Effect of family history on outcome in German patients treated with radical prostatectomy for clinically localised prostate cancer

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1. Introduction

A positive family history (FH) is an established risk factor for the development of prostate cancer (CaP). The risk of developing the disease rises with increasing number,[1–4] degree (first-degree) and early age of onset of affected family members.[5] Conflicting data exist whether a positive FH has an impact on oncological outcome after curative local treatment. Kupelian et al. described an elevated risk for biochemical recurrence in patients with a positive FH following radical prostatectomy (RP) or radiation therapy.[6,7] These results could not be reproduced by other studies.[8–11] Some authors described an association with prognostic clinico-pathologic features such as elevated preoperative PSA-values,[12,13] perineural infiltration and positive lymph node status[14] but not with progression after curative local treatment. Differences in pathological characteristics and oncological outcome may only be evident in subsets of patients with a positive FH which may produce

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contradictory results in different study populations. Consequently, subclassification of patients with a positive family history is essential.

In the present study we assessed clinico-pathologic characteristics and biochemical-recurrence free survival (bRFS) of sporadic, familial and hereditary CaP patients treated with RP for clinically localised CaP from the German database 'Familial Prostate Cancer'. We performed a risk-stratified analysis using the D'Amico risk group classification.

2. Materials and methods

Patients who underwent RP between 1994 and 2008 were identified from the German database 'Familial Prostate Cancer'. This prospective multi-centre database has been described in detail by Paiss et al.[10,15] In short, the self-reported family history of CaP patients was used to recruit relatives also affected by CaP. All families were Caucasian. Only patients who received RP for definitive local treatment were included in the present study independent of an adjuvant therapy. By 2009, sufficient data were available to analyse clinical records and follow-up questionnaires of 8041 patients with CaP. Biochemical recurrence was defined by a PSA-value greater than 0.2 ng/ml.

FH was defined as sporadic prostate cancer (SPC – patients with no family history of PC), familial prostate cancer (FPC – clustering of at least two first-degree relatives with PC in one family, patients with hereditary PC excluded) or hereditary prostate cancer according to the Johns Hopkins Criteria (HPC – clustering of at least three affected relatives from three generations, at least three affected first degree relatives or at least two affected relatives with an age of onset of 55 years or less).

Clinical and pathological stages were determined according to UICC TNM 2002. Age of onset was defined by the date of a positive biopsy. On analysis, patients were divided into two groups with an age of onset < or ⩾65 years. According to D'Amico criteria,[16] patients were classified as having low risk (preoperative Gleason Score ⩽6 and clinical tumour stage <cT2b and initial PSA-level <10 ng/ml), intermediate risk (preoperative Gleason Score seven or clinical tumour stage cT2b-c or initial PSA-level 10–20 ng/ml) or high risk CaP (preoperative Gleason Score 8–10 or clinical tumour stage >cT2c or initial PSA-level >20 ng/ml). Tumour extension was classified by presence of organ-confined disease (⩽pT2c and pN0), seminal vesical invasion (pT3b) and lymph node metastasis (pN1).

Associations between risk group and clinico-pathologic parameters adjusted for FH and between FH and clinico-pathologic parameters adjusted for risk group were analysed using Cochran–Mantel–Haenszel tests. Kaplan–Meier curves and 95% confidence intervals (CI) for biochemical recurrence-free survival were calculated and a log rank test was used to compare bRFS curves between risk groups and FH groups. The simultaneous impact of risk group and FH on bRFS rates was analysed in a multiple proportional hazards regression. An additional proportional hazards model was fitted to test for interaction between the factors risk group and FH. Hazard ratios with 95% CI and p-value were calculated.

3. Results

Table 1 lists detailed information on risk group and FH. Out of 8041 patients 5756 (71.6%) met the criteria for SPC, 1779 (22.1%) for FPC and 506 (6.3%) for HPC. When classified by D'Amico criteria, patients at intermediate risk were most prevalent (51.9%) followed by low risk (26.1%) and high risk (22.0%).

Table 2 lists data on clinico-pathologic characteristics according to FH and D'Amico classification. Analysis of associations showed an association of age of onset <65 years with family history adjusted for D'Amico classification ($p < 0.001$). With a median age of onset of 63.0 years in FPC and 64.0 years in HPC, patients with a positive FH were 1–2 years younger at the time of diagnosis than patients with sporadic prostate cancer with a median age of onset of 65.0 years. As expected, D'Amico classification showed a strong association with organ-confined disease ($p < 0001$), seminal vesical invasion ($p < 0.001$) and lymph node status ($p < 0.001$) adjusted for FH. FH adjusted for D'Amico classification showed no association with organ confined disease ($p = 0.524$), seminal vesical invasion ($p = 0.733$) or lymph node metastasis ($p = 0.992$) (Table 2).

Median follow-up time for all patients was 4.4 years (maximum follow-up time 18.2 years). Table 3 shows 5- and 10-year bRFS rates following RP stratified by D'Amico criteria and FH. Overall, patients with SPC, FPC and HPC had similar bRFS rates ($p = 0.999$). In the subgroup of patients with high risk and hereditary CaP the lowest bRFS rate at 5 (52.9%) and 10 (30.7%) years was observed. However, this trend was statistically insignificant ($p = 0.267$, Fig. 1c).

Table 1 – Distribution of patients according to preoperative data on family history and risk group classification (D'Amico criteria).

Level of risk	No. (%) patients per subgroup			
	Family history			Total
	SPC	FPC	HPC	
Low	1545 (26.9)	442 (24.8)	113 (22.3)	2100 (26.1)
Intermediate	2961 (51.4)	941 (52.8)	267 (52.8)	4169 (51.9)
High	1250 (21.7)	396 (22.3)	126 (24.9)	1772 (22.0)
Total	5756 (100)	1779 (100)	506 (100)	8041 (100)

SPC, sporadic prostate cancer; FNPC, familial non-hereditary prostate cancer; HPC, hereditary prostate cancer.

Table 2 – Frequency of clinico-pathologic characteristics stratified by family history and risk group classification. Frequencies of age of onset <65 years, organ confined disease, seminal vesical invasion and positive lymph node status are displayed as number of affected patients per subgroup.

Level of risk	No. (%) affected patients per subgroup			
	Family history			Total
	SPC	FPC	HPC	
Low				
Age of onset <65 years	762 (49.3)	252 (57.0)	61 (54.0)	1075 (51.2)
Organ confined disease	1066 (88.7)	321 (86.8)	84 (84.0)	1471 (88.0)
Seminal vesicle invasion	29 (1.9)	8 (1.9)	2 (1.8)	39 (1.9)
Positive lymph node status	15 (1.2)	6 (1.8)	2 (2.1)	23 (1.4)
Intermediate				
Age of onset <65 years	1383 (46.7)	530 (56.3)	147 (55.1)	2060 (49.4)
Organ confined disease	1471 (61.2)	510 (63.7)	146 (60.3)	2127 (61.7)
Seminal vesicle invasion	353 (12.6)	93 (10.4)	40 (15.8)	486 (12.9)
Positive lymph node status	181 (6.9)	43 (5.2)	21 (8.6)	245 (6.6)
High				
Age of onset <65 years	599 (47.9)	224 (56.6)	67 (53.2)	890 (50.2)
Organ confined disease	354 (33.1)	115 (32.6)	31 (27.9)	500 (32.6)
Seminal vesicle invasion	358 (32.8)	108 (30.7)	33 (31.7)	499 (32.3)
Positive lymph node status	290 (24.9)	85 (23.4)	31 (26.3)	406 (24.6)
Total				
Age of onset <65 years	2744 (68.2)	1006 (25.0)	275 (6.8)	4025 (100.0)
Organ confined disease	2891 (70.5)	946 (23.1)	261 (6.4)	4098 (100.0)
Seminal vesicle invasion	740 (72.3)	209 (20.4)	75 (7.3)	1024 (100.0)
Positive lymph node status	486 72.1)	134 (19.9)	54 (8.0)	674 (100.0)
Association with family history adjusted for risk group classification				*p*-Value[a]
Age of onset <65 years				<0.001
Organ confined disease				=0.524
Seminal vesicle invasion				=0.733
Positive lymph node status				=0.992
Association with risk group classification adjusted for family history				*p*-Value[a]
Age of onset <65 years				=0.412
Organ confined disease				<0.001
Seminal vesicle invasion				<0.001
Positive lymph node status				<0.001

SPC, sporadic prostate cancer; FNPC, familial non-hereditary prostate cancer; HPC, hereditary prostate cancer.

[a] Cochran–Mantel–Haenszel-test.

In a multiple proportional hazards regression assessing the impact of FH and risk group simultaneously, patients with SPC (HR 1.0, 95% CI [0.9;1.2]) and FPC patients (HR 1.0, 95% CI [0.9;1.2]) were at a similar risk of developing biochemical recurrence compared to patients with HPC ($p = 0.954$, Table 4a). Patients with intermediate risk cancer had a 2-fold higher risk (HR 2.0, 95% CI [1.7;2.3]) and patients with high risk cancer a 3-fold higher risk (HR 3.0, 95% CI [2.6;3.5]) of developing biochemical recurrence compared to low risk cancer patients ($p < 0.001$, Table 4a). No important interaction could be found when extending the proportional hazards model to include the interaction between family history and risk group ($p = 0.199$, Table 4b). This is confirmed by Fig. 1a–c comparing bRFS between family history groups within each risk group.

4. Discussion

It has been estimated that familial prostate cancers account for up to one fourth and that HPC accounts for 9% of all prostate cancers.[17] With 22% FPC and 6% HPC patients our study population corresponds well with this estimation.

Consistent with other studies early age of onset segregated patients with a positive family history from SPC patients.[8,9,18,19] In 2002, Bratt et al. described a median age of onset of 68 years in HPC patients which was 6 years less than in patients with prostate cancer in the general Swedish population.[9] As age <55 is one out of three definitions of HPC according to the Johns Hopkins criteria, the finding of earlier diagnosis in HPC may reflect a bias to some degree. However, in our study FPC patients who were not defined by an age criterion were also younger than sporadic cases at the time of diagnosis. Marotte et al. explained earlier diagnosis in patients with a positive FH by more aggressive screening due to a rising alertness in men with affected family members and their treating doctors.[20] Current American Cancer Society Guidelines[21] recommend risk-based PSA-screening starting at age 40, 45 or 50 depending on the number of affected first-degree relatives that were diagnosed having

Table 3 – Five- and 10-yr-Biochemical recurrence-free survival rate stratified by family history and risk group classification (D'Amico criteria).

Level of risk	Biochemical recurrence free survival rate % (95% CI)			
	Family history			Total
	SPC	FPC	HPC	
Low				
5-yr	83.8 (80.7; 86.4)	83.8 (78.3; 88.0)	82.5 (70.4; 90.0)	83.7 (81.1; 85.9)
10-yr	63.6 (52.8; 72.6)	70.7 (55.7; 81.5)	68.6 (40.6; 85.4)	64.7 (55.6; 72.3)
Intermediate				
5-yr	70.6 (68.4; 72.8)	71.2 (67.3; 74.6)	75.4 (68.9; 80.8)	71.2 (69.3; 72.9)
10-yr	47.1 (42.9; 51.2)	42.9 (36.2; 49.5)	54.2 (43.7; 63.5)	46.7 (43.4; 50.0)
High				
5-yr	59.4 (56.0; 62.6)	60.6 (54.5; 66.1)	52.9 (42.3; 62.5)	59.2 (56.3; 61.9)
10-yr	35.9 (31.4; 40.4)	42.4 (35.0; 49.5)	30.7 (20.5; 41.4)	37.0 (33.4; 40.6)
Total				
5-yr	70.9 (69.3; 72.5)	71.4 (68.6; 74.0)	71.0 (66.1; 75.4)	
10-yr	47.0 (43.9; 50.0)	47.5 (42.6; 52.2)	48.7 (41.1; 55.9)	

SPC, sporadic prostate cancer; FPC, familial prostate cancer; HPC, hereditary prostate cancer.

CaP before age 65. This is in contrast with current European guidelines on CaP in which PSA-screening based on family history is not recommended.[13,22] It might be interesting whether different guideline recommendations in USA and Europe have an impact on age of onset in men with affected relatives in future studies.

To date, Kupelian and colleagues reported the only two studies describing a significant lower bRFS rate in patients with positive FH independent of treatment modality.[6,7] Other authors described an association of positive FH with different prognostic clinico-pathologic features whereas an association with cancer progression could not be established again.

In an Italian surgical series Sacco et al. found a lower frequency of positive margin status ($p = 0.011$), perineural infiltration ($p = 0.028$) and positive lymph nodes ($p = 0.005$) in 76 patients with a positive FH compared to 530 SPC patients.[14] Despite the association with prognostic pathologic characteristics an association between positive FH and bRFS or cancer-specific survival was not present. Furthermore, Roehl et al. described an association of FH with positive surgical margins with positive FH ($p = 0.03$) but not with bRFS ($p = 0.3$) in a surgical series comprising 3478 CaP patients.[11] As differences in clinico-pathologic features or oncological outcome may only be evident in patients with hereditary CaP, conflicting results of the aforementioned studies may be due to a lacking differentiation between familial CaP and hereditary CaP. Therefore, several studies described the oncological outcome related to classification of SPC, FNPC or HPC.

Siddiqui et al. analysed 3560 prostate cancer patients treated with RP including 865 FNPC and 133 HPC patients.[12] Besides from increased preoperative PSA-levels in HPC patients ($p = 0.04$), differences in clinico-pathologic characteristics, bRFS or cancer-specific survival were not observed. In a study that investigated patients treated with watchful waiting, RP, radiotherapy or androgen-deprivation therapy, Bratt et al. also found no difference in cancer-specific survival between 201 HPC and 402 SPC patients.[9] Peters et al. analysed the effect of FH on outcomes in patients treated with brachytherapy by risk, simultaneous to our study. They discovered a trend towards improved biochemical control in intermediate risk patients with a positive FH which did not reach a statistically significant level ($p = 0.076$).[23] Consequently, several authors concluded that FH had no impact on oncological outcome after curative treatment for localised prostate cancer.[9,11,12,14,23]

Nevertheless, inherited susceptibilities have been identified that go along with phenotypic differences in subgroups of HPC-patients. Smith et al. reported the first putative hereditary CaP locus, HPC1, located on chromosome 1q24-q25 by a genome-wide scan. They studied 91 families from North America and Sweden with an average number of 4.9 CaP cases in each family. A subsequent study of the characteristics of HPC1-linked families suggested that the evidence for linkage was primarily from families with four or more close relatives with the disease, an early mean age at diagnosis <65 years and proportionally more advanced-stage disease.[24,25] Subsequently, several susceptibility genes were identified showing a correlation with phenotypic differences such as HPC20 which has been correlated with late-onset disease[26] and PCAP which was more common in patients with early age at onset.[27,28] However, the susceptibility genes detected so far do not account for the majority of HPC and the

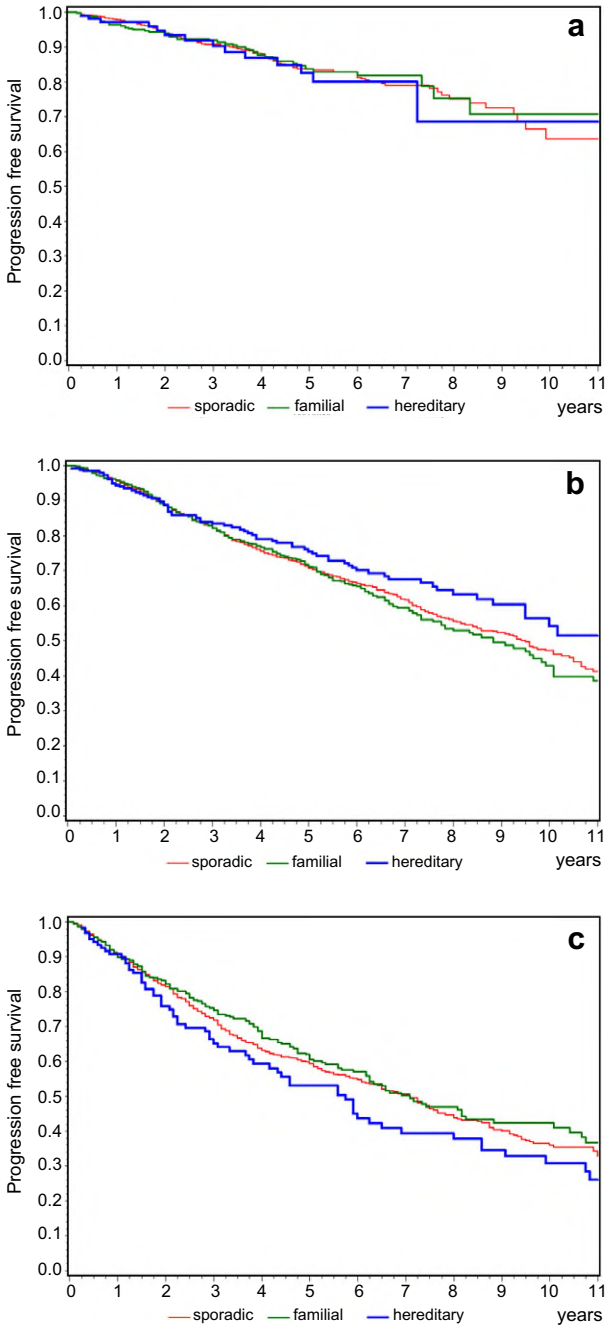

Fig. 1 – Biochemical recurrence free survival stratified by family history and (a) low risk ($p = 0.821$), (b) intermediate risk ($p = 0.157$) and (c) high risk prostate cancer ($p = 0.267$).

Table 4a – Multiple proportional hazards regression assessing the impact of family history and risk group on biochemical recurrence free survival (bRFS) simultaneously.

Prognostic factor	HR	95% CI	p-Value[a]
Risk group			
Intermediate versus low	2.0	[1.7; 2.3]	<0.001
High versus low	3.0	[2.6; 3.5]	
Family history			
Sporadic versus hereditary	1.0	[0.9; 1.2]	0.954
Familial versus hereditary	1.0	[0.9; 1.2]	

HR, hazard ratio; CI, confidence interval.
[a] Chi-Square test.

Table 4b – Multiple proportional hazards regression assessing the impact of family history, risk group and the interaction between family history and risk group on biochemical recurrence free survival (bRFS).

Prognostic factor	HR	95% CI	p-Value[a]
Risk group			
Intermediate versus low	1.4	[0.8; 2.5]	<0.001
High versus low	3.0	[1.7; 5.3]	
Family history			
Sporadic versus hereditary	0.8	[0.5; 1.4]	0.812
Familial versus hereditary	0.8	[0.5; 1.4]	
Interaction risk group and family history			
Intermediate sporadic versus low hereditary	1.4	[0.8; 2.6]	0.199
Intermediate familial versus low hereditary	1.5	[0.8; 2.8]	
High sporadic versus low hereditary	1.0	[0.6; 1.8]	
High familial versus low hereditary	1.0	[0.5; 1.8]	

HR, hazard ratio; CI, confidence interval.
[a] Chi-Square test.

results seem to be population-specific leading to disparate findings in confirmation studies with different populations.[29] At present the definition for inherited forms of CaP still is a clinical definition.

In our study, we determined the impact of FH stratified by risk in a German surgical multi-centre series on clinico-pathologic characteristics and bRFS. By substratification of patients in SPC, FNPC, HPC as well as low, intermediate and high risk cancer, we sought to determine whether differences in oncological outcome existed in subgroups of patients with a positive FH. As a result, FH in contrast to D'Amico classification showed no association with clinico-pathologic characteristics or bRFS. Interestingly, the subgroup of patients with HPC and high risk cancer had numerically the lowest bRFS rate at 5 (52.9%) and 10 (30.7%) years post-operatively. However, the bRFS of this subgroup did not differ considerably from patients with SPC and high risk cancer or FNPC and high risk cancer ($p = 0.267$).

One limitation of our study is the short time of follow-up, half of the patients had a shorter follow-up than 4.4 years. Long-term follow-up needs to be awaited in order to determine the impact of FH on cancer-specific survival in the three risk-groups. Furthermore, follow-up was not available for all patients. Remaining patients might not have been accessible due to early death and patients with aggressive prostate cancer might have been missed. Anyhow, bRFS was available for 5718 patients which, to date, is the largest published cohort based on FH.

Another limitation of our study is that we focused on autosomal dominant inherited prostate cancer as defined by the Johns Hopkins Criteria. The majority of studies support an

autosomal dominant mode of inheritance, but autosomal recessive and X-linked models also have been supported.[17]

We used the D'Amico classification in order to risk-stratify patients pre-operatively. The CAPRA or Stephenson model would probably have been more precise but the percentage of positive prostate biopsies was not available. Furthermore, the histopathologic specimens were not centrally reviewed.

These possible confounders need to be taken into account when interpreting our data.

5. Conclusions

In the present study we analysed the impact of FH on preoperative clinical data in CaP patients treated with RP. Patients with a positive FH were 1–2 years younger at the time of CaP diagnosis compared to SPC patients. BRFS in patients with prostate cancer was considerably influenced by risk group but independent of FH. Cross-classification of FH and D'Amico classification did not show a subgroup with an elevated risk for biochemical recurrence.

Conflict of interest statement

None declared.

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