a]Regression model included terms for the following: age (categorical); sex (binary); residence (categorical); urban years (continuous); rural years (continuous); education (categorical); family history of cancer in first degree (binary); body mass index (categorical); smoking status (categorical); alcohol status (categorical); red meat intake (continuous); and dietary energy (continuous). Intakes of tea (continuous), mate (categorical) and coffee (categorical) were included in each model, excluding the variable of interest. Menopausal status (binary) was included for data analyses in women.

Table 4. Stratified adjusted[a] ORs and 95% CIs of colorectal cancer for drinkers[b] of each main infusion, compared to their respective reference category (non-drinkers)

Variables	*Categories*	*Tea drinkers*	*Mate drinkers*	*Coffee drinkers*
		OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*
BMI	NW	0.54 (0.36–0.80)	0.83 (0.56–1.25)	0.81 (0.54–1.21)
	OW/OB	0.73 (0.53–1.01)	0.68 (0.48–0.98)	0.74 (0.51–1.06)
Vegetables	Low	0.72 (0.51–1.03)	0.71 (0.49–1.03)	0.89 (0.61–1.31)
	High	0.57 (0.40–0.82)	0.76 (0.52–1.12)	0.67 (0.46–0.99)
Fruits	Low	0.81 (0.57–1.14)	0.83 (0.55–1.24)	0.63 (0.43–0.93)
	High	0.52 (0.36–0.75)	0.67 (0.47–0.96)	0.88 (0.60–1.28)
Red meat	Low	0.59 (0.40–0.86)	0.78 (0.52–1.16)	0.83 (0.55–1.27)
	High	0.70 (0.50–0.97)	0.70 (0.49–0.99)	0.71 (0.50–1.02)
Dietary energy	Low	0.63 (0.44–0.89)	0.89 (0.60–1.31)	0.89 (0.61–1.32)
	High	0.62 (0.44–0.89)	0.63 (0.43–0.92)	0.66 (0.45–0.96)
FH of cancer	No	0.59 (0.44–0.80)	0.84 (0.60–1.16)	0.89 (0.64–1.22)
	Yes	0.73 (0.47–1.14)	0.57 (0.35–0.92)	0.55 (0.34–0.90)
Smoking	Never	0.77(0.53–1.10)	0.67 (0.46–0.96)	0.82 (0.52–1.28)
	Ever	0.53 (0.38–0.76)	0.87 (0.58–1.30)	0.75 (0.54–1.06)
Alcohol	Never	0.80 (0.57–1.13)	0.81 (0.57–1.16)	1.10 (0.76–1.60)
	Ever	0.49 (0.34–0.71)	0.67 (0.45–1.00)	0.55 (0.37–0.82)

Abbreviations: BMI, body mass index; CI, confidence interval; FH of cancer, family history of cancer in first-degree relatives; NW, normal weight; OR, odds ratio; OW/OB, overweight/obese. [a]Regression model included terms for the following: age (categorical); sex (binary); residence (categorical); urban years (continuous); rural years (continuous); education (categorical); family history of cancer in first degree (binary); body mass index (categorical); smoking status (categorical); alcohol status (categorical); red meat intake (continuous); and dietary energy (continuous). Intakes of tea (continuous), mate (categorical) and coffee (categorical) were included in each model, excluding the variables of stratification for each analysis. Low and high categories were derived from median values of each variable. [b]Ever drinkers of tea, 'mate' and coffee.

Table 5. Adjusted[a] ORs and 95% CIs of colorectal cancer for intake of main infusions and stratified by age groups

Variables	*Categories*	*Ages ⩽ 59 (n = 865)*	*Ages 60–69 (n = 1012)*	*Ages ⩾ 70 (n = 1128)*
		OR (95% CI)	*OR (95% CI)*	*OR (95% CI)*
Tea (cups/year)	ND	Ref. (—)	Ref. (—)	Ref. (—)
	Drinkers	0.66 (0.41–1.05)	0.62 (0.40–0.96)	0.67 (0.45–1.01)
Trend		0.08	0.03	0.056
Mate (l/day)	ND	Ref. (—)	Ref. (—)	Ref. (—)
	0.1–0.9	0.56 (0.29–1.11)	0.76 (0.44–1.32)	0.63 (0.40–1.01)
	1.00	1.23 (0.67–2.26)	0.73 (0.44–1.23)	0.65 (0.41–1.01)
	⩾1.01	0.96 (0.54–1.74)	0.83 (0.48–1.44)	0.49 (0.29–0.83)
Trend		0.37	0.64	0.02
	Drinkers	0.94 (0.54–1.64)	0.76 (0.47–1.21)	0.60 (0.40–0.91)
Trend		0.84	0.25	0.015
Coffee (cups/year)	ND	Ref. (—)	Ref. (—)	Ref. (—)
	Drinkers	1.04 (0.67–1.64)	0.67 (0.49–1.08)	0.52 (0.32–0.84)
Trend		0.85	0.10	0.008

Abbreviation: CI, confidence interval; ND, non-drinker; OR, odds ratio; Ref., reference. [a]Regression model included terms for the following: sex (binary); residence (categorical); urban years (continuous); rural years (continuous); education (categorical); family history of cancer in first degree (binary); body mass index (categorical); smoking status (categorical); alcohol status (categorical); red meat intake (continuous); and dietary energy (continuous). Intakes of tea (continuous), mate (categorical) and coffee (categorical) were included in each model, excluding the variable of interest.

activity,[40] but also induce apoptosis and cytotoxicity in human HT-29 CRC cells independently of p53 status.[16]

A role for nitric oxide synthase, nuclear factor kappa-B and cyclooxygenase-2 has been described as linked to colonic carcinogenesis.[46] Combination of quercetin and 'mate' saponins resulted in synergistic interaction inhibiting both nitric oxide and prostaglandin E2 production and suppressed production of interleukin-6 and interleukin-1β, which resulted in inhibition of nuclear translocation of nuclear factor kappa-B. Quercetin enhances hypoxia-mediated apoptosis via direct inhibition of adenosine monophosphate kinase activity in HCT116 colon cancer.[47] Quercetin could protect DNA both by reducing oxidative DNA damage and by enhancing DNA repair through modulation of DNA repair enzyme expression.[48] 'Mate' infusion reduced the proliferating cell nuclear antigen expression and lowered aberrant crypt foci number in the colon.[41] Luteolin, a flavonoid present in

this infusion, has antioxidant and antiproliferative properties. Published reports showed that luteolin reduces tumor numbers, inhibits lipid peroxidation and restores antioxidant enzymes during induced CRC in rats.[49] Its supplementation elevates intracellular reduced glutathione.[50] Therefore, the antioxidant, anti-inflammatory and antiproliferative capabilities of 'mate' might partially explain our results.

Because of the homology between the androgen androstenedione—the main aromatase substrate—and ursolic acid, configuration of the latter was seen as appropriate to recognize the active site of the enzyme and to block aromatization.[51] 'Mate' components such as oleanolic acid and ursolic acid, as well as theaflavins from black tea, exert an aromatase-inhibitory activity,[52] and this might explain in part their antitumour property. Moreover, theaflavins have antioxidant, immune-enhancing and anti-inflammatory capabilities.[33] Anti-estrogenic properties have also been documented for two carotenoids: β-carotene and lycopene.[53] Among carotenoids, at least in older women, β-carotene levels were found independently and inversely associated with estradiol.[54] Several compounds are able to simultaneously display antioxidant and anti-estrogenic capabilities, and as a consequence, a combined protective activity against CRC could be better displayed among women than among men. As breast and CRC have similar PIK3CA, BRAF and KRAS mutation spectra,[55] a putative combined protective effect of the studied infusions being exerted differently regarding sex should not be ruled out. The present study revealed different effects for high intakes in each sex: a significant OR = 0.58 among women and a nonsignificant OR = 0.81 among men. As the mean intake for each sex is different (0.89 vs 1.07 l/day, women vs men, $P < 0.001$, data not shown), results cannot be explained by a higher mean intake among women. Conversely, our estimations suggest that 'mate' intake might have different, stronger effects on women, and this could depend on the anti-estrogenic capabilities.

A recent review[56] described important features of estrogen receptors β (ERβ), linking them to colorectal carcinogenesis. According to these authors, ERβ—the predominant ERs expressed in both normal and malignant colonic epithelium—coexist with limited or no expression of ERα in the colon, and are responsible of tumor-suppressive functions in CRC. Indeed, the knowledge about the role of some the infusions' components on ERs will be helpful to explain certain findings of epidemiologic studies like the present one.

Finally, some considerations regarding coffee intake should be made. It displayed significant protective associations only among men (OR = 0.59 for male drinkers), among the oldest subset (OR = 0.52) and in alcohol drinkers (OR = 0.55). Although the average intake was rather similar between sexes (29 vs 26 cups/year for men and women, data not shown), results suggest a better putative protection among men. A recent communication supports our findings related to coffee intake and alcohol among men.[57] In fact, coffee intake and its association with CRC were also thoroughly studied,[19,58–60] indicating that it has been associated to the reduction of colorectal adenomas in men.[61,62] Concerning females, an increased CRC incidence was reported among moderate and high coffee drinkers.[63]

Findings suggest a potential preventive effect for the three infusions in CRC, among other arguments, based on the inverse risk associations shown for the high intakes of red meat, energy and alcohol, which are recognized risk factors for the disease.[6,8,9] Furthermore, potential benefits could be expected from the combination of the analyzed infusions, also in dietary styles including a high intake of vegetables and fruits.

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 and displayed high correlations.[20] The validation was projected to be done, but due to sudden budgetary cuts, which took place in the early 2000s—as a consequence of the most severe financial crisis in the story of our country—it has never been performed later. It would have been desirable to count on information about cancer stages at the moment of diagnosis and a complete discrimination for tumor sub-sites within colon and rectum. However, such data were unavailable as at the time of interviews they were not routinely requested, only the pathologic verification of cancer lesions within the colorectal site being mandatory. Epidemiologic research on cancer in Uruguay continued with the remaining data bases—as the one used for the present study—and without funds to update or improve them. Therefore, we were not able to make deeper analyses in search for relationships between tea, 'mate' or coffee intake and those other pathologic items.

As both groups of participants were drawn from low socioeconomic strata, which are treated in the public health hospitals of Montevideo, selection bias appears to be unlikely. On the other hand, recall bias is more difficult to rule out in retrospective studies like the present one, having around 7% of ages ⩾ 80. As controls were very similar to cases concerning diet and sociodemographic variables it is possible that misclassification was non-differential. Therefore, a possible consequence could be the observation of attenuated effects and closer to the null.

Among the strengths, the sample size ($n = 3005$), a case:control ratio close to 1:4 and a reasonable age distribution (global P-value = 0.42), including subjects of four different public hospitals, allowed us to achieve good coverage and to reduce at least in part the possibility of biasing results. Also to be mentioned as a strength is the fact that the study population included subsets from the whole country, and times of data collection were coincident. Cases were microscopically confirmed by expert pathologists. Finally, a high participation was achieved (globally around 97.5% of patients within the proposed age limits), reducing the likelihood of selection bias. This is probably due to the fact that this population is very cooperative. Albeit it is not possible to completely avoid any bias, including recall bias, we think that results were not chance findings.

As conclusions, and recognizing the aforementioned limitations, we found evidence of different significant inverse associations for tea, 'mate' and coffee intake and CRC risk. The strongest associations were found for tea intake in both sexes. High 'mate' intake was only significantly associated for women and high coffee intake was associated only among men. Concerning age strata, high intakes of all infusions derived into significant or marginally inverse ORs for ages ⩾ 70. To our knowledge, this is the first epidemiologic study reporting inverse results on 'mate' intake and CRC. This infusion might broaden the scope of preventive habits, if further studies confirm our present findings.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1 Barrios E, Garau M, Alonso R, Musetti C. *IV Atlas of Cancer Incidence in Uruguay*. Comision Honoraria de Lucha Contra el Cancer: Montevideo, Uruguay, 2014 (in Spanish).
2 Ferlay J, Soerjomataram I, Ervik M, Eser S, Mathers C, Rebelo M *et al. GLOBOCAN 2012 v1.0*, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer, 2013. Available at http://globocan.iarc.fr (accessed on 24 August 2015).
3 Vassallo JA, De Stefani E, Barrios E, Ronco A. *Cancer Incidence in Uruguay 1991*. Comision Honoraria de Lucha Contra el Cancer: Montevideo, Uruguay, 1996 (in Spanish).

4 Speedy AW. Global production and consumption of animal source foods. *J Nutr* 2003; **133**: 4048S–4053S.
5 De Stefani E, Deneo-Pellegrini H, Mendilaharsu M, Ronco AL. Meat intake, heterocyclic amines and risk of colorectal cancer: a case-control study in Uruguay. *Int J Oncol* 1997; **10**: 573–1580.
6 De Stefani E, Deneo-Pellegrini H, Ronco AL, Correa P, Boffetta P, Aune D *et al.* Dietary patterns and risk of colorectal cancer: a factor analysis in Uruguay. *Asian Pac J Cancer Prev* 2011; **12**: 753–759.
7 De Stefani E, Ronco AL, Boffetta P, Deneo-Pellegrini H, Correa P, Acosta G *et al.* Nutrient-derived dietary patterns and risk of colorectal cancer: a factor analysis in Uruguay. *Asian Pac J Cancer Prev* 2012; **13**: 231–235.
8 World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. WCRF/AICR: Washington, DC, USA, 2007.
9 Hastert TA, White E. Association between meeting the WCRF/AICR cancer prevention recommendations and colorectal cancer incidence: results from the VITAL cohort. *Cancer Causes Control* 2016; **27**: 1347–1359.
10 Comision Honoraria de Lucha Contra el Cancer. *Knowledge, Beliefs, Attitudes and Practices Related to Cancer: Population Survey*. Technical cooperation PNUD/BID. Comision Honoraria de Lucha Contra el Cancer: Montevideo, Uruguay, 1993 (in Spanish).
11 Loomis D, Guyton KZ, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V *et al.* Carcinogenicity of drinking coffee, mate, and very hot beverages. *Lancet Oncol* 2016; **17**: 877–878.
12 International Agency for Research on Cancer. Coffee, tea, mate, methylxanthines and methylglyoxal. *IARC Monogr Eval Carcinog Risks Hum* 1991; **51**: 1–513.
13 International Agency for Research on Cancer. *Report of the Advisory Group to Recommend Prioritiies for IARC Monographs during 2015-2019: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Lyon, France, 2014. Report No. 14/002.
14 Ronco AL, De Stefani E, Mendoza B, Deneo-Pellegrini H, Vazquez A, Abbona E. Mate intake and risk of breast cancer: a case-control study. *Asian Pac J Cancer Prev* 2016; **17**: 1453–1461.
15 Ronco AL, De Stefani E, Mendoza B, Vazquez A, Abbona E, Sanchez G *et al.* Mate and tea intake, dietary antioxidants and risk of breast cancer: a case-control study. *Asian Pac J Cancer Prev* 2016; **17**: 2923–2933.
16 de Mejia EG, Song YS, Heck CI, Ramirez-Mares MV. Yerba mate tea (*Ilex paraguariensis*): phenolics, antioxidant capacity and in vitro inhibition of colon cancer cell proliferation. *J Funct Foods* 2010; **2**: 23–34.
17 Zapaterini JR, Bidinotto LT, Rodrigues MAM, Barbisan LF. Chemopreventive effects of mate against mouse mammary and colon carcinogenesis. *Hum Exp Toxicol* 2010; **29**: 175–185.
18 Dik VK, Bas Bueno-de-Mesquita H, Van Oijen MGH, Siersema PD, Uiterwaal CS, VanGils CH *et al.* Coffee and tea consumption, genotype-based CYP1A2 and NAT2 activity and colorectal cancer risk—results from the EPIC cohort study. *Int J Cancer* 2014; **135**: 401–412.
19 Guertin KA, Lotfield E, Boca SM, Sampson JN, Moore SC, Xiao Q *et al.* Serum biomarkers of habitual coffee consumption may provide insight into the mechanism underlying the association between coffee consumption and colorectal cancer. *Am J Clin Nutr* 2015; **101**: 1000–1011.
20 Ronco AL, De Stefani E, Boffetta P, Deneo-Pellegrini H, Acosta G, Mendilaharsu M. Food patterns and risk of breast cancer: a factor analysis study in Uruguay. *Int J Cancer* 2006; **119**: 1672–1678.
21 Mazzei ME, Puchulu MR, Rochaix MA, Table of food chemical composition. In: Cenexa y Feiden (ed.), 2nd edn. Buenos Aires, Argentina, 1995 (in Spanish).
22 Breslow NE, Day NE. *Statistical Methods in Cancer Research: Volume 1. The analysis of Case-control Studies*. International Agency for Research on Cancer Science Pub 32, Lyon, France, 1980.
23 Yu F, Jin Z, Jiang H, Xiang C, Tang J, Li T *et al.* Tea consumption and the risk of five major cancers: a dose–response meta-analysis of prospective studies. *BMC Cancer* 2014; **14**: 197.
24 Rosa LS, Silva NJA, Soares NCP, Monteiro MC, Teodoro AJ. Anticancer properties of phenolic acids in colon cancer—a review. *J Nutr Food Sci* 2016; **6**: 2.
25 Dominianni C, Huang WY, Berndt S, Hayes RB, Ahn J. Prospective study of the relationship between coffee and tea with colorectal cancer risk: The PLCO Cancer Screening Trial. *Br J Cancer* 2013; **109**: 1352–1359.
26 Henning SM, Wang P, Abgaryan N, Moura de Oliveira D, Zhang Y, Lee RP *et al.* Phenolic acid concentrations in plasma and urine from men consuming green or black tea and potential chemopreventive properties for colon cancer. *Mol Nutr Food Res* 2013; **57**: 483–493.
27 Zhang YF, Qin X, Jian L, Wang P, Zhang HW, Zhou L *et al.* Tea consumption and the incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Eur J Cancer Prev* 2015; **24**: 353–362.
28 Wang ZH, Gao QY, Fang JY. Green tea and incidence of colorectal cancer: evidence from prospective cohort studies. *Nutr Cancer* 2012; **64**: 1143–1152.
29 Fujiki H, Sueoka E, Watanabe T, Suganuma M. Primary cancer prevention by green tea, and tertiary cancer prevention by the combination of green tea catechins and anticancer compounds. *J Cancer Prev* 2015; **20**: 1–4.
30 Butt MS, Ahmad RS, Sultan MT, Qayyum MMN, Naz A. Green tea and anticancer perspectives: updates from last decade. *Crit Rev Food Sci Nutr* 2015; **55**: 792–805.
31 Sun CL, Yuan JM, Koh WP, Yu MC. Green tea, black tea and colorectal cancer risk: a meta-analysis of epidemiologic studies. *Carcinogenesis* **27**: 1301–1309.
32 Pan MH, Lai CS, Wang H, Lo CY, Ho CT, Li S. Black tea in chemo-prevention of cancer and other human diseases. *Food Sci Hum Wellness* 2013; **2**: 12–21.
33 Butt MS, Imran A, Sharif MK, Ahmad RS, Xiao H, Imran M *et al.* Black tea polyphenols: a mechanistic treatise. *Crit Rev Food Sci Nutr* 2014; **54**: 1002–1011.
34 Gosslau A, En Jao DL, Huang MT, Ho CT, Evans D, Rawson NE *et al.* Effects of the black tea polyphenol theaflavin-2 on apoptotic and inflammatory pathways in vitro and in vivo. *Mol Nutr Food Res* 2011; **55**: 198–208.
35 Cordero-Herrera I, Martín MA, Bravo L, Goya L, Ramos S. Epicatechin gallate induces cell death via p53 activation and stimulation of p38 and JNK in human colon cancer SW480 cells. *Nutr Cancer* 2013; **65**: 718–728.
36 De Stefani E, Moore M, Aune D, Deneo-Pellegrini H, Ronco AL, Boffetta P *et al.* Maté consumption and risk of cancer: a multi-site case-control study in Uruguay. *Asian Pac J Cancer Prev* 2011; **12**: 1089–1093.
37 Shan JZ, Xuan YY, Zheng S, Dong Q, Zhang SZ. Ursolic acid inhibits proliferation and induces apoptosis of HT-29 colon cancer cells by inhibiting the EGFR/MAPK pathway. *J Zhejiang Univ Sci B* 2009; **10**: 668–674.
38 Xavier CPR, Lima CF, Preto A, Seruca R, Fernandes-Ferreira M, Pereira-Wilson C. Luteolin, quercetin and ursolic acid are potent inhibitors of proliferation and inducers of apoptosis in both KRAS and BRAF mutated human colorectal cancer cells. *Cancer Lett* 2009; **281**: 162–170.
39 Ramos AA, Pereira-Wilson C, Collins AR. Protective effects of ursolic acid and luteolin against oxidative DNA damage include enhancement of DNA repair in Caco-2 cells. *Mutat Res* 2010; **692**: 6–11.
40 Puangpraphant S, Berhow MA, Gonzalez de Mejia E. Mate (*Ilex paraguariensis* St. Hilaire) saponins induce caspase-3-dependent apoptosis in human colon cancer cells in vitro. *Food Chem* 2011; **125**: 1171–1178.
41 Puangpraphant S, Dia VP, Gonzalez de Mejia E, Garcia G, Berhow MA, Wallig MA. Yerba mate tea and mate saponins prevented azoxymethane-induced inflammation of rat colon through suppression of NF-kB p65ser^{311} signaling via IkB-a and GSK-3b reduced phosphorylation. *Biofactors* 2013; **39**: 430–440.
42 Heck CI, de Mejia EG. Yerba Mate Tea (*Ilex paraguariensis*): a comprehensive review on chemistry, health implications, and technological considerations. *J Food Sci* 2007; **72**: R138–R151.
43 Bracesco N, Sánchez AG, Contreras V, Menini T, Gugliucci A. Recent advances on Ilex paraguariensis research: minireview. *J Ethnopharmacol* 2011; **136**: 378–384.
44 Zang LL, Wu BN, Lin Y, Wang J, Fu L, Tang Z. Research progress of ursolic acid's anti-tumor actions. *Chin J Integr Med* 2014; **20**: 72–79.
45 Kashyap D, Tuli HS, Sharma AK. Ursolic acid (UA): a metabolite with promising therapeutic potential. *Life Sci* 2016; **146**: 201–213.
46 Pandurangan AK, Esa NM. Dietary non-nutritive factors in targeting of regulatory molecules in colorectal cancer: an update. *Asian Pac J Cancer Prev* 2013; **14**: 5543–5552.
47 Kim HS, Wannatung T, Lee S, Yang WK, Chung SH, Lim JS *et al.* Quercetin enhances hypoxia-mediated apoptosis via direct inhibition of AMPK activity in HCT116 colon cancer. *Apoptosis* 2012; **17**: 938–949.
48 Min K, Ebeler SE. Quercetin inhibits hydrogen peroxide-induced DNA damage and enhances DNA repair in Caco-2 cells. *Food Chem Toxicol* 2009; **47**: 2716–2722.
49 Pandurangan AK, Esa NM. Luteolin, a bioflavonoid inhibits colorectal cancer through modulation of multiple signalling pathways: a review. *Asian Pac J Cancer Prev* 2014; **15**: 5501–5508.
50 Pandurangam AK, Ganapasam S. Luteolin modulates cellular thiols on azoxymethane-induced colon carcinogenesis. *Asian J Exp Biol Sci* 2013; **4**: 245–250.
51 Gnoatto SCB, Dassonville-Klimpt A, Da Nascimento S, Galéra P, Boumediene K, Gosmann G *et al.* Evaluation of ursolic acid isolated from *Ilex paraguariensis* and derivatives on aromatase inhibition. *Eur J Med Chem* 2008; **43**: 1865–1877.
52 Way TD, Lee HH, Kao MC, Lin JK. 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* 2004; **40**: 2165–2174.
53 Sommer A, Vyas KS. A global clinical view on vitamina A and carotenoids. *Am J Clin Nutr* 2012; **96**: 1204S–1206S.
54 Maggio M, De Vita F, Lauretani F, Bandinelli S, Semba RD, Bartali B *et al.* Relationship between carotenoids, retinol and estradiol levels in older women. *Nutrients* 2015; **7**: 6506–6519.

55 Hollestelle A, Elstrodt F, Nagel JHA, Kallemeijn WW, Schutte M. Phosphatidylinositol-3-OH kinase or RAS pathway mutations in human breast cancer cell lines. *Mol Cancer Res* 2007; **5**: 195–201.
56 Caiazza F, Ryan EJ, Doherty G, Winter DC, Sheahan K. Estrogen receptors and their implications in colorectal carcinogenesis. *Front Oncol* 2015; **5**: 19.
57 Goodman BA. Can coffee ameliorate the cancer risks associated with low-moderate alcohol consumption in men? *J Food Nutr Disor* 2014; **3**: 6.
58 Li G, Ma D, Zhang Y, Zheng W, Wang P. Coffee consumption and risk of colorectal cancer: a meta-analysis of observational studies. *Publ Health Nutr* 2012; **16**: 346–357.
59 Schmit SL, Rennert HS, Rennert G, Gruber SB. Coffee consumption and the risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2016; **25**: 634–639.
60 Akter S, Kashino I, Mizoue T, Matsuo K, Ito H, Wakai K *et al.* Coffee drinking and colorectal cancer risk: an evaluation based on a systematic review and meta-analysis among the Japanese population. *Jpn J Clin Oncol* 2016; **46**: 781–787.
61 Nakamura T, Ishikawa H, Mutoh M, Wakabayashi K, Kawano A, Sakai T *et al.* Coffee prevents proximal colorectal adenomas in Japanese men: a prospective cohort study. *Eur J Cancer Prev* 2016; **25**: 388–394.
62 Budhathoki S, Iwasaki M, Yamaji T, Sasazuki S, Tsugane S. Coffee intake and the risk of colorectal adenoma: the colorectal adenoma study in Tokyo. *Int J Cancer* 2015; **137**: 463–470.
63 Groessl EJ, Allison MA, Larson JC, Ho SB, Snetslaar LG, Lane DS *et al.* Coffee consumption and the incidence of colorectal cancer in women. *J Cancer Epidemiol* 2016, **2016**: 6918431.