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ROLE OF HEREDITY IN PATIENTS WITH PROSTATE CANCER

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Summary

We distinguish three epidemiological forms of prostate cancer (PCa): 1) sporadic – occurring randomly in the population; 2) familial – unpredictable and weak clustering of PCa in families; and 3) hereditary – strong clustering and early onset of PCa. It was estimated that approximately 10-20% of patients with PCa have a positive family history. Twenty-eight (3.3%) of 827 patients with histopathologically confirmed PCa in our study had a positive family history with one of the first degree relative (father, son or brother) affected by the disease. Median age of the patients with familial PCa was 67.5 years and it was significantly lower than in sporadic cases (median 72.0 years) (p=0.018). We assessed no significant difference between the groups in the pretreatment prostatic specific antigen (PSA) level, Gleason score distribution, median time to progression and overall mortality. Patients with positive family history on PCa had a significantly higher tumor stage at presentation (p<0.01), higher frequency of tumor progression (p=0.013) and higher tumor-specific mortality (p=0.027) during the follow-up.

In conclusion, because of earlier onset and possible more aggressive nature of the familial PCa, positive familial history must be taken into consideration when to start PSA screening and when to indicate prostate biopsy in men with slightly elevated PSA.

KEYWORDS: *prostate cancer, familial prostate cancer, hereditary prostate cancer*

ULOGA NASLIJEĐA U BOLESNIKA S RAKOM PROSTATE

Sažetak

U epidemiološkom pogledu kod karcinoma prostate razlikujemo tri oblika: 1) sporadični, koji se javlja nasumično u populaciji, 2) obiteljski, koji obilježava nepredvidivo češće pojavljivanje u pojedinim obiteljima i 3) nasljedni oblik s izrazito čestim pojavljivanjem unutar pojedinih obitelji čiji članovi obolijevaju u značajno ranijoj životnoj dobi. Danas se procjenjuje da 10-20% svih bolesnika s karcinomom prostate ima pozitivnu obiteljsku anamnezu. Kod naših smo 827 bolesnika s patohistološki dokazanim karcinomom prostate u 28 (3,3%) slučajeva utvrdili pojavu bolesti kod nekog od srodnika prvog reda (očevi, sinovi, braća). Median dobi bolesnika u trenutku postavljanja dijagnoze bio je značajno niži kod obiteljskog oblika bolesti (67,5 godina) u odnosu na slučajeve sa sporadičnim pojavljivanjem (72,0 godina) (p=0,018). Nismo utvrdili statistički značajne razlike između skupina bolesnika sa sporadičnim i obiteljskim oblikom bolesti s obzirom na srednju vrijednost prostatičnog specifičnog antigena (PSA), raspodjelu gradusa (Gleason score), srednje vrijeme do progresije bolesti, kao niti razliku u ukupnom mortalitetu. Bolesnici s pozitivnom obiteljskom anamnezom pokazivali su statistički značajno viši stadij bolesti u trenutku postavljanja dijagnoze (p<0,01), češću pojavu progresije bolesti (p=0,013) te imali viši tumor-specifični mortalitet (p=0,027) tijekom praćenja.

U zaključku ističemo da, s obzirom na pojavu obiteljskog oblika karcinoma prostate u muškaraca značajno mlađe dobi i njegovu moguću agresivniju prirodu, pozitivnu obiteljsku anamnezu treba ozbiljno uzeti u obzir prilikom postavljanja indikacije za početak praćenja PSA, odnosno, biopsiju prostate kod muškaraca s umjereno povišenim PSA.

KLJUČNE RIJEČI: *karcinom prostate, obiteljski karcinom prostate, nasljedni karcinom prostate*

INTRODUCTION

Hereditary factor has early been recognized as a significant risk factor in PCa. Familial aggregation of PCa was first reported by Morganti et al. (1) in 1956, but the concept of hereditary PCa was not established until 1992 when Carter et al. (2) published their results from segregation analysis of 691 men with localized PCa.

Since that time many studies assessed that men with one first-degree relative with prostate cancer has 2- to 4-fold risk of developing prostate cancer, while men with two or three affected first-degree relatives has 5- to 11-fold risk, respectively (3,4,5).

Presently, we can distinguish three epidemiological forms of PCa: 1) Sporadic – occurring randomly in the population; 2) Familial – unpredictable and weak clustering of PCa in families; and 3) Hereditary – strong clustering and early onset of PCa (6). It was estimated that approximately 10-20% of patients with PCa have a positive family history which increases the lifetime risk of the disease (3,4,7). The risk of developing PCa is related not only to the number of affected relatives but to the age at which they were diagnosed. All published reports agree that the risk of developing PCa is higher for those men whose first-degree relatives were diagnosed with PCa in younger age (2,6,8).

Familial form of clustering PCa is presumed to be related to multifactorial genetic and/or environmental factors, while hereditary pattern of clustering is most likely to be explained by Mendelian autosomal-dominant inheritance of a rare high-risk allele. Eighty-eight percent of carriers of this rare gene, which appears in general population with frequency of 0.36%, develop PCa by age 85 years (2,3). It was estimated that this gene can be found in approximately 9% of all patients with PCa and in as many as 43% of early-onset cases (i. e. men younger than 55 years) (2,3).

There are many studies comparing clinical and prognostic characteristics of familial and sporadic PCa with no conclusive answers to the questions: Is familial PCa a different disease? Is it more aggressive and associated with poorer prognosis (3,6-10)?

The aim of our study was to assess clinical and prognostic properties of the patients with familial history of PCa treated in our institution.

MATERIALS AND METHODS

We analyzed retrospectively a database of 827 patients with histopathologically confirmed PCa between January 1994 and June 2011 in Karlovac General Hospital. Twenty-eight (3.3%) of them had a positive family history with at least one of the first degree relative affected by PCa. The other 799 patients had no history of PCa among their relatives and they represented a control group of the patients with sporadic PCa. The standard work-up consisted of physical examination, routine laboratory with PSA testing, 6- to 12-core transrectal ultrasound-guided biopsy and bone scan. Pelvic CT scan was indicated in selected cases. After clinical staging 5 patients underwent radical prostatectomy, 3 patients radical radiotherapy, while in the remaining 20 patients, according to their higher clinical stage or age, a hormonal therapy was indicated. The follow-up consisted of 3- to 6-months checkups with rectal examination and PSA testing. Repeat bone scintigraphy or pelvic CT scan was indicated on an individual basis. Standard criteria for the tumor progression defined by the Guidelines of the European Association of Urology from 2009 were used (11).

Statistics: Student´s T-test was used for testing a difference between quantitative parameters and χ^2-test for testing a difference between the groups in a distribution of qualitative parameters

RESULTS

Twenty-eight (3.3%) of 827 nonscreened patients with histopathologically confirmed PCa had a positive family history with one of the first degree relative affected by the disease. There were 8 pairs of brothers and 6 pairs of fathers and sons and these patients were considered as patients with familial PCa. No patient met criteria to be considered a hereditary PCa. A comparison of clinical, pathological and prognostic characteristics of the groups with familial and sporadic PCa is shown in Table 1. Median age of the patients with familial PCa was 67.5 years (range 52-87) and it was significantly lower than in sporadic cases (median 72, range 47-93) (p=0.018). The rate of the patients younger than 55 years was 10.7 % among

the patients with familial form of PCa and it was significantly higher than between the patients with sporadic PCa (1.6%) (p=0.012). There was no significant difference in PSA level between the patients with familial PCa (median 18.5 ng/mL, range 4.7-2589.0) and the patients with sporadic PCa (21.0 ng/mL, range 0.4-5000.0), but there was significantly higher frequency of the patients with PSA higher than 1000 ng/ml in the familial group than in the sporadic one (p<0.01). The patients with familial PCa had a significantly higher tumor stage than the patients in the sporadic group (p<0.01) with 46.2 % patients with metastatic disease at diagnosis. There was no difference in the distribution of the patients between the groups according to Gleason score of the tumor (Table 1).

Table 1.

DEMOGRAFIC, CLINICAL AND PROGNOSTIC DIFFERENCES BETWEEN THE PATIENTS WITH FAMILIAL AND SPORADIC PROSTATE CANCER

	Patients with familial prostate cancer	Patients with sporadic prostate cancer	p
Number of patients	28	799	
Age, years Median Range	 67.5 52-87	 72 47-93	0.018
Age <55 years (N) (%)	3 (10.7)	13 (1.6)	0.012
PSA, ng/ml Median Range	 18.5 4.7-3589.0	 21 0.4-5000.0	NS
PSA, ng/ml (N) <9.9 10.0-49.9 50.0-1000.0 >1000.0 PSA x	 9 9 5 4 1	 229 227 207 33 53	<0.01
Stage (N) $T_{1-2}N_0M_0$ $T_3N_0M_0$ $T_{1-4}N_1$ and/or M_1	 6 9 13	 357 311 131	<0.01
Pathologic grade (N) Gleason score ≤6 Gleason score 7 Gleason score >7 Gleason score x	 8 11 8 1	 160 441 160 38	NS
Progression (N) (%)	17 (60.7)	299 (37.4)	0.013
Time to progression Median, months Range	 26 4-48	 18 1-120	NS
Overall mortality (N) (%)	14 (50.9)	299 (37.4)	NS
Tumor specific mortality (%)	12 (42.8)	195 (24.4)	0.027

The median follow-up of the patients with familial PCa was 27.5 months (range 1-135). During the follow-up, signs of biochemical or clinical progression were noticed in 17 (60.7%) patients with familial PCa and in 299 (37.4%) with sporadic PCA (p=0.013). Median time to progression was longer in familial cases than in sporadic ones (26 month, range 4-48 vs. 18 months, range 1-120), but the difference was not statistically significant. During the follow-up, overall 14 (50.0%) patients died in the familial group and 299 (37.4%) in the sporadic group (overall mortality). Tumor specific mortality was significantly higher in the patients with familial than in those with sporadic PCa (42.8 % vs. 24.4%) (p=0.027).

DISCUSSION

The generally accepted definition of hereditary PCa includes nuclear families with 3 cases of PCa, families with PCa in each of 3 generations in the paternal or maternal lineage and families with 2 men diagnosed with the disease before age 55 years (3). It was estimated that of all the patients with PCa, 5-10% has this form of PCa and in the other 5-10% has a familial form of PCa (2,10). In our study, no patient met criteria for hereditary PCa, so all of our 28 patients with genealogical clustering were considered familial prostate cancers. The absence of patients with the hereditary form of PCa in our study and lower rate of patients with familial PCa (3.3%) can be explained by the fact that our patients, in contrast to the most published series, were not diagnosed through a PCa screening program. That is the reason why the patients with familial PCa in our study are 3-7 years older at diagnosis than patients in screening-based studies (6,12). According to the observations of the most published studies, we found that patients with familial PCa were significantly younger than sporadic cases with a significantly higher rate of patients younger than age 55 years (6,7,10). Most authors report no difference in the PSA value between the patients with familial and sporadic PCa (6,7,12). We assessed no difference in median PSA value as well, but observed a significantly higher rate of patients with PSA >1000

ng/mL in the group with positive familiar history. Reports about tumor stage of the familial PCa are controversial. Some studies assessed a higher stage of familial PCa cases in comparison to sporadic ones (7,13), and the other found no difference (6,10). In our nonscreening-originated patients with familial PCa there was a significantly higher rate of patients with metastatic disease in comparison to the control group. There was no difference in pathologic grade (Gleason score) between familial and sporadic cases in most published studies (6,7,9,10,13). Our results are in agreement with this observation. Most studies assessed no difference in outcome between familial and sporadic PCa (2,3,10,13). Only Kupelian et al. reported a higher risk of relapse after radical prostatectomy in familial cases than in sporadic ones (7). When comparing a cause of death between our patients with sporadic and familial PCa who died during the follow-up, we assessed that a significantly higher rate of patients died of PCa in the familial group (42.8%) than in the sporadic one (24.4%).

Although there is no conclusive evidence that familial and hereditary PCa are more aggressive forms of PCa, all authors agree that positive family history, because of 5-7 years earlier onset of the disease, must be taken into consideration when to start PSA screening and when to indicate prostate biopsy in men with slightly elevated PSA. Most guidelines recommend that screening among men in families with hereditary PCa is reasonable to be initiated at least 5 years before the earliest age at diagnosis in the family, and at least 10 years before the age at which metastatic disease appeared (14). Taking into consideration strong evidence for an increased positive predictive value of PSA in men from families with hereditary PCa, prostate biopsy should be indicated in all cases with PSA value >3 ng/ml (7,14). In case of negative first biopsy they should undergo repeat biopsy or reexamination in short time intervals.

REFERENCES

1. Morganti G, Gianferrari L, Cresseri A, Arrigoni G, Giovati G. Recherces clinico-statistiques et genetiques sur les neoplasises de la prostate. Acta Genet 1956; 6:304.
2. Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC. Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci USA 1992;89:3367.
3. Carter BS, Bova GS, Beaty TH et al. Hereditary prostate cancer: epidemiologic and clinical features. J Urol 1993;150:797-802.
4. Cussenot O, Valeri A, Meria P et al. Genetic aspects in cancers of the prostate. Path Biol 1996;44:737-43.
5. Johns LE, Houlston RS. A systematic review and meta-analysis of familial prostate cancer risk. BJU Intern 2003;91:789-94.
6. Sacco E, Prayer-Galetti T, Pinto F. et al. Familial and hereditary prostate cancer by definition in an Italian surgical series: clinical features and outcome. Eur Urol 2005;47:761-8.
7. Kupelian PA, Klein EA, Witte JS, Kupelian VA, Suh JH. Familial prostate cancer: a different disease? J Urol 1997;158:2197-201.
8. Brandt A, Bermejo JL, Sundquist J, Hemminki K. Age-specific risk of incident prostate cancer and risk of death from prostate cancer defined by the number of affected family members. Eur Urol 2010;58:275-80.
9. Bastacky SI, Wojno KJ, Walsh PC, Carmichael MJ, Epstein JI. Pathological features of hereditary prostate cancer. J Urol 1995;158:987-92.
10. Bratt O, Damber JE, Emanuelsson M, Grönberg H. Hereditary prostate cancer: clinical characteristics and survival. J Urol 2002;167:2423-6.
11. Heidenreich A, Bolla M, Joniau S., et al. Guidelines on prostate cancer in EAU Guidelines. EAU, ed. 2009: 106-36.
12. Aprikian AG, Bazinet M, Plante M et al.: Family history and the risk of prostatic carcinoma in a high risk group of urological patients. J Urol 1995;154:404-5.
13. Roemerling S. Roobol MJ, de Vries SH, Gosselaar C, van der Kwast TH, Schröder FH. Prevalence, treatment modalities and prognosis of familial prostate cancer in a screened population. J Urol 2006;175: 1332-6.
14. Bratt 0. Hereditary prostate cancer: clinical aspects. J Urol 2002;168:906-13.

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