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Original article

PROSTATE CANCER AND BENIGN PROSTATE CHANGE – ARE THERE DIFFERENCES IN DEMOGRAPHIC AND BEHAVIOR CHARACTERISTICS?

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Abstract

Prostate cancer (CaP) is one of the major causes of cancer-related mortality worldwide. The incidence rate increases up to 1 in every 52 men aged 50 - 59 years. The variability in distribution is due to the demographic, behavior, and genetic differences, as well as the lifestyle and the health system quality. The aim of this study was to present and compare the demographic and behavior characteristics of patients with malignant and benign prostate change.

This was a prospective clinical study, conducted during 2018-2020, at the University Clinic for Urology, Clinical Centre "Mother Teresa", Skopje, Republic of North Macedonia. The study analyzed 90 patients with prostate cancer (CaP), and 106 patients with benign prostate change (BeP). The average age of patients from CaP/ BeP group was 69.2 ± 6.9 *vs*. 68.4 ± 6.3 years (p = 0.3696). No significant difference was found in patients from both groups related to BMI (p=0.3009), nutritional status (p=0.4634), smoking status (p=0.4831), clinical symptoms (p=0.6951). Patients in CaP group had 2.83 times more history of father with prostate cancer, for OR = 2.83 [95% CI (1.03-7.83)], and 12.11 times significantly more close family members with other malignancies than those in the BeP group, for OR=12.11 [95% CI (2.71-54.02)]. We need more extensive research in this field, having in mind the multiethnic aspect which will help us in more effective prevention and early diagnosis of prostate cancer in our country.

Keywords: prostate cancer, benign prostate change, demographic characteristics, behavior characteristics, family history

Introduction

The incidence of prostate cancer (CaP) is continually increasing due to the life span prolongation and the new diagnostic procedures, such as PSA test (prostate-specific antigen test), transrectal ultrasonography and magnetic resonance. Although only 1 in 350 men under the age of 50 years will be diagnosed with prostate cancer, the incidence rate increases up to 1 in every 52 men aged 50 - 59 years. The incidence rate is nearly 60% in men over the age of 65 years[1-8]. Prostate carcinoma incidence is highest in the USA, Canada and the Scandinavian countries, and it is lowest in China and other Asian countries. The variability in distribution of this disease in

the world is due to genetic differences, lifestyle, quality of the health system or a combination of all these factors.

Only about half of the patients diagnosed with CaP will develop significant symptoms, and <20% will die. The diagnosis of early-stage CaP is imperative for its successful management, since the inevitable emergence of androgen insensitivity in late-stage tumors leads to a significant mortality[6,7].

Possible causes of CaP are unclear although increasing age, race and previous family history of the disease are known as risk factors[5,6]. Various perceptions of CaP have been documented in the literature and this may influence screening and treatment of CaP in both developed and developing countries, besides the disparities in the availability of diagnostic CaP tests.

Considering the public health significance of CaP, public health programmes should go beyond awareness creation to organise educational campaigns for all socio-demographic groups. These programmes should provide clarity on the health benefits of early screening, health-seeking choices and healthy lifestyles to prevent prostate cancer.

PSA as the most widely used tumor marker for detection of CaP, alone or combined with its derivates, can be used as a screening tool for diagnosis before clinical development of the disease and its recurrences. It can often lead to overtreatment due to overdiagnosis of CaP, and its baseline values do not allow prediction of disease behavior and prognosis[3].

The aim of this study was to present and compare the demographic and behavior characteristics of patients with malignant and benign prostate change.

Material and methods

This was a prospective clinical study which was implemented during the period of two years, 2018-2020, at the University Clinic for Urology, Clinical Centre "Mother Teresa", Skopje, Republic of North Macedonia.

The examined group included patients with prostatic cancer (CaP), whereas the control group included patients with benign prostate change (BeP). The inclusion criteria involved men aged ≥40 and ≤85 years, PSA>4ng/ml and/or positive rectal toucher (suspect digito-rectal examination). Patients with other types of malignant diseases, severe general and locoregional disease, incurable condition, dementia, rational judgment disorder, more serious cardiovascular diseases and coagulopathy were excluded from this study. Participation in the study was voluntary. The implementation of this study was approved by the Ethics Committee of the Medical Faculty at Ss. Cyril and Methodius University in Skopje.

The analysis of patients from CaP/ BeP groups included: age, BMI, nutritional status, alcohol consumption, smoking status, clinical symptoms and family history of prostate cancer and / or other malignant disease.

In the study, we defined as smokers those persons who had a history of smoking for more than 20 cigarettes per day, i.e., smoking for over 20 years. Positive status for alcohol consumption was defined as alcohol use more than three times a week. According to the international reference values for nutritional status, patients were divided into four groups: a) underweight (<18.5 kg /m²); b) normal weight (18.5–24.9 kg/m²); c) overweight (25-29.9 kg/m²); and d) obese (≥30 kg/m²).

Statistical analysis

The data obtained in the study were analyzed with the SPSS software package, version 22.0 for Windows. Qualitative and quantitative series were analyzed with measures of central tendency (mean, median, range), as well as by dispersion measures (standard deviation). The Shapiro-Wilk W test was used to determine the normality of frequency distribution of age, and BMI. Association between qualitative variables (nutritional status, family history, alcohol consumption, smoking, and clinical symptoms) were checked using the Pearson Chi square test and Fisher exact test. Mann Whitney U test was used to compare differences between two independent groups when the parameters were either ordinal or continuous. The independent-samples t-test was used to compare the means between two CaP/ BeP groups. Difference test was used to compare the proportions. A two-sided analysis with a significance level of $p<0.05$ was used to determine the statistical significance.

Results

The study analyzed 90 patients with prostate cancer (CaP), and 106 patients with benign prostate change (BeP). The average age of patients in CaP/ BeP groups was 69.2 ± 6.9 years with min / max of 50/ 85 years *vs.* 68.4 ± 6.3 years with min / max of 55/ 82 years, respectively. Fifty percent of patients in CaP/ BeP groups were under the age of 70 *vs*. 68 years, respectively, with no significant difference between the two groups related to age (T-test $_{(194)} = 0.8993$; $p = 0.3696$).

Majority of patients from both groups were with completed secondary school education, 53(63.86%) in CaP, and 69(66.35%) in BeP. The smallest proportion of patients from both groups were with high education, 11(13.25%) from CaP and 20(19.23%) from BeP. No significant difference was found related to the level of education between patients from both groups (X^2=2,8596; df=2; p=0,2393).

The average level of BMI in patients from CaP group was 27.3 ± 3.9 kg/m² with min/ max of 18.8/39.2 kg/m² and 50% of them with BMI <27.0 for Median IQR = 27(24.5-29.3) years). In BeP group, the average BMI was 26.7 ± 3.6 kg/m² with min/ max 19. 1/37.2 kg/m² and 50% with BMI <26.6 kg/m². No significant difference was found between patients from both groups related to BMI (Z=1.0344; p=0.3009).

Table 1. Comparison of selective parameters by groups

Parameters	Study groups		p
	CaP (N=86)	BeP (N=102)	
Nutritional status			
underweight	-	-	
normal weight	25 (29.07%)	38 (37.25%)	X^2=1.5383; df=2; p=0.4634
overweight	43 (50%)	47 (46.08%)	
obese	18 (20.93%)	17 (16.67%)	
Smoking			
No	66 (75%)	74 (70.48%)	X^2=0.4918; df=1; p=0.4831
Yes	22 (25%)	32 (29.52%)	
Alcohol consumption			
No	47 (53.41	75 (70.75%)	X^2=6.1984; df=1; p=0.0128*
Yes	41 (46..59%)	31 (29.25%)	
Clinical symptoms			
No	19 (21.11%)	20 (18.87%)	X^2=0.1537; df=1; p=0.6951
Yes	71 (78.89%)	86 (81.13%)	

X^2 = Pearson Chi-square test; *Significant for $p<0.05$

The largest number of patients from both groups were overweight, presented with 43 (50%) patients in CaP group and 47 (46.08%) in BeP group. Obese were 18(20.9%) patients from CaP group and 17(16.7%) from BeP group. None of the patients in both groups was underweight. No significant association was found between nutritional status and the group to which respondents belonged (p=0.4634) (Table 1).

There were 22 (25%) smokers in CaP group of patients, and 32 (29.52%) in BeP group. No significant association was found between smoking status and the group to which the patients belonged (p=0.4831) (Table 1).

For the purposes of the study, we defined a positive status of alcohol consumption if respondents drank alcohol more than three times a week. Forty-one patients (46.6%) in CaP group were alcohol consumers while in BeP group 31 (29.5%). Patients from CaP group consumed alcohol 2.11 times more than those from BeP group for OR = 2.11 [95% CI (1.17-3.81)].

There was no significant association of presence/absence of clinical symptoms and the group (CaP/ BeP) to which patients belonged (p=0.6951) (Table 1).

In CaP group, with a positive family history of prostate cancer were bordering non-significant proportion of 19 (22.62%) patients, compared to 12 (12.12%) patients from BeP group (p=0.0592) (Table 2).

Table 2. Analysis of family history for malignant diseases by groups

Family history	Study groups		p
	CaP	BeP	
Ca prostate - family history			
No	65 (77.38%)	87 (87.88%)	
Yes	19 (22.62%)	12 (12.12%)	X^2=3.5592; df=1; p=0.0592
Total	84 (45.90%)	99 (54.10%)	
Ca prostate - father			
No	71 (84.52%)	93 (93.94%)	X^2=4.329; df=1; p=0.0374*
Yes	13 (15.48%)	6 (6.06%)	
Ca prostate - brother			
No	78 (92.86%)	93 (93.94%)	X^2=0.087; df=1; p=0.7682
Yes	6 (7.14%)	6 (6.06%)	
Other Ca in the close family			
No	73 (81.11%)	104 (98.11%)	
Yes	17 (18.89%)	2 (1.89%)	[1]p=0.00006*
Total	90 (45.92%)	106 (54.08%)	
Other Ca - sister/ brother			
No	86 (95.56%)	105 (99.06%)	
Yes	4 (4.44%)	1 (0.94%)	[1]p=0.1213
Total	90 (45.92%)	106 (54.08%)	
Other Ca - parents			
No	79 (87.78%)	105 (99.06%)	
Yes	11 (12.22%)	1 (0.94%)	[1]p=0.0010*
Total	90 (45.92%)	106 (54.08%)	

X^2 = Pearson Chi-square test; [1]Fisher exact test; *Significant for p<0.05

We found that 13 (15.48%) of respondents in CaP group and 6 (6.06%) in BeP group had a history of prostate cancer in their father (Table 2). Patients in CaP group had 2.83 times more often a history of prostate cancer in their father than those in BeP group for OR = 2.83 [95% CI (1.03-7.83)]. Six (7.14%) of patients in CaP group had a brother with prostate cancer and 6

(6.06%) in BeP group (p=0.1213). None of respondents had the presence of prostate cancer history in both father and brother (Table 2). In CaP group alone, the percentage of cases with a history of prostate cancer in their father was significantly higher compared to a history of prostate cancer in their brother (Difference test: Difference 36.84% [(5.15-59.77) CI 95%]; p=0.0250). The same analysis applied in BeP group did not indicate a significant difference in the percentage of father / brother affected by prostate cancer (p = 1.000).

A history of other malignant diseases in the close family was significantly more present among patients in CaP group -17(18.89%%) than in BaP group - 2(1.89%) (p=0.00006). Patients with prostate cancer (CaP) had 12,11 times significantly more close family members with other malignancies than those in BeP group for OR=12.11 [95% CI (2.71-54.02)].

Four (4.44%) patients in CaP group had a brother /sister with a history of other malignant disease *versus* 1(0.94%) in BaP group (p=0.1213). Parents with history of malignant diseases were significantly more present in CaP group - 11(12.22%) than in BaP group - 1(0.94) (p=0.0010). In CaP group, the percentage of history of cancer in one of the parents was significantly higher compared to that in the sibling (Difference 51.18% [(17, 59-71.43) CI 95%]; p=0.003), i.e., in the grandparents (Difference 62.95% [(30.18-79.88) CI 95%]; p=0.0003). The same analysis applied in BeP group did not indicate a significant difference in the percentage of prostate cancer in parents or siblings. There was no case of other malignant disease in grandparents in BeP group.

The average number of persons with malignant diseases in the wider family in the group with CaP compared to BeP was 1.2 ± 0. 6 with min / max of 1/3 and Median IQR 1(1-3) *vs.* 1.0 ± 0.0 with min/max 1/1 and Median IQR 1(1-1), respectively. There was no significant difference between patients in CaP / BeP group related to the number of members with other malignancies in the extended family (Z=3.3985; p=0.6902).

Regarding cancers present in the wider family, in the CaP group we saw the presence of 11 types, of which generally each occurred once - 1 (5.6%), with the exception of breast cancer in 4 cases and gastric and lung cancer registered in two cases - 2 (11.1%). Only two patients in BeP group had a positive family history of another malignant disease. In one case, it was uterine cancer, and in the other, it was bladder cancer (Figure 1).

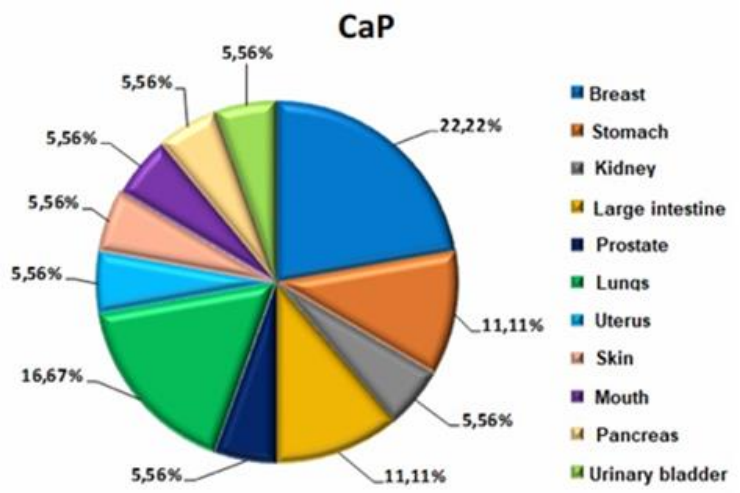

Fig. 1. Distribution of other carcinomas present in the wider family in the CaP group

Discussion

Prostate cancer (CaP) is one of the most prevalent diseases diagnosed in the Americas and Western countries, and it is also one of the major causes of cancer-related mortality worldwide. The prevalence is particularly high in developed societies and those characterized by so-called westernization of daily life[9,10].

The chance of developing CaP increases with age. The prevalence of latent prostate cancer cases increases with age and reaches about 40% in people over the age of 80[11-13]. In our study, fifty percentage of people in CaP or BeP group were under the age of 70 or 68, respectively. For $p > 0.05$, we did not find a statistically significant difference between the two groups (CaP / BeP) in terms of patient age.

Screening and early detection of prostate cancer is associated with the level of patients' education[14]. The lower the education of patients, the greater the chance that prostate cancer will be present at a more advanced stage. Regarding the level of education in both groups, the most numerous were respondents with secondary education, followed by primary and higher / higher in the group with CaP and in the group with BeP; second in representation were those with higher / higher and primary education. No statistically significant association was found between the level of education and the group to which the respondents belonged, but we found that in CaP group there were insignificantly more people with lower education compared to BeP group.

The largest prospective study, which included 950,000 men and 33,314 cases of prostate cancer from Norway, reported a 9% higher risk of prostate cancer in obese men with a higher risk in those who were obese up to 45 years of age[15]. In a recent meta-analysis that included data from 31 prospective studies and 25 case-control studies, the overall risk of being diagnosed with prostate cancer associated with normal BMI in adults was 5% higher with each 5-unit BMI increase. Together, these data suggest that higher levels of BMI in adults lead to a modest positive increase in the overall risk of prostate cancer and advanced disease[16].

In our research an analysis was made according to the body mass index (BMI), and additionally according to the international reference values and the corresponding cut-off values for BMI. Respondents were divided into four groups according to the degree of nutrition and in both groups the most numerous were the malnourished respondents followed by the normally malnourished and obese, and in both groups, there were no respondents in the classification malnourished. The analysis, for $p > 0.05$, did not indicate a statistically significant association between BMI and the degree of nutrition and the group to which the subjects belonged (prostate cancer / benign changes).

Smoking can affect carcinogenesis indirectly by affecting the circulating hormones in the body and directly by exposing carcinogens to cigarettes. In a study of 753 respondents aged 40-64, Plaskon LA. *et al.* noted a modestly positive association between smoking and the incidence of prostate cancer, and smoking cessation reduces the risk of disease, especially if it is longer than 10 years[17].

Regarding the smoking status obtained by a personal statement within the anamnesis, for $p > 0.05$, we did not find a statistically significant association between smoking and the two groups (CaP / BeP) to which respondents belonged.

A prospective study conducted at the Harvard University followed 7612 Harvard alumni (mean age 66.6 years) from 1988 through 1993, during which 366 cases of incident prostate cancer occurred. Self-reported alcohol consumption was assessed at baseline from wine, beer, and liquor intake. A positive correlation was found between alcohol consumption and the

incidence of prostate cancer, and men who drank alcohol during the 11-year period had almost twice the risk of prostate cancer compared to men who did not[18].

In our study we also found a statistically significant association between alcohol consumption and the group to which respondents belonged ($p = 0.0128$). CaP group drinkers consumed 2.11 times more alcohol than those with benign prostatic hyperplasia.

The first reports of a family genetic cluster were published in the mid-20th century and suggest that the risk of developing prostate cancer is higher in those who have a first-degree relative with the disease. Subsequent control cases and cohort studies have confirmed this observation[19]. Twin studies also suggest a genetic component, with higher correlation rates for monozygotic than dizygotic twins. The results of a meta-analysis by Zegers *et al.* demonstrate that the relative risk increases depending on the number of affected family members, their degree of kinship, and the age of onset of the disease[13,20].

Our analysis indicated that in CaP group, 22.62% were with a positive family history of prostate cancer and in BeP group this proportion was 12.12%. For $p>0.05$, we did not find a statistically significant association between a family history of prostate cancer and the group to which subjects belonged, but we found that the proportion of subjects with a positive family history of prostate cancer was slightly higher in CaP group. Our individual analysis only in CaP group showed that the percentage of a father with a prostate cancer by was significantly higher than in a brother ($p<0.05$).

Grönberg *et al.* also found that men with at least two close relatives with prostate cancer had a very high risk of developing prostate cancer before the age of 70. Men who have not been diagnosed with cancer and are in families with two or more cases of prostate cancer have a very high risk of developing prostate cancer at a young age[21]. Cumulative risks in these families are 5%, 15% and 30% according to age 60 years, 70 years and 80 years, respectively, compared to only 0.45%, 3% and 10%, respectively, of the same age in the general population[21].

We established a significant association between the presence of other malignant diseases in the family and the group to which the respondents belonged. Respondents with prostate cancer (CaP) had 12,109 times significantly more family members with other malignancies compared to those in BeP group. There is a higher incidence of prostate cancer in relatives of breast cancer patients. Anderson *et al*. and Sellers *et al.* reported twice the risk of familial breast cancer when prostate cancer was present in the family history[22, 23]. In our study, the analysis in CaP group showed that the percentage of cancer in one of the parents was significantly higher compared to that in the sibling. Carter *et al.* and Isaacs *et al*. have shown a significant association of prostate cancer with brain tumors[24-26].

Conclusion

Due to the high percentage of this malignancy in the analyzed age range, this problem seems to impact the quality of life in the remaining years of life and must be regarded a possible health concern. We found a significant association between the presence of other malignant diseases in the family of patients in the group with CaP. Additionally, we found a higher incidence of CaP in alcohol consumers, but we did not find BMI and smoking to be strongly associated with CaP. However, it is necessary to promote recommendations for lifestyle modifications related to the risk of prostate cancer. Taking into account the fact that the study group was homogeneous with reference to nationality, there is a need for more extensive research in this field, having in mind the multiethnic aspect that will help us in more effective prevention and early diagnosis of prostate cancer in our country.

Conflict of interest statement. None declared.

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