ORIGINAL ARTICLE

Familial, Hereditary and Sporadic Characterization of Prostate Cancer & Impact on Diagnostic Modalities

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ABSTRACT

Background: A family history of prostate cancer has been associated with increased risk of prostate cancer development, but the risks were inconsistent in terms of the affected family members and the data on prostate cancer characterization with respect to family history of disease among Pakistani men is limited.

Objective: To characterize prostate cancer based on family history into familial including hereditary and sporadic cases and to investigate the association with diagnostic modalities; age of patient at diagnosis and pathological tumor grade.

Methods: A self-administered written questionnaire was forwarded to 100 patients diagnosed with prostate adenocarcinoma, containing questions about age at diagnosis and cases of prostate cancer in family. The information regarding age of patient at diagnosis, cases of prostate cancer in relative, pathological tumor grade and age at death for all relatives affected by prostate cancer was acquired. The data was validated through the biopsy report of patient and medical records of relative affected by prostate cancer, provided by patient respectively. Patients were then divided into three groups according to their family history: familial prostate cancer (FPC), hereditary prostate cancer (HPC) and sporadic prostate cancer (SPC) groups.

Results: 17% of the patients were categorized in the FPC group, of which 2% were identified as having HPC and 81% were assigned SPC group. Overall, there was no significant statistical difference between groups and study variables.

Conclusion: We found no difference in age and pathological tumor grade, in patients diagnosed with adenocarcinoma of prostate following TURP. These results are consistent with previous studies except that patients with HPC in previous studies were significantly younger at diagnosis.

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INTRODUCTION

Prostate cancer is the second most common malignancy in men globally.[1] According to a recent statistics, prostate cancer is the fourth most common tumor of men in Pakistan.[2] Several established risk factors such as obesity, diet, steroid hormones and family history are associated with the development of this tumor.[3] Among those, positive family history of prostate cancer is the strongest identified risk factor of this tumor.[4] Individuals with a positive family history of disease are at increased risk for prostate cancer development at an early age however, the link of pathological tumor grade with family history remains unclear.[5]

Carter and colleagues was the first to classify prostate cancer based on family history into three categories; hereditary, familial and non-familial (sporadic) tumors.[6] Hereditary prostate cancer (HPC) is described as a cluster of three or more first-degree relatives; (father, brother or son) affected with prostate cancer, or at least two or more first- or second-degree relatives diagnosed with prostate cancer under the age of 55, or prostate cancer in each of three generations in the paternal or maternal lineage.[6] Familial prostate cancer (FPC) is characterized as, history of prostate cancer in either one first-degree relative; (father, brother or son) or two or more second-degree relatives; (grandfathers, uncles, nephews, or half-siblings) within paternal or maternal family; whereas non-familial (sporadic) prostate cancer implies that, no member of a family has been previously diagnosed with prostate cancer.[6] The review of scientific literature reveals that approximately 10% - 20% of the men diagnosed with prostate cancer bear the family history of the disease.[7] This accounts for about two-fold increase risk of tumorigenesis with a positive family history.[4]

This study was carried out to characterize Sporadic (SPC) and familial prostate cancer (FPC) including hereditary prostate cancer (HPC) and to investigate the impact of family history on age of patient at diagnosis and pathological tumor grade. If significant association is determined than, future studies may focus on the molecular and genetic characterization of the study samples.

METHODOLOGY

The ethical approval was sought from Institutional Review Board (IRB) of Dow University of Health Sciences (DUHS) to collect prostate biopsy samples diagnosed with adenocarcinoma. The samples were collected from Dow Diagnostic Research & Reference Laboratory (DDRRL), during the period of January 2009 to December 2013. These patients underwent transurethral resection of prostate (TURP) at various hospitals of Karachi. A panel of histopathologist reviewed each case and a final diagnosis of adenocarcinoma was given by consensus. The biological aggressiveness of the tumor was determined, according to Gleason's grading system of prostate adenocarcinoma.

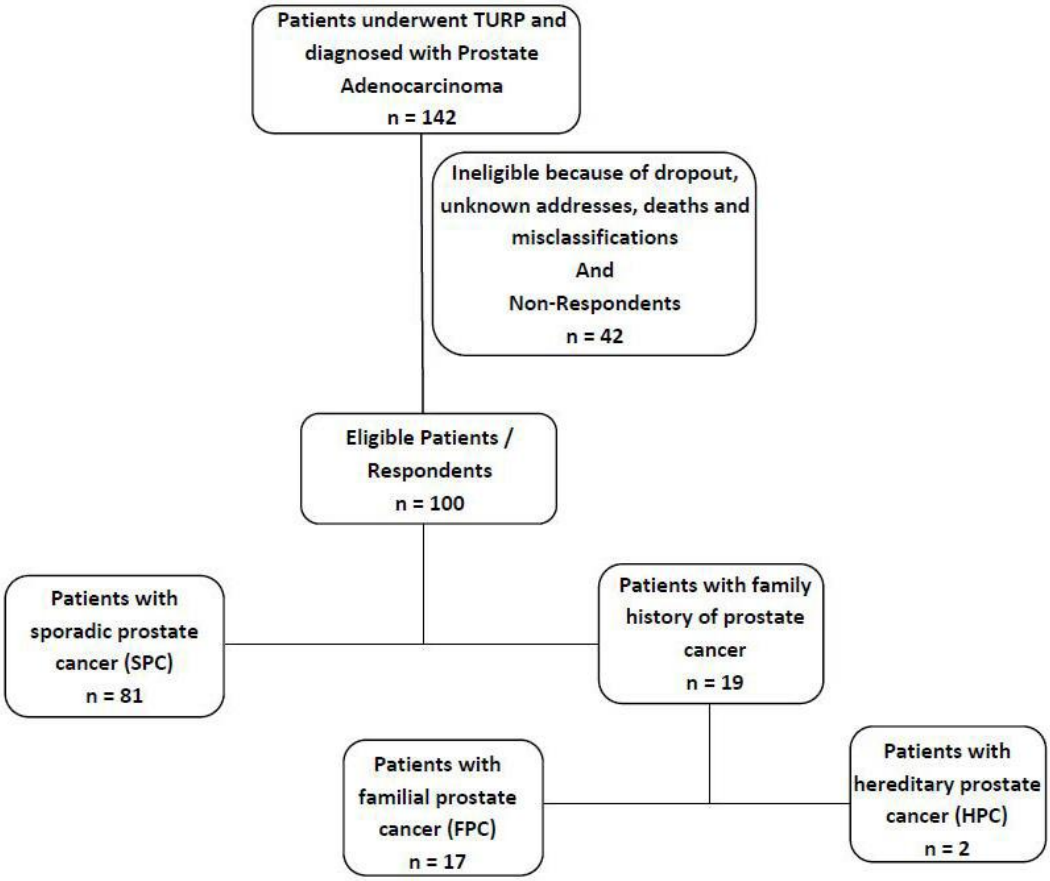
Written and informed consent was obtained from all participants and a self-administered written questionnaire was forwarded to patients diagnosed with the prostate adenocarcinoma. The data regarding patient age at diagnosis, family history of prostate cancer and age at death for all relatives affected by prostate cancer was obtained. The age of patient at diagnosis was further confirmed by the biopsy report. All questionnaires were evaluated for positive and negative family history of prostate cancer and medical records of the relatives affected from prostate cancer were acquired from the patients, to confirm the family history of disease. Positive family history respondents, who were unable to provide medical evidence of tumor in relative were excluded from the study. The respondents were classified into three groups: 1) participants with Familial (FPC), 2) patients with hereditary

prostate cancer (HPC); and 3) subjects with Sporadic prostate cancer (SPC), according to the criteria described by Carter *et al* (Table 1).[6] The recruitment procedure of the participants is summarized in Figure 1.

Because familial prostate cancer are known to have early onset of disease and suspected to be more aggressive, we therefore divide the diagnostic modalities into two groups; age (patients aged ≤ 65 years and those with >65 years of age) and pathological tumor grade (≤7 Gleason's score and >7 Gleason's score). This will allow us to set lower and higher criteria for age and tumor grade parameters, for statistical analyses.

Statistical analysis was performed by SPSS 21.0 (The Statistical Package for the Social Sciences, Chicago, USA) package program. Correlation between categorical variables with FPC and HPC was evaluated by Fisher's Exact Test, whereas correlation with SPC was assessed by Binary Logistic Regression. Means were assessed by standard deviation. In all tests, minimum limit of significance was determined as 0.05 ($p<0.05$).

Figure 1. Flow chart of participants recruitment procedure



RESULTS

Of the 100 respondents, 17 (17%) fulfilled the criteria of familial prostate cancer and were hence assigned to the FPC, whereas 2 (2%) were characterized as hereditary prostate cancer (HPC). The rest of the 81 (81%) cases were classified in SPC. Overall, there were no significant statistical differences between groups and tumor variable. The distribution of research parameters and their statistical evaluation is summarized in Table 2.

Table 1. Distribution of Groups between Patients with Positive versus Negative Family History of Prostate Cancer.

Family History	FPC		HPC		SPC	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
First Degree Relative	11	64.7	0	0	0	0
Second Degree Relative	6	35.2	2	100	0	0

Table 2. Distribution of familial (FPC), hereditary (HPC) and sporadic (SPC) prostate cancer.

Parameters	FPC		P-Value[a]	HPC		SPC		P-Value[b]
	No. of Patients	%		No. of Patients	%	No. of Patients	%	
Age (years)			0.67*					0.06[#]
<65	10	58.8		1	50	32	39.5	
>65	7	41.1		1	50	49	60.4	
Gleason Score			0.32*					0.43[#]
<7	8	47.0		0	0	37	45.6	
>7	9	52.9		2	100	44	54.3	

[a] p-values for comparisons between FPC and HPC; [b] p-value for comparisons with SPC; *Fisher Exact test; and [#]Binary Logistic Regression test.

DISCUSSION

Positive family history is one of the most consistent established risk factor for prostate cancer.(4) Several cohorts have previously reported a strong link of familial clustering with the development of prostate cancer.[6,8,9] In this study, we assessed the diagnostic parameters of FPC, HPC and SPC. We found that, the FPC accounted for 17%, HPC for 2%; and SPC for 81% of all prostate cancer cases. These findings are consistent with previously reported data.[4,10]

There were no significant statistical differences between FPC, HPC and SPC and tumor variables (Table 2). These findings are in agreement with previous reports; Gronberg *et al.* detected no significant difference in age and tumor grade between 249 SPC, 46 HPC and 258 FPC cases.[11]

Younger age at diagnosis among cases with family history is expected for a genetically determined disease.[4] Previously, diagnostic modalities; age and pathological tumor grade was investigated by Valeri *et al,* in cases with FPC, HPC, and SPC. Younger age in HPC cases was the only significant parameter documented in that study.[12] Sacco et al reported similar findings.[10] However contrary to previous reports, we were unable to determine a significant association of age with tumor groups, although majority of cases presents with early onset of disease, particularly in FPC and HPC groups. This discrepancy of age may explained by the lack of PSA based screening in our country and late presentation of symptoms, which might have delayed the diagnosis of tumor.

The pathological characteristic of familial disease remains controversial.[13] Some reported a positive association with low grade or localized tumor, whereas others linked it with high grade or stage.[12,14-16] However, in many recent studies, no statistical difference of FPC, HPC and SPC with tumor grade was observed.[4,13] Our finding is in line with recent studies. The possible explanation is either vast numbers of patients with aggressive disease are likely to die early and therefore might not included in this study or tumor grade may not have any relationship with family history.

There are several limitations in this study. First, the small sample size particularly in HPC group and misclassification; as operational definition of HPC is based on epidemiological data, which makes it difficult to distinguish true hereditary tumors from non-hereditary tumors. Moreover, HPC families may include members with likely "phenocopies". Such limitations can be

addressed by molecular and genetic characterization using larger set of samples. Second, all study subjects underwent TURP surgery and they might not be representative for the whole spectrum of prostate cancer. Third, the biopsy reports of the patients were limited to grading only, we therefore unable to include staging parameter for assessment in present investigation.

CONCLUSION

No differences were observed between tumor variables and HPC, FPC, and SPC groups. However, our data confirmed the findings of previous studies that patients with a family history were more frequently younger than sporadic cases. Therefore, we suggest extensive study with a larger sample size along with genetic and molecular analyses, to further investigate the characterization of prostate cancer and its impact on diagnostic modalities.

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