Artigo original

Prostate cancer profiles and associated factors in Criciúma – Santa Catarina, Brazil

Perfil e fatores associados ao câncer de próstata em Criciúma – Santa Catarina, Brasil

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ABSTRACT

Background: Prostate cancer is the second most incident of the male population in Brazil. The aim of this study is to analyze the frequency of risk factors associated to the evolution of the prostate cancer and the impact of conducting examinations in the age range (55-69 years old), in assisting health professionals to manage and prevent the disease. **Methods:** A case-control study was performed on patients from 2011 to 2016 in Criciúma – SC, Brazil. The sample was divided into two groups, one with biopsy for prostate adenocarcinoma (case; n = 124) and the other with a negative biopsy (control; n = 251). The following variables were compared between the two groups: age, family history of prostate cancer, prostate specific antigen, and altered digital rectal examination. **Results:** In the case group, ranging between 55-69 years old, there was a significant higher of altered digital rectal examination ($p < 0.001$, odds ratio 15.5 and positive predictive value 91.3%), prostate-specific antigen ≥ 4 ng/mL ($p < 0.001$, odds ratio 7.02 and positive predictive value 56.2%) and when both exams were altered ($p < 0.001$, odds ratio was 19.63 and the positive predictive value was 90.5%). **Conclusion:** This findings show that, mainly between 55-69 years old, there is a significant correlation between positive biopsy, altered digital rectal examination, and PSA ≥ 4 ng/mL.

Keywords: Prostate-Specific Antigen. Digital Rectal Examination. Risk Factors. Prostatic Neoplasms. Prostate.

RESUMO

Objetivo: O câncer de próstata é o segundo mais incidente na população masculina no Brasil. O objetivo do estudo é analisar a frequência dos fatores de risco associados ao desenvolvimento do câncer de próstata e o impacto da realização de exames na faixa etária de rastreamento (55-69 anos), auxiliando os profissionais de saúde no manejo e prevenção da doença. **Método:** Foi realizado um

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estudo caso-controle no período de 2011 a 2016 em Criciúma – SC, Brasil. A amostra foi dividida em dois grupos, um com biópsia de adenocarcinoma de próstata (casos; n = 124) e outro com biópsia negativa (controles; n = 251). Entre ambos os grupos, foram comparadas as variáveis: idade, história familiar de câncer de próstata, antígeno prostático específico e toque retal alterado. **Resultados:** No grupo dos casos, na faixa etária entre 55-69 anos, ocorreu maior significância de toque retal alterado (p < 0,001; odds ratio 15.5 e valor preditivo positivo 91,3%), antígeno prostático específico ≥ 4 ng/mL (p < 0,001; odds ratio 7.02 e valor preditivo positivo 56,2%) e quando os dois exames estavam alterados (p < 0,001; odds ratio 19.63 e valor preditivo positivo 90,5%). **Conclusão:** Há evidências, principalmente entre 55-69 anos, de maior correlação de biópsia positiva, toque retal alterado e PSA ≥ 4 ng/mL.

Palavras-chave: Antígeno Prostático Específico. Exame Retal Digital. Fatores de Risco. Neoplasias da Próstata. Próstata.

INTRODUCTION

Prostate cancer is the second most incident form of cancer of the male population in Brazil, behind only non-melanoma skin cancer.[1] In 2017, prostate, lung and bronchial and colorectal represented 42% of all cases of cancers in men, and it is responsible for 1 in 5 new diagnoses.[2] It has an annual incidence rate of 233,000 cases in the United States and 382,000 cases in Europe.[3] In Brazil, there were estimated 68,000 new cases in 2018, representing a problem of public health.[1]

The risk factor is something that alters the possibility of an individual acquiring a disease; however, having a risk factor does not necessarily indicate that the disease will actually evolve. While some patients have more than one risk factor and do not develop the disease, others may have few or none of the known factors and develop the disease.[4]

The risk factors for prostate cancer are not totally known, but three are well-established: advanced age, ethnicity, and heredity, that this, unmodifiable risk factors.[5] It is an age-related neoplasm in which 75% of cases occur in men over 65 years. The studies show a direct association between the increased risk of prostate cancer and family members with the same disease.[6] Prostate adenocarcinoma is one of the most hereditary neoplasms with a hereditary factor, with an estimated 42% of the risk attributed to genetic factors.[7] The influence of modifiable factors (smoking, alcoholism, diet, obesity, vasectomy, and previous history of sexually transmitted disease) is uncertain.[8] Knowledge about the factors related to the development of prostate cancer is fundamental, since, in addition to helping in better clinical management, it is also a means for the elaboration of preventive measures in relation to the onset and development of the disease.

The prostate cancer mortality rate decreased by about 50% due to improvements in detection and early treatment.[2] However, screening through prostate-specific antigen (PSA) has also attributed to excessive diagnosis and treatment, and the need to perform the test was widely debated.[7] In some men, the disease would never become symptomatic during life and treatment would not provide benefits, called *overdiagnosis*,[9] explaining in autopsy studies the high prevalence of undetected prostate cancer.[10]

The particular contribution of the current study is to analyze the frequency of risk factors (age and family history) associated with prostate cancer development and the impact of PSA and digital rectal examination (DRE) in the age group of screening (55-69 years old), assisting health professionals in the management and prevention of the disease.

METHODS

It was a case-control study in which patients' charts of prostate biopsies were analyzed, and they were attended in private clinics of Criciúma (SC) between 2011 to 2016. The sample consisted of 375 patients' charts that were divided into two groups, one group with positive biopsy for adenocarcinoma of the prostate (case: n = 124) and the other with negative biopsy (control; n = 251). Between the two groups, the following variables were compared: age, family history (FH) of prostate cancer, PSA, and altered DRE.

The inclusion criteria were: patients who underwent prostate biopsy, family history of prostate cancer, altered DRE, and PSA. The exclusion criteria were: incomplete medical records, other histological types of prostate cancer other than adenocarcinoma. Controls were selected among those who performed the biopsy but found a negative result for malignancy.

The study was approved by the Ethics and Research Committee of Universidade do Extremo Sul Catarinense (UNESC) under the number 1.870.176/2016 and CAAE 62768416.9.0000.0119, and it was initiated after the signing of the Confidentiality Agreement and approval of the study by the aforementioned committee.

The data collected was analyzed using the IBM Statistical Package for Social Sciences (SPSS) software version 22.0. Qualitative variables were expressed by means of frequency and percentage.

The statistical tests were performed with a significance level α = 0.05 and, thus, with a confidence interval (CI) of 95%.

The investigation of the existence of an association between the qualitative variables was performed through the Chi-square test and the Fisher's exact test, followed by residue analysis when statistical significance was observed.

After the univariate and bivariate analysis, a logistic regression analysis was performed using the odds ratio (OR) as a measure of the strength of association between the variables.

RESULTS

This study analyzed only the medical records of patients who underwent prostate biopsy, selecting the sample from the inclusion and exclusion criteria, already mentioned, totaling 375 medical records. The groups (positive biopsy, n = 124) and control (negative biopsy, n = 251) were divided into patients younger than 54 years old, aged 55-69 and older than 70 years old, resulting in 14 patients with adenocarcinoma of the prostate: 14 (11.3%), 79 (63.7%), and 31 (25%) cases, respectively. (Table 1).

Table 1

General characteristics of the samples searched

	Prostate Cancer				Confidence interval 95%	
	Yes	No	p value	odds ratio	Lower	Upper
	n = 124	n = 251				
Age (years)						
≤ 54	14 (11.3)	25 (9.0)				
55-69	79 (63.7)	126 (50.1)				
≥ 70	31 (25.0)	100 (39.9)	0.017	2.02	1.24	3.31
Family History						
Yes	15 (12.1)	13 (5.2)	0.017	2.52	1.16	5.48
No	109 (87.9)	238 (94.8)				
Altered digital rectal examination						
Yes	32 (25.8)	12 (4.8)	<0.001	2.82	1.93	4.13
No	92 (74.2)	23 (95.2)				

Fonte: Ives YK, et al. Prostate cancer profiles and associated factors in Criciúma – Santa Catarina, Brazil; 2019.

When comparing the family history, there were found 15 (12.1%) patients in the case group concerning the other with negative biopsy, being statistically significant (p = 0.017; OR 2.52; 95% CI 1.16-5.48).

In the group with prostate cancer, the presence of altered DRE (nodularity, induration, and asymmetry) totaled 32 (25.8%) cases and represented statistical significance (p < 0.001). It can be noticed that the presence of family history (p = 0.017)

and altered DRE ($p < 0.001$) were initially significant for the presence of prostate cancer. However, by including both factors in a logistic regression equation, only altered DRE remained significant ($p < 0.001$; OR 2.82; IC 95% 1.93-4.13).

The case and control groups were divided into PSA < 4 and ≥ 4 ng/mL and multivariate analysis was performed at ages between 55-69 and > 70 years old and altered DRE was used to determine whether there was a relationship between the factors jointly and not only in a way independent. In patients aged 55-69 years old, it was found OR 7.02 if PSA ≥ 4 ng/mL with $p < 0.001$ (95% CI 3.29-14.98), OR 15.5 if altered DRE with $p < 0.001$ (95% CI 3.33-72.57) and, if both factors are present, there is OR 19.63 of positive biopsy with $p < 0.001$ (95% CI 4.43-87.05). In the group > 70 years old, both PSA ≥ 4 ng/mL and altered DRE were not significant ($p = 0.063$ and 0.095, respectively) and also associated ($p = 0.053$).

DISCUSSION

The National Cancer Institute stipulates age as the leading risk factor for prostate cancer, as approximately 75% of cases occur after the age of 65.[6] Age is widely discussed in the literature as a parameter for screening and risks and benefits. Based on clinical trials, the American Urological Association (AUA) and the Canadian Task Force on Preventive Health Care consider that patients aged 55-69 years old are candidates for screening and are not recommended for those over 70.[11] Our study demonstrated that the highest percentage of positive biopsies were in the indication range of screening (63.7%) with OR 2.02 (95% CI 1.24-3.31) and, in the not recommended range, the results of the DRE and PSA ≥ 4 ng/mL were not statistically significant ($p = 0.063$ and $p = 0.095$, respectively). The United States Preventive Services Task Force (USPSTF) states that screening between 55-69 years old should be individualized based on professional judgment and patient decisions, assessing the consequences and benefits, since for every 1,000 men selected there would be prevention of 1-2 deaths from prostate cancer and 3 cases of prostate cancer, but 1 in 5 cases develop incontinence and 2 in 3 erectile dysfunction after radical prostatectomy and more than half acquire sexual impotence after chemotherapy, exposing that net benefit caused by the tracing is small (level of evidence C).[12] In some men, the disease would never become symptomatic during life and treatment would not provide them with benefits, being called *overdiagnosis*. Mainly in > 70 years old, this phenomenon occurs in 20-50% of those diagnosed by screening.[11] In the present study, > 70 years old, 23.7% of positive biopsies occurred. The Ministry of Health also does not indicate the population screening, due to lack of evidence that treatment in the early stages has an effectiveness that exceeds the risks of adverse effects, and should also be individualized cases.[13]

Current literature considers family history as one of the few established risk factors for prostate cancer and is used as a parameter for disease screening.[5] In a randomized study that evaluated 10,311 men aged 55-70 years old, it was shown a greater risk OR = 1.61 (95% CI 1.20-2.16) compared to the non-FH group.[3] Likewise, in another study with 23,702 patients, the presence of FH represented a higher risk of adenocarcinoma relative risk (RR) 1.31 ($p < 0.001$).[14] The results of our study showed that 12.1% of the cases were associated with a higher number of patients with adenocarcinoma ($p = 0.017$) with OR = 2.52 (95% CI 1.16 - 5.48) compared to the control group, but it lost significance after being included in a logistic regression analysis, since patients with FH sought medical care due to the variable itself, causing a confounding event in the sample. Although family history is a method used to determine the risk of developing the disease,[15] it is present in <10% of men.[16] In this respect, it is worth noting the reason for the variable being incorporated in risk calculators currently available.[5] Besides, the American Cancer Society (ACS), the AUA, and the National Comprehensive Network (NCCN) recommend early and selective screening in men with a positive family history of prostate cancer.[17]

The most common tests used for the diagnosis of prostate cancer are: DRE, PSA, and biopsy guided by transrectal ultrasonography.[18] PSA is a protein secreted by acinar cells of the prostate. PSA serum levels in clinical use since 1986 are the tumor

marker, although the usefulness of screening for prostate cancer is controversial and widely debated in the literature, is useful for diagnosis.[19] According to the NCCN, there is no PSA level below which the risk of prostate cancer can be excluded. The disease is generally suspected on altered DRE examination, whether or not accompanied by elevated PSA level. The definitive diagnosis depends on the histopathological result.[20] In a cohort study with 4,932 men, it was found that patients between the ages of 57-61 in a multivariate analysis, PSA ≥ 3 ng/dL (HR 1.13 and 95% CI 1.12-1.14) and FH positive (HR 1.6 and 95% CI 1.24-2.14) were independent predictors for prostate cancer (all with $p < 0.001$).[3] In our study, patients between 55-69 years old, in a multivariate analysis, either independently, PSA ≥ 4 ng/dL (OR 8.51 and 95% CI 4.11-17.64) and FH positive (OR 2.75 and 95% CI 1.02-7.43), as associated, were significant ($p = 0.0001$ and $p = 0.034$, respectively). We did not find in the literature a study that also analyzed, in the range of age for tracing, both factors.

DRE can detect palpable abnormalities (nodules, asymmetry, and induration) in the posterior and lateral regions of the prostate gland where most cancers arise, but in other areas that may also be affected by the disease, are not reachable by the exam.[21] In a study of 6,630 patients aged 50-96 years old, PSA ≥ 4 ng/dL (OR = 8.36, 95% CI 5.38-12.98, and $p = 0.0001$) showed a positive predictive value (PPV) of 32% and altered DRE (OR = 2.82, IC 95% 1.93-4.13 and $p = 0.0001$) PPV of 21%. When both exams were altered, the PPV was 49%.[22] In the present study, PSA ≥ 4 ng/dL (OR = 7.02, 95% CI 3.29-14.98 and < 0.0001) presented a PPV of 56.2%, the altered DRE (OR = 15.5, CI 95% 3.33-72.57 and $p < 0.0001$) 91.3% and, when associated (OR = 19.63, 95% CI 4.43-87.05 and < 0.0001), 90.5%. In > 70 years old, the PPV was respectively 30.3%, 46.2%, and 50%. In a study of 1,472 patients, it was demonstrated that no PSA level was associated with a 100% PPV and a negative biopsy could occur at almost any level of PSA.[23]

CONCLUSION

There is evidence that the age group between 55-69 years old shows a higher correlation with positive biopsy, altered DRE, and PSA ≥ 4 ng/mL, corroborating with literature the importance of evaluation in this profile of patients. In the population above the age of 70, it is necessary to consider the cost-benefit of the treatment of the disease, since, in addition to the effects that the treatment can trigger, many will be asymptomatic.

REFERENCES

1. Instituto Nacional de Câncer. Estimativa 2018: Incidência de Câncer no Brasil. Rio Janeiro: INCA, 2017. Available from: http://www1.inca.gov.br/estimativa/2018/estimativa-2018.pdf. Accessed in 2018 (June 08).
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67:7–30. doi: 10.3322/caac.21387
3. Randazzo M, Müller A, Carlsson S, Eberli D, Huber A, Grobholz, et al. A positive family history as a risk factor for prostate cancer in a population-based study with organised prostate-specific antigen screening: results of the Swiss European Randomised Study of Screening for Prostate Cancer (ERSPC, Aarau). BJU Int. 2016;117:576–583. doi: 10.1111/bju.13310
4. American Cancer Society. Prostate Cancer Prevention and Early Detection. 2016. Available from: www.cancer.org/acs/groups/cid/documents/webcontent/003182-pdf.pdf. Accessed in: 2016 (nov).
5. European Association of Urology. Guidelines on Prostate Cancer. 2016. Available from: https://uroweb.org/guideline/prostate-cancer/>. Accessed in 2018 (May 23).
6. Instituto Nacional De Câncer. Monitoramento das ações de controle do câncer de próstata. São Paulo: INCA, 2014. Available from: http://www1.inca.gov.br/inca/Arquivos/informativo-deteccao-precoce-numero2-2017.pdf. Accessed in 2018 (May 23).
7. Rudichuk L, Vogel KJ, Wang C, Helfand BT, Selkirk CG. Urologists' current practices in screening and treating men with a family history of prostate cancer. Urology. 2017;99:180-185. doi: 10.1016/j.urology.2016.07.032; PMID: 27645528.
8. Sawada N. Risk and preventive factors for prostate cancer in Japan: The Japan Public Health Center-based prospective (JPHC) study. J. Epidemiol. 2017;27(1):2-7. Doi: 10.1016/j.je.2016.09.001; PMID: 28135193.
9. Fenton JJ, Weyrich MS, Durbin S, et al. Prostate-Specific Antigen–Based Screening for Prostate Cancer: Evidence Report and Systematic Review for the U.S. Preventive Services Task Force. JAMA. 2018;319(18):1914-31. doi:10.1001/jama.2018.3712
10. Jahn JL, Giovannucci EL, Stampfer MJ. The high prevalence of undiagnosed prostate cancer at autopsy: implications for epidemiology and treatment of prostate cancer in the Prostate-Specific Antigen-Era. Int J Cancer. 2015;137(12):2795-802. doi:10.1002/ijc.29408

11. Bell N, Connor GS, Shane A et al. Canadian Task Force on Preventive Health Care. Recommendations on screening for prostate cancer with the prostate-specific antigen test. CMAJ. 2014;186(16):1225-34. doi:10.1503/cmaj.140703

12. Draft Recommendation Statement: Prostate Cancer: Screening. U.S. Preventive Services Task Force. April 2017. Available from: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/prostate-cancer-screening1. Accessed in 2018 (May 23).

13. Ministério da Saúde. Comissão Nacional de Incorporação de Tecnologias no SUS. Diretrizes Diagnósticas e Terapêuticas do Adenocarcinoma de Próstata. Relatório de Recomendação. Brasília, 2015. Available from: conitec.gov.br/images/Consultas/Relatorios/2015/DDT_Adenocarcinomadeprostata_CP.pdf. Accessed in 2018 (May 23).

14. Saarimäki L, Tammela TL, Määttänen L, et al. Family history in the Finnish Prostate Cancer Screening Trial. Int. J. Cancer, 2015;136(9):2172–7. Doi:10.1002/ijc.29243; PMID: 25274038.

15. Helfand BT, Kearns J, Conran C, Xu J. Clinical validity and utility of genetic risk scores in prostate cancer. Asian J of Androl. 2016;18(4):509-514. Doi:10.4103/1008-682X.182981; PMID: 27297129.

16. Goh CL, Schumacher FR, Easton D,et al. Genetic variants associated with predisposition to prostate cancer and potential clinical implications. J Intern Med. 2012(271):353–65. doi:10.1111/j.1365-2796.2012.02511.x

17. Brawley OW, Gansler T. Introducing the 2010 American Cancer Society prostate cancer screening guideline. CA Cancer J Clin. 2010;60:68–9. Doi:10.3322/caac.20067; PMID: 20200111.

18. Lopes PM, Sepúlveda L, Ramos R, Sousa P. The role of transrectal ultrasound in the diagnosis of prostate cancer: new contributions. Radiol Bras. 2015;48(1):7-11. DOI: 10.1590/0100-3984.2013.0010; PMID: 25798001.

19. Pentyala S, Whyard T, Pentyala S et al. Prostate cancer markers: An update. Biomed Rep. 2016;4(3): 263–268. doi: 10.3892/br.2016.586

20. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. Version I, 2016. Available from: http://www.jnccn.org/content/suppl/2016/01/04/14.1.19.DC1/0019.pdf. Accessed in 2018 (May 23).

21. Parker C, Gillessen S, Heidenreich A, Horwich A; ESMO Guidelines Committee. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(5),69-77. doi: 10.1093/annonc/mdv222; PMID: 26205393.

22. Catalona WJ, Richie JP, Ahmann FR, et al. Comparison of Digital Rectal Examination and Serum Prostate Specific Antigen in the Early Detection of Prostate Cancer: Results of a Multicenter Clinical Trial of 6,630 Men. J Urol, 2017;197:2S, S200-S207. doi: 10.1016/j.juro.2016.10.073; PMID: 28012755.

23. Janbaziroudsari H, Mirzaei A,Maleki N. Association of serum prostate-specific antigen levels with the results of the prostate needle biopsy. Bull Cancer. 2016;103(9):730-4. doi: 10.1016/j.bulcan.2016.05.006; PMID: 27345449.