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Alcohol Drinking, Non-alcoholic Beverages and Risk of Advanced Prostate Cancer among Uruguayan Men

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Abstract

Background: Loss of the membrane endopeptidase CD10 plays an important role in the development of neuropeptide-mediated androgen-independent prostate cancer cell growth. The aim of this study was to investigate the potential prognostic value of the CD10/neuropeptide axis with regard to prostate-specific antigen (PSA) failure after radical prostatectomy (RP) in early prostate cancer (PC) patients.

Methods: Tumor samples from 70 early PC patients who underwent RP were immunohistochemically evaluated for expression of CD10 and endothelin-1 (ET-1). The examined parameters were prospectively correlated with time to PSA failure and combined with Gleason grade and pathological TNM stage.

Results: Membranous and apical cytoplasmic expression of CD10 was directly correlated with time to PSA failure ($P < 0.001$). Cytoplasmic ET-1 was inversely correlated with time to PSA relapse ($P = 0.002$). CD10 and ET-1 were inversely interrelated ($P < 0.001$). CD10 expression ($P = 0.012$) and stage ($P = 0.013$) were independent predictors of biochemical recurrence.

Conclusion: CD10 and ET-1 follow inverse patterns of expression in tumors of early PC patients, in accordance with their biological roles and molecular interrelations. Evaluation of CD10 expression in early PC might contribute to a better prediction of PSA relapse-free survival after RP.

Keywords: Prostate cancer; *Mate* consumption; Alcohol; Coffee; Tea; Soft drinks

Introduction

Prostate cancer is the second leading cancer site in Uruguay, following lung cancer [1]. In a recent Uruguayan publication, prostate cancer was shown to display an age-standardized incidence rate of 76.5 per 100,000 men [1].

According to the World Cancer Research Fund/American Institute for Cancer Research [2], diets high in calcium (diets with whole milk, cheese, butter, cheese) are a probable cause of this malignancy, whereas lycopene, and selenium are probably protective factors.

Numerous studies, employing traditional reductionist approaches including case-control, cohort, and randomized trials, showed largely null results for alcoholic beverages, and a paucity of studies on *mate*, coffee, tea, and soft drinks and risk of prostate cancer [2,3]. For this reason we decided to conduct a case-control study on beverages (alcoholic and non-alcoholic) and prostate cancer risk, in order to evaluate the effect of these agents in the Uruguayan male population.

Material and Methods

In the time period 1996-2004 all cancers of the oral cavity, pharynx, esophagus, stomach, colon, rectum, larynx, lung, breast, prostate, bladder and kidney and a large pool of controls were conducted in the four major public health hospitals of Montevideo.

Selection of cases

All newly diagnosed and microscopically confirmed cases of advanced prostate cancer were considered eligible for this study. The initial number of cases was 370 and 25 patients refused the interview, leaving a final total of 345 cases (response rate 93.2 %). All the cases were adenocarcinomas and they were classified by the Gleason score [4] as follows: Score 5 or less: 4 %, score 6: 44 %, score 7: 35 %, and score 8 or more: 17 %.

Selection of controls

In the same time period and in the same hospitals, 1,414 men with non-neoplastic conditions not related to smoking, drinking, and without recent changes in their diets were randomly selected for this study. Eighty-five (85) patients refused the interview leaving a final total of potential controls of 1,346 patients (response rate 95.2 %). From this pool, 1,296 controls were randomly selected and frequency matched to the cases on age and residence. These controls presented the following diagnostic conditions: eye disorders (289 patients, 22.3 %), abdominal hernia (279, 21.5 %), fractures (158, 12.2 %), urinary stones (113, 8.7 %), injuries (104, 8.0 %), diseases of the skin (103, 8.0

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%), varicose veins (72, 5.6 %), acute appendicitis (64, 4.9 %), hydatid cyst (54, 4.2 %), blood disorders (42, 3.2 %), and bone diseases (18, 1.4 %).

Interviews and questionnaire

All the interviews were conducted face-to-face by two trained workers of non medical occupation. These interviews were performed only in the hospitals for both series of participants. Proxy interviews were not accepted. The questionnaire included sections on sociodemographics, occupational history, self-reported family history of cancer among first-degree relatives, anthropometric measures, a complete smoking history, a complete drinking history, a complete history of non-alcoholic beverages (including *mate,* coffee, tea, soft drinks consumption), history of sexual practices, and a food frequency questionnaire (FFQ) on 64 foods. This FFQ allowed the estimation of total energy intake, and it was considered to be representative of the usual Uruguayan diet. Finally, the FFQ was tested for reproducibility with good results [5].

Beverages

The following beverages were included into the study: total alcohol drinking, mate consumption, black coffee, white coffee, black tea, tea with milk, soft drinks, and whole milk.

Statistical analysis

The odds ratios of advanced prostate cancer were estimated by unconditional multiple logistic regression [6] following the model which included the following terms: age (continuous), residence (categorical, 3 strata), education (categorical, 3 strata), income (categorical, 3 strata), BMI (continuous), smoking intensity (continuous), years of smoked (continuous), total energy and each beverage. All the estimations were conducted using the STATA software release 10 [7].

Results

The distribution of cases and controls by sociodemographics and selected risk factors is shown in Table 1. Age, residence, and urban/rural status were very similar among both series of participants. Also education was similar among cases and controls, but monthly income was higher among cases when compared with controls (global p-value=0.12). Cases showed a much higher proportion of relative weight compared with controls (OR 2.0, 95 % CI 1.4-2.9). Smoking duration was protective when cases were compared with controls. These results were similar when cases with metastatic disease were compared with the control group.

Odds ratios of advanced prostate cancer for alcoholic beverages are shown in Table 2. Current drinkers showed a reduction in risk of 59 %, when compared with never drinkers. Total alcohol drinking was negatively associated with risk of advanced prostate cancer (OR 0.57, 95 % CI 0.34-0.94, p-value for linear trend=0.09). The same effect was observed for years of drinking alcohol (OR 0.57, 95 % CI 0.31-1.03, p-value for linear trend=0.003).

Odds ratios of advanced prostate cancer for *mate* consumption are shown in Table 3. *Mate* drinking (in liters per day) displayed an increased risk of 2.69 (95 % CI 1.62-4.49, p-value for linear trend <0.0001). Also, the number of years of mate drinking was directly associated with prostate cancer (OR for drinkers of 60 years or more 1.79, 95 % CI 1.11-2.89, p-value for linear trend=0.02). Cumulative exposure to *mate* (*mate* years) was also directly associated with prostate cancer (OR 1.99, 95 % CI 1.25-3.18, p-value for linear trend=0.0004).

	Cases	Controls				
Variable	**Category**	**No**	**%**	**No**	**%**	**Global p-value**
Age (years)	40-49	3	0.9	11	0.9	
	50-59	24	6.9	88	6.8	
	60-69	115	33.3	424	32.7	
	70-79	164	47.5	633	48.8	
	80-89	39	11.3	140	10.8	0.99
Residence	Montevideo	176	51.0	664	51.2	
	Other counties	169	49.0	632	48.8	0.94
Urban/rural status	Urban	247	71.6	929	71.7	
	Rural	98	28.4	367	28.3	0.97
Education	0-2	107	31.0	395	30.5	
(years)	3-5	133	38.6	488	37.6	
	6+	105	30.4	413	31.9	0.88
Income	<=144	101	29.3	494	38.1	
(US dollars)	145+	128	37.1	498	38.4	
	Unknown	116	33.6	304	23.5	0.12
BMI[1]	<=22.8	53	15.4	324	25.0	
	22.9-24.9	85	24.6	324	25.0	
	25.0-27.1	100	29.0	324	25.0	
	27.2+	107	31.0	324	25.0	0.001
Years smoked	Never smokers	92	26.7	233	17.9	
	1-29	34	9.9	190	14.7	
	30-39	45	13.0	219	16.9	
	40-49	64	18.5	316	24.4	
	50+	110	31.9	338	26.1	0.0001
No patients		345	100.0	1296	100.0	

Table 1: Distribution of cases and controls by sociodemographics and selected risk factors.

Finally, drinkers of very hot *mate*, compared with drinkers of warm *mate,* showed an OR of 3.18, (95 % CI 1.87-5.39, p-value for linear trend <0.0001).

Odds ratios of advanced prostate cancer for coffee, tea, and soft drinks are shown in Table 4. Black coffee was directly associated with risk of prostate cancer (OR for drinkers of seven or more cups of week compared with never drinkers 1.41, 95 % 1.02-1.95, p-value for linear trend=0.02). The same increased risk was observed for white coffee, even after adjusted for whole milk. On the other hand, black tea was significantly protective (OR 0.43, 95 % CI 0.22-0.81, p-value for linear trend=0.0001). Both tea with milk and soft drinks were not associated with risk of advanced prostate cancer (p-value for trend=0.92). Finally, four or more spoons of added sugar were positively associated with risk of prostate cancer (OR 2.22, 95 % CI 1.20-4.13, p-value for linear trend <0.0001).

Alcohol variable	Category	Cases/Controls	OR	95 % CI
Alcohol status	Never drinkers	140/340	1.0	reference
	Former drinkers	94/221	0.94	0.66-1.34
	Current drinkers	111/735	0.41	0.30-0.56
		p-value for trend	<0.0001	
Total alcohol[2]	Never drinkers	140/340	1.0	reference
	1-60	61/363	0.41	0.29-0.59
	61-120	58/261	0.55	0.38-0.81
	120-240	60/189	0.83	0.56-1.23
	241+	26/143	0.57	0.34-0.94
		p-value for trend	0.09	
Years of drinking	Never drinkers	140/340	1.0	reference
	1-39	44/374	0.47	0.31-0.71
	40-49	57/310	0.47	0.33-0.69
	50-59	88/222	0.67	0.46-0.96
	60+	22/50	0.57	0.31-1.03
		p-value for trend	0.003	
Alcohol years	Never drinkers	140/340	1.0	reference
	1-29	43/344	0.34	0.23-0.51
	30-59	75/314	0.58	0.41-0.83
	60+	89/289	0.70	0.49-0.99
		p-value for trend	0.07	

[1]Adjusted for age, residence, education, income, body mass index, smoking intensity, years smoked, *mate* consumption, and total energy.
[2]In ml of ethanol per day.

Table 2: Odds ratios of advanced prostate cancer for alcoholic beverage[1].

Variable	Category	Cases/Controls	OR	95 % CI
Mate status	Never drinkers	32/154	1.0	reference
	Former drinkers	30/66	2.45	1.32-4.54
	Current drinkers	283/1076	1.60	1.03-2.47
		p-value for trend	0.14	
Mate drinking	Never drinkers	32/154	1.0	reference
(liters per day)	0.1-0.9	57/278	1.12	0.68-1.86
	1.0-1.9	180/628	1.70	1.08-2.68
	2.0+	76/236	2.69	1.62-4.49
		p-value for trend	<0.0001	
Years of drinking	Never drinkers	32/154	1.0	reference
	1-49	62/445	1.43	0.84-2.43
	50-59	98/363	1.64	1.03-2.63
	60+	153/334	1.79	1.11-2.89
		p-value for trend	0.02	
Mate years	Never drinkers	32/154	1.0	reference
	1-49	75/413	1.24	0.77-2.01
	50-59	101/334	1.81	1.12-2.90
	60+	137/395	1.99	1.25-3.18
		p-value for trend	0.0004	
Mate temperature	Warm	43/210	1.0	reference
	Hot	227/827	1.50	1.02-2.19
	Very hot	43/105	3.18	1.87-5.39
		p-value for trend	<0.0001	

[1]Adjusted for age, residence, education, income, body mass index, smoking intensity, years smoked, alcohol drinking, and total energy intake.

Table 3: Odds ratios of advanced prostate cancer for *mate* consumption[1].

Beverage	Cups per week	Cases/Controls	OR	95 % CI
Black coffee	0	155/729	1.0	reference
	1-6	102/299	1.33	0.96-1.84
	7+	88/268	1.41	1.02-1.95
		p-value for trend	0.02	
White coffee	0	187/856	1.0	reference
	1-6	81/231	1.17	0.83-1.65
	7+	77/209	1.51	1.07-2.12
		p-value for trend	0.02	
Black tea	0	307/996	1.0	reference
	1-6	26/186	0.46	0.29-0.72
	7+	12/114	0.43	0.22-0.81
		p-value for trend	0.0001	
Tea with milk	0	295/1103	1.0	reference
	1-6	28/132	0.56	0.34-0.91
	7+	27/61	1.47	0.88-2.45
		p-value for trend	0.88	
Soft drinks	0	85/324	1.0	reference
	1-4	86/324	0.88	0.59-1.32
	5-6	95/324	1.04	0.70-1.53
	7+	79/324	0.95	0.65-1.39
		p-value for trend	0.92	
Added sugar	1	256/1096	1.0	reference
(tea spoon)	2	31/97	1.98	1.23-3.19
	3	40/86	2.03	1.31-3.15
	4+	18/37	2.22	1.20-4.13
		p-value for trend	<0.0001	

[1]Adjusted for age, residence, education, income, body mass index, smoking intensity, years smoked, alcohol drinking, *mate* consumption, whole milk, added sugar, and total energy intake.

Table 4: Odds ratios of advanced prostate cancer for other non-alcoholic beverages[1].

Variable	OR	95 % CI	z	p-value
Mate consumption	1.44	1.23-1.69	4.48	<0.0001
Black tea	0.54	0.40-0.71	-4.32	<0.0001
Sugar	1.31	1.12-1.53	3.39	0.001
Smoking duration	0.85	0.76-0.95	-2.89	0.004
Black coffee	1.26	1.07-1.47	2.81	0.005

[1]Adjusted for age, residence, education, income, body mass index, and total energy intake.

Table 5: Final model on beverages and advanced prostate cancer, fitted by forward stepwise method[1].

The final model, fitted by stepwise forward method, is shown in Table 5. This model included *mate* consumption, black tea, added sugar, years smoked, and black coffee. The odds ratio for these terms was 7.28 (95 % CI 4.98-11.7).

Discussion

Alcohol drinking has been studied in numerous reports and the role of alcoholic beverages has been considered without clear evidence in risk of prostate cancer. Thirty three (33) case-control studies and 17 prospective studies have dealt with the role of alcohol in the risk of prostate cancer [3,8]. Five case-control studies discriminated prostate cancer in localized and advanced. Two prospective cohort studies stratified its general population in localized and advanced prostatic carcinoma and the results were null [9,10]. On the other hand, years of drinking total alcohol was inversely associated with the risk of advanced prostate cancer. Thus, our results are somehow conflictive and do not support the existence of any clear associations between alcohol drinking and prostate cancer. Moreover, our findings suggest a protective role of alcohol drinking in advanced prostate cancer.

Conversely, in the present study *mate* consumption was positively associated with prostate cancer with a significant dose-response. Also years of drinking *mate* and cumulative exposure to *mate* clearly increased the risk of prostate cancer. Drinkers of very hot *mate* showed a three-fold increased risk of prostate cancer when compared with drinkers of warm *mate*. In a previous multi-site study on *mate* drinking and cancer [11], *mate* consumption increased the risk of prostate cancer in 70 % with a clear gradient. The same was observed regarding the role of hot *mate* drinking.

Mate is a hot infusion originated in the herb *Ilex paraguariensis*. According to Heck and de Mejía [12] *mate* contains numerous chemical substances considered protective like chlorogenic acid. The first report on the presence of benzopyrene in *mate* was attributed to Rüschenburg [13]. It is important to note that benzo[*a*]pyrene was considered by IARC as carcinogenic to humans [14]. The first epidemiologic study on *mate* and esophageal cancer suggested that thermal injury could be responsible for the damage to the esophageal mucosa leading to esophagitis, favoring the carcinogenic role of tobacco and alcohol in this organ [15]. Subsequent studies on *mate* consumption and esophageal cancer [16-21] confirmed this increased risk. Also the IARC monograph on *mate* [22] concluded that hot *mate* drinking is probably carcinogenic to humans (2 A of IARC), whereas *mate* per se was not evaluable.

The leading author of the first study (Dr. Juan Alberto Vassallo, personal communication) suggested that *mate* could be carcinogen for sites distant from the esophageal mucosa. This observation prompted several studies in organs not in contact with the beverage, like lung [23], kidney [24], and bladder [25,26]. The results of these studies replicated the increased risks which were originally observed in squamous cell carcinoma of the esophagus.

The mechanism(s) of *mate* effect in mouth, pharynx, esophagus, lung, bladder, and kidney could be due to the combination of thermal injury and substances like benzo[*a*]pyrene [27,28]. Brazilian authors conducted several experimental studies, both in vivo and in vitro, which replicated the findings of previous epidemiological studies [29,30]. More recently, a study by Fagundes et al. [31] reported the presence of metabolites of benzo[*a*]pyrene in the urine of healthy volunteers of Rio do Grande do Sul, Brazil who were *mate* drinkers. Furthermore other studies conducted in the National Cancer Institute in USA, concluded that the presence of benzo[*a*]pyrene in *mate* drinks is likely [27,32]. We have compared the effect of mate in patients with metatatic disease, but the results were not significant. Thus, the presence of carcinogens in *mate* could explain the the effect of *mate* on distant organs, such as the prostate. Unfortunatelly, we were not able to measure the presence of benzo[*a*]pyrene in the present study.

Our study also explored the effect of coffee, tea, and soft drinks. Whereas coffee increased the risk of prostate cancer moderately and black tea was inversely associated with this malignancy, soft drinks were not associated with advanced prostate cancer. In a monograph by IARC [22], there was no evidence of a relationship between these and prostate cancer. On the other hand, green tea, and particularly, the interaction between green tea and lycopene [33-35] was strongly

protective against the risk of prostate cancer. It has been suggested that coffee could increase the risk and that effect could be due not to its content caffeine, but to added sugar which elevated the insulinemia. On the other hand, caffeine elevates the blood levels of cholesterol, a potential risk factor for prostate cancer [36].

The relationship between refined carbohydrates and an increased risk of prostate cancer could be due to the effect of IGF-1, inhibitor of apoptosis [37]. Furthermore, the relationship between body mass index and IGF-1 is complex but suggests that BMI increased the risk of prostate cancer through the intake of refined carbohydrates. In our study, added sugar doubled the risk of prostate cancer.

Like other case-control studies, the present study has limitations. The major limitations are related to selection bias and recall bias. We have tried to minimize selection bias frequency matching cases and controls on age and residence. Concerning recall bias, it could led to misclassification, while differential misclassification could result in biased elevated risks. Nevertheless this bias is unlikely to occur in our study, since the Uruguayan population is not bound to be familiar with the role of diet in prostate cancer. On the other hand, our study has its strengths. Perhaps the major strength is related to the high response rate, both for cases and controls. Another strength is the microscopic validation of the cases, which were examined by pathologists with expertise in prostate carcinoma. Finally, cases and controls derived from the same health care system.

In summary, in our study, *mate* consumption, black tea, and refined carbohydrates (sugar) were strongly associated with risk of advanced prostate cancer. Perhaps, the major finding, related to the effect of *mate* consumption, suggests that further studies on this beverage are needed, including also limited prostate cancer (stage I).

Disclosures

The authors declare no conflicts of interest.

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