



Risk factors of prostate cancer: a case-control study in Northeast Brazil

Fatores de risco do câncer de próstata: estudo caso-controle no Nordeste do Brasil

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ABSTRACT

This case-control study aimed on the identification of factors that modified prostate cancer risk of patients in a public hospital of Paraíba. Data from 91 patients with prostate cancer and 91 age-matched (± 5 years) healthy controls were obtained from medical records and personal interviews. Odds ratios (ORs) and confidence intervals (CIs) were determined using regression analysis. Patients and controls were on average 69.56 (SD= 8.31) and 68.32 (SD= 7.68) years old ($p = 0.297$). In a model of multiple regression analysis, Afrodescendants and men who ever smoked had a 4.150 and 3.939 times increased risk ($p < 0.001$; $p < 0.001$). Family history of first-degree relatives was associated with a 6.967 ($p < 0.001$) increased risk of prostate cancer. African ancestry, smoking and family history increased the risk of prostate cancer. Recommendations of health authorities regarding prostate cancer screening could stronger focus on men with these risk factors.

Keywords: Prostate cancer. Risk factors. African continental ancestry group. Tobacco use disorder. Family health history.

RESUMO

Este estudo caso-controle teve como objetivo identificar os fatores que modificam o risco de câncer de próstata em pacientes de um hospital público da Paraíba. Dados de 91 pacientes e 91 controles saudáveis pareados por idade (± 5 anos) foram obtidos de prontuários médicos e entrevistas pessoais. A razão de chance e os intervalos de confiança foram determinados por meio de análise de regressão. Pacientes e controles tinham em média 69,56 (DP = 8,31) e 68,32 (DP = 7,68) anos ($p = 0,297$). Afrodescendentes e homens que já fumaram, tiveram um risco 4,150 e 3,939 vezes maior ($p < 0,001$; $p < 0,001$). A história familiar aumentou o risco 6,967 vezes ($p < 0,001$). Ascendência africana, tabagismo e história familiar aumentaram o risco de câncer de próstata. As recomendações das autoridades de saúde em relação ao rastreamento do câncer de próstata poderiam se concentrar mais nos homens com esses fatores de risco.

Palavras-chave: Câncer de próstata. Fator de risco. Afrodescendente. Tabagismo. História médica familiar.

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INTRODUCTION

According to the International Agency for Research on Cancer in 2018,

1,276,106 new cases of prostate cancer (PC) were registered worldwide¹. This corresponds to 7.1% of all cancers in men¹. In Brazil, for each of the years 2021 and

2022, were predicted 65.840 new cases of PC². Incidence increased between 2005 and 2020 from 51.00 to 62.95 new cases per 100.000 men^{2,3}. The northern part of Brazil, embracing mainly Amazonia, is characterized by a low incidence that increased from 20.00 to 29.39 cases per 100.000 men during the same time span^{2,3}. This is in sharp contrast to the Brazilian Northeast that changed from a low to high incidence region: In 2005 the incidence of 34.00 cases per 100.000 men was lower than in southern regions of the country³. In 2020 the prediction of 72.35 cases per 100.000 men in contrast, was higher than for all other Brazilian regions².

The gain of life expectation in Northeast Brazil may be one important factor to explain the increase of disease incidence². However, life expectation and mean age of adult men are nearly identical among populations of North and Northeast Brazil indicating the existence of additional factors that increase risk of PC among men in the latter population². One factor may be ancestry: Northeast Brazil has a high level of admixture among European settlers, Native Americans, and enslaved Africans⁴. The contribution of African ancestry is stronger than in other Brazilian regions.⁴ Incidence of PC varies strongly among human populations and in western countries it is higher among individuals of African ancestry^{5,6}.

Family history and taller height are further non-modifiable risk factors of prostate cancer⁷⁻¹⁰. Among modifiable risk factors, obesity and weight gain were

positively associated with PC^{11,12}. In prospective studies a larger waist circumference also increased risk of PC^{11,12}. Few cohort studies indicated an increased risk of prostate cancer due to smoking, but without showing a dose-response relationship^{13,14}. These studies also revealed that current smokers, who have PC, doubled the risk of dying from the disease^{13,14}. Furthermore, previous meta-analysis indicated that consumption of alcohol increased risk of disease^{11,12}. Physical activity and several dietary factors instead, like consumption of fish, coffee, tomatoes and its products, can have a protective function^{11,12}.

Previous Brazilian cross-sectional studies characterized clinical and socio-demographic variables of PC patients in a descriptive way¹⁵⁻¹⁸. A database study indicated an increased mortality rate of prostate cancer in geographic regions of Brazil with higher consumption of alcoholic drinks, respectively production of soybeans and maize¹⁹. Authors argued that this might indicate an association between risk of PC and use of pesticides¹⁹. The unique two Brazilian case-control studies performed in the states of Bahia and Santa Catarina addressed on risk associated ancestry and family history of PC^{20,21}.

To the best of our knowledge there do not exist Brazilian case-control studies so far, that aimed on the identification of anthropometric measures and life-style related risk factors others than the consumption of alcohol. Increasing rates of disease in Northeast Brazil and missing

studies underline the need to understand better risk factors of PC in this population. Here we performed a case-control study in Northeast Brazil, based on hospital admission of prostate cancer patients in the years 2019 and 2020. Anthropometric measures, the life style related risk factors smoking and alcohol consumption, ancestry, family history and socio-economic variables, were compared between cases and controls.

METHODOLOGY

STUDY POPULATION

The data sampling protocol was reviewed and approved by the Brazilian National Ethics Research Committee (CAAE plataforma Brasil: 18518819.4.0000.5187). Written informed consent was obtained from all participants. Consent to publish data anonymously was obtained from each participant of the control group. PC patients and healthy controls were recruited from the reference center for cancer treatment, “Fundação Assistencial da Paraíba” Hospital (FAP), in Campina Grande, State of Paraíba, Northeast Brazil. Campina Grande is situated inland, about 120 km away from João Pessoa, the state capital on the Atlantic coast. With about 400,000 inhabitants, it is the second largest urban center of Paraíba.

DATA SAMPLING

Sampling was performed between

January and March 2020, respectively September 2020 and February 2021. Only PC patients with hospital admission in the years 2019 and 2020 were included in the study. All data of PC patients were obtained from medical records of the medical archive of the FAP hospital. Data of PC patients were registered before initiation of treatment by medical staff during hospital admission. Data of age-matched (± 5 years) healthy controls were obtained from face-to-face interviews. All interviews were conducted by one of the authors using a questionnaire to which participants responded verbally. Interviews of controls were performed in a social room of the hospital. Healthy controls were visitors of non-cancer patients in the FAP hospital and asked directly to participate in the study. Men were eligible as controls if they were aged ≥ 40 years and did not have any type of diagnosed chronic disease.

The basic education level was defined as ≤ 8 years of basic school education. Middle and high education levels were defined as between 8–12 years and above 12 years, respectively. Minimum wage and multiples thereof were used to define income. This is a popular and well-known method used to define economic level among low- and middle-class subjects. Less than minimum wage was defined as “basic” income, whereas income equivalent to one and two times the minimum wage was defined as “middle” income. More than two times the minimum wage was defined as “high” income. The minimum wage in 2020 was

R\$1045.00/month (US\$201.34/month; 31st December 2020). Family history was stated as information if any first-degree relative had PC. Self-information about ancestry was obtained from controls and PC patients in interviews and medical records. Information about smoking referred to the question if the participant was smoking or ever had smoked. Ancestry was self-informed by participants. We refer to African ancestry if the participant informed African or mixed European- African ancestry. Work with physical effort referred on the labour of participants: Farmers and craftsmen worked with physical effort.

STATISTICAL ANALYSIS

All statistical analyses were performed using the SPSS STATISTICS™ software (SPSS; IBM company; version 24). The t-test was applied to compare continuous variables. Fisher's exact test and Pearson's chi-square (χ^2) test were used to analyze categorical variables. To quantify associations among variables and risk of

PC, nominal logistic regression analysis was applied. Results were presented as adjusted odd ratios (OR), 95% confidence interval (CI) and p-value of likelihood ratio tests. Significant univariate regression analysis variables were used for regression modeling with multiple adjusted variables. Variables with significance levels less than 0.2 in the univariate analysis were included in the model. Then, variables with significance level less than 0.05 were kept in the model. Backward selection was used when significant variables were selected. The final model was tested for fitness using the likelihood ratio test.

RESULTS

Clinic- histopathological data of the 91 PC patients were summarized in Table 1. All PC patients had tumors of stage I, II or III, whereas stage IV was missing (Table 1). Gleason of nine and PSA ≥ 20 was only detected among patients in advanced stage III of disease (p =0.001; p <0.001; Table 1).

Table 1. Clinic- histopathological data and treatment of PC patients (N= 91)

TNM	All	I	II	III	P value
	N (%)	N (%)	N (%)	N (%)	
		48 (52.75%)	14 (15.38%)	29 (31.87%)	
TNM ¹		I and II		III	
Gleason					
≤6	21 (23.08%)	16 (25.81%)		5 (17.24%)	0.001
7	30 (32.97%)	24 (38.71)		6 (20.69%)	
8	33 (36.26%)	22 (35.48)		11 (37.93%)	
9	7 (7.69%)	-		7 (24.14%)	
PSA					
<10	49 (53.85%)	47 (75.81%)		2 (6.90%)	<0.001
10-19,99	15 (16.48%)	15 (24.19%)		-	
20-49,99	13 (14.29%)	-		13 (44.83%)	
50-99,99	4 (4.39%)	-		4 (13.79%)	
≥100	10 (10.99%)	-		10 (34.48%)	
Treatment					
Prostatectomy	7	7 (11.29%)		-	0.401
HT	23	10 (16.13%)		13 (44.83%)	
RT	24	18 (29.03%)		6 (20.68)	
HT and RT	15	8 (12.90)		7 (24.14%)	
Active vigilance	1	1 (1.61%)		-	
Missing	21	18 (29.03%)		3 (10.35%)	

¹Early (I and II) versus late (III) stage; Abbreviations: HT= Hormonal therapy; RT= Radiotherapy. Source: Research data.

Patients and controls had a mean age of 69.56 (SD= 8.31) and 68.32 (SD= 7.68) years (p = 0.297). Anthropometric measures weight, height and BMI were not significantly different between cases and controls of the study (Table 2). If asked about their ancestry, 67 (73.60%) PC patients and 41 (45.10%) controls informed African or mixed ancestry (p <0.001; Table

2). Family history of PC was a characteristic of 26 (28.90%) patients and 6 (6.60%) controls (p <0.001; Table 2). Of all PC patients and controls 53 (58.24%) and 22 (24.20%) ever smoked (p <0.001; Table 2). All together 41 (45.60%) PC patients, and 26 (28.60%) controls informed to consume alcohol (p =0.021; Table 2). Of all PC patients 42 (62.70%) worked with

physical effort compared to 31 (34.10%) in the control group ($p < 0.001$; Table 2). Regarding employment, 29 (31.9%) and 8 (8.8%) of all cases and controls worked in agriculture ($p < 0.001$). Among PC patients

and controls 23 (25.27%), respectively, 9 (9.89%) were analphabetic ($p < 0.001$; Table 2). Income and civil state were not significantly different between both groups ($p = 0.587$; $p = 1.00$).

Table 2. Baseline characteristics of PC patients and controls of the study group.

	Case (N= 91)	Control (N= 91)	p value
Mean weight (kg)	74.44(SD=13.15)	76.51(SD=12.82)	0.285
Mean height (cm)	167 (SD= 0.071)	168 (SD= 0.061)	0.504
Mean BMI	26.61 (SD=4.28)	27.20 (SD=4.46)	0.364
	N (%)	N (%)	
Ancestry			
Caucasian	24 (26.40%)	50 (54.90%)	<0.001
African	67 (73.60%)	41 (45.10%)	
Family history			
Yes	26 (28.90%)	6 (6.60%)	<0.001
No	64 (71.10%)	85 (93.40%)	
Missing	1		
Smoking			
Yes	53 (58.24%)	22 (24.20%)	<0.001
No	38 (41.76%)	69 (75.80%)	
Alcohol consumption			
Yes	41 (45.60%)	26 (28.60%)	0.021
No	49 (54.40%)	65 (71.40%)	
Missing	1		
Working with physical effort			
Yes	42 (62.70%)	31 (34.10%)	<0.001
No	25 (37.30%)	60 (65.90%)	
Missing	24		
Education level			
Analphabetic	23 (25.27%)	9 (9.89%)	<0.001
Basic	53 (58.24%)	39 (42.86%)	
Middle	9 (9.89%)	30 (32.97%)	
High	6 (6.59%)	13 (14.28%)	

Source: Research data

Regression analysis of single variables indicated that PC patients had a 3.404 (95%CI: 1.83- 6.35) times increased chance of African ancestry and a 5.755 (95%CI: 2.23-14.80) times increased chance of family history compared to controls (p <0.001; p <0.001; Table 3). Chance of PC patients to work with physical effort, to smoke and consume alcohol was 3.252 (95%CI: 1.68-6.27), 4.374 (95%CI: 2.31-8.25), respectively, 2.092 (95%CI: 1.13-3.87) times increased compared to the controls (p <0.001 p <0.001; p =0.019; Table 3). PC patients had

5.537 (95%CI: 1.6-19.07) times increased chance to be alphabetic compared to controls (p <0.001; Table 3).

To identify independent variables, regression modeling was performed. In the final model PC patients had a 4.150 (95%CI: 2.02-8.51) increased chance of African ancestry and a 6.967 (2.43-19.97) times increased chance of family history (p <0.001; p <0.001; Table 3). If compared to the controls, PC patients had a 3.939 (1.96-7.93) times increased chance of ever smoking (p <0.001; Table 3).

Table 3. Odds ratios (OR) and confidence intervals (95%CI) are shown for single (OR_{CRUDE}), and a model, of adjusted (OR_{ADJUSTED}) variables

		Case (N = 91)	Control (N =91)	OR _{CRUDE} (95% CI)	PLRT	OR _{ADJUSTED} (95% CI) ¹	PLRT
		N (%)	N (%)				
Age categories	<60	13 (14.28%)	9 (9.89%)	1.625 (0.45-5.82)	0.272		
	60-69	31 (34.07%)	43 (47.25%)	0.811 (0.28-2.33)			
	70-79	39 (42.86%)	30 (32.97%)	1.463 (0.50-4.24)			
	≥ 80	8 (8.79%)	9 (9.89%)	Ref.			
Ancestry	African	24 (26.40%)	50 (54.90%)	3.404* (1.83-6.35)	<0.001	4.150* (2.02-8.51)	<0.001
	European	67 (73.60%)	41 (45.10%)	Ref.		Ref.	
Family history	Yes	26 (28.57%)	6 (6.60%)	5.755* (2.23-14.80)	<0.001	6.967* (2.43-19.97)	<0.001
	No	64 (70.33%)	85 (93.40%)	Ref.		Ref.	
Smoking	Yes	53 (58.24%)	22 (24.20%)	4.374* (2.31-8.25)	<0.001	3.939* (1.96-7.93)	<0.001
	No	38 (41.76%)	69 (75.80%)	Ref.		Ref.	
Alcohol consumption	Yes	41 (45.60%)	26 (28.60%)	2.092 (1.13-3.87)	0.019		
	No	49 (54.40%)	65 (71.40%)	Ref.			

Working with physical effort	Yes	42 (46.15%)	31 (34.10%)	3.252* (1.68-6.27)	<0.001
	No	25 (27.47%)	60 (65.90%)	Ref.	
Education Level	Analphabetic	23 (25.27%)	9 (9.89%)	5.537* (1.6-19.07)	<0.001
	Basic	53 (58.24%)	39 (42.86%)	2.944 (1.02-8.43)	
	Middle	9 (9.89%)	30 (32.97%)	0.650 (0.19-2.20)	
	High	6 (6.59%)	13 (14.28%)	Ref.	

¹Variables in the model were adjusted among each other and for age; *p <0.001.

Source: Research data

DISCUSSION

Despite the random selection of the healthy controls in the reference center, some of their socio-economic characteristics were markedly different compared to the patients. Patients had more often a lower education level and worked more often with physical effort compared to controls. Of all PC patients about 32% were employed in agriculture. Data indicated that men with lower socio-economic levels respectively, men working in agriculture, were more vulnerable to disease and this raises the question of underlying causes.

PC patients informed more often African or mixed ancestry, whereas the controls informed more often European ancestry. Data indicated that in the study population risk of PC was positively associated with African ancestry. This finding is in agreement with literature about associations between PC incidence and the ancestry of patients^{11,12}. In the United States African-American men have the highest prostate cancer incidence and mortality rate^{5,22}. Positive association between

increased PC risk and African ancestry is also reflected in data obtained from African men in Europe and Carribeans¹². The positive association between African ancestry and PC risk has a strong genetic component^{11,12}. Interestingly, a recent genome wide association study of a Latin admixed population, identified genetic risk variants that were significantly associated with African ancestry²³. However, the fact that incidence rates of PC in sub-Saharan populations are much less high compared to African-American men, indicates additional life-style related risk factors that may differ among populations of African ancestry²⁴.

In the present study PC patients informed more often family history of PC compared to controls. The association of family history and risk of PC in the present study is in agreement with established knowledge about the disease. In literature family history represents a well-established risk factor of PC^{8,25,26}. In a large Swedish database study men with a father or brother diagnosed with PC, had a two-to threefold increased risk of disease and in the case of

both, the risk was about ninefold higher⁷. In a recent prospective study of 37.000 men, family history of PC was associated with a 68% increased risk of incidence and a 72% increased risk of lethality²⁷.

Smoking was positively associated with increased risk of PC among men of the Brazilian study group. Smoking may have an effect on PC risk by its carcinogenic potential and increasing sex hormone levels among smokers¹². However, few studies indicated a 2- 3 times increased risk of PC among smokers^{13,14}. Studies that associated PC incidence with smoking, neither indicated a dose- response effect, nor did they include data about diet¹². The association between smoking and incidence of PC remains unclear. The positive association between current smoking of PC patients and mortality risk in contrast, is well established^{13,28,29}. Smoking patients doubled the risk from dying of disease^{11,12}. Furthermore, mortality risk was dose respondent during the time interval of 10 years before diagnosis of PC²⁹.

Of all PC patients more than one-third was employed in agriculture. A previous Brazilian database study associated increase PC risk with employment in agriculture and speculated about a possible link between the use of agrototoxic chemicals and disease¹⁹. However, this study did not show a direct association between use of agrototoxic chemicals and PC risk¹⁹. Furthermore, in the study of Silva and colleagues (2015)¹⁹, important risk factors like smoking and dietary habits were not included. High

incidence of PC among men working in agriculture could also be explainable by accumulation of such life style related risk factors.

The present study had several important limitations: In the present study we did not include data about time intervals of smoking and quantity of smoked cigarettes. The low number of patients included in the study and missing data about nutrition was a severe limitation. As nutrition may also have differed among cases and controls, it may have obscured results of the present study sample. Information about ancestry was based on subjective information about participants of a population with an extreme high degree of admixture. Subjective information was a source of uncertainty that may have obscured the possible association between risk of PC and ancestry. The recruitment of controls was stochastic, but the possibility of a selection bias cannot be eliminated.

CONCLUSION

African ancestry, family history and smoking increased the risk of PC among men of Paraíba, Northeast Brazil. Health authorities could recommend preferentially PC screening for men who bear one, or combinations of these risk factors. These disease promoting characteristics were more often identified among men with lower socio-economic levels, working with physical effort in agriculture. Health authorities that promote prevention

programs of PC, should have a stronger focus on these men.

To elucidate the effect of ancestry in more detail, molecular ancestry markers should be included in future studies of this highly admixed population. To detect possible dose-response effects of smoking, data of time intervals of smoking, respectively, quantity of smoked cigarettes should be analyzed. Additionally, future case-control studies should also include detailed information about diet and nutritional factors. In general, larger studies including more patients and controls are needed to identify risk factors of PC among men of this population in more detail.

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