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ORIGINAL ARTICLE

Impact of a family history of prostate cancer on clinicopathologic outcomes and survival following radical prostatectomy

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Abstract
Purpose While a family history (FH) of prostate cancer represents an established risk factor for prostate cancer diagnosis, conflicting data exist regarding the oncologic importance of FH. Herein, we evaluated the association of FH with clinicopathologic outcomes among men undergoing radical prostatectomy (RP).
Methods We identified 16,472 men who underwent RP between 1987 and 2010 at Mayo Clinic. Patients were considered to have a positive FH if at least one first-degree relative had been diagnosed with prostate cancer. Survival was estimated using the Kaplan–Meier method. The associations of FH with clinicopathologic features and survival were evaluated using logistic and Cox regression analyses.
Results Overall, 5323 (32.3 %) men reported a FH of prostate cancer. Median follow-up was 9.9 years (IQR 5.9, 15.5). Patients with a FH were significantly more likely to have low-risk disease (47.7 vs. 43.0 %; $p < 0.0001$) and were significantly more likely to have organ-confined disease at RP (79.2 vs. 74.4 %; $p < 0.0001$). Men with FH had a significantly higher 10-year cancer-specific (99 vs. 97 %; $p < 0.001$) and overall survival (92 vs. 85 %; $p < 0.001$) than men without FH. Moreover, on multivariable analysis, FH of prostate cancer remained independently associated with reduced cancer-specific (HR 0.68; $p = 0.003$) and all-cause mortality (HR 0.69; $p < 0.0001$).
Conclusion In this surgical population, FH of prostate cancer was associated with lower-risk disease at diagnosis, more favorable pathology at RP, and significantly better cancer-specific and overall survival. These results may be utilized for patient counseling.

Keywords Localized prostate cancer · Family history · Oncologic outcomes · Radical prostatectomy

Abbreviations

FH	Family history
PCa	Prostate cancer
RP	Radical prostatectomy
IQR	Interquartile range
PSA	Prostate-specific antigen
PFS	Systemic progression-free survival
BCR	Biochemical recurrence
CSM	Cancer-specific mortality
ACM	All-cause mortality
PLCO	Prostate, lung, colorectal, and ovarian

Introduction

In 2015, it is estimated that 220,800 men in the USA will be diagnosed with prostate cancer (PCa) and 27,540 will die of the disease [1]. Family history (FH) is an established risk factor for the diagnosis of prostate cancer [2–5]. Indeed, a first-degree relative with PCa has been found to double an individual's relative risk of diagnosis, and this risk increases further with the number, degree, and age of onset of affected family members [4, 5]. Recent studies in PSA screened populations have noted that FH is likewise associated with increased prostate cancer incidence [6, 7] and mortality [6].

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However, the impact of FH on oncologic outcomes, particularly following definitive local therapy, has not been well established [2, 8–11]. While some groups have noted an adverse association of FH with survival outcomes [2], other studies have not found similar results [8–16]. The contemporary association of FH with oncologic outcomes following local therapy may in fact be influenced by early detection and stage migration related to PSA screening. As such, we evaluated the association of FH of prostate cancer with clinicopathologic and oncologic outcomes among patients treated with radical prostatectomy.

Materials and methods

Following Institutional Review Board approval, we reviewed our institutional Prostatectomy Registry to identify 20,167 patients who underwent RP between 1987 and 2010 at Mayo Clinic. From this, 368 patients were not used because their surgery was not RP (either open or laparoscopic), there were 844 patients dropped because they were foreigners without guarantee of follow-up, there were 1991 patients with preoperative treatment that were not used. There were 209 patients dropped without family history information and 272 patients were not considered because they did not give authorization to use their records, finally 11 patients clinical T-stage 4 or with clinical positive nodes were not used. This left a cohort of 16,472 patients.

A positive FH was defined here as the presence of one or more first-degree relatives (father, brother, or son) diagnosed with prostate cancer prior to patient diagnosis. Additional clinicopathologic features recorded included age at surgery, year of surgery, body mass index (BMI), prostate volume, preoperative PSA, clinical tumor stage according to the American Joint Committee on Cancer 2010 staging, D'Amico risk group [17], pathologic TNM stage, Gleason score at RP, surgical margin status, tumor volume, and receipt of adjuvant as well as salvage radiotherapy and androgen deprivation therapy.

Multiple surgeons performed RP using standard techniques. Postoperative follow-up, including physical examination and serum PSA measurement, was not standardized given the retrospective nature of the cohort, but was generally performed quarterly for the initial 2 years, semiannually for the next 2 years, and annually thereafter. BCR was defined as a single postoperative PSA of 0.4 ng/ml or greater [18, 19]. For men followed elsewhere, the Prostatectomy Registry monitors outcomes annually by correspondence.

Continuous features were summarized with medians and interquartile ranges (IQRs), while categorical features were summarized with frequency counts and percentages. Survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariable associations of clinicopathologic features with biochemical recurrence (BCR), systemic progression-free survival (PFS), cancer-specific mortality (CSM), and all-cause mortality (ACM) were evaluated using Cox proportional hazards regression models. Two Cox models were constructed: one limited to preoperative features and another that included postoperative features as well. Results are summarized with the hazard ratios (HR) and 95 % confidence intervals (CI). Survival was estimated from the date of surgery to the date of BCR, death, or last follow-up. Statistical analysis was performed using SAS software package (SAS Institute, Inc.: Cary, NC). All tests were two-sided, with $p < 0.05$ considered statistically significant.

Results

A total of 16,472 patients with cT1-3N0 prostate cancer underwent RP and were included in the study. Of these, 5323 (32.3 %) had a FH of prostate cancer. Clinicopathologic features, stratified by FH of prostate cancer, are presented in Table 1. As can be seen, patients with a FH of prostate cancer were younger (median age 62.0 vs. 64.0 years; $p < 0.0001$) and more likely to have low-risk disease by D'Amico criteria (47.7 vs. 43.0 %; $p < 0.0001$) than those without a FH of PCa. Median follow-up after RP was 9.9 years (IQR 5.9, 15.5), during which time 4484 men experienced BCR, 1050 men experienced systemic progression, and 4430 died, including 558 who died of prostate cancer.

At RP, patients with FH of prostate cancer were found to have significantly more favorable pathologic findings than patients without a FH (Table 2). Specifically, men with FH had a lower pathologic Gleason score ($p = 0.001$) and a lower prevalence of seminal vesicle invasion (8.1 vs. 11.2 %; $p < 0.0001$), extracapsular extension (20.7 vs. 25.4 %; $p < 0.0001$), and lymph node-positive disease (3.4 vs. 4.7 %, $p = 0.0006$). After adjusting for relevant clinicopathologic features, a FH of PCa remained independently associated with a lower likelihood of non-organ-confined disease at surgery (OR: 0.84; $p = 0.0007$) (Table 3).

Next, we examined oncologic outcomes stratified by FH of prostate cancer (Figs. 1, 2, 3). Notably, we determined that men with FH of prostate cancer had better 10-year BCR (73 vs. 71 %; $p = 0.004$), CSS (99 vs. 97 %; $p < 0.001$), and OS (92 vs. 85 %, $p < 0.001$) than men without FH. Two separate multivariate models were constructed to further evaluate the association of FH with survival outcomes. In a multivariable model restricted to preoperative variables (Table 4), we found that FH was independently associated with significantly decreased risks of systemic progression (HR 0.80; $p = 0.008$), CSM (HR 0.62; $p = 0.0003$), and

Table 1 Clinical characteristics stratified by family history

	Overall Cohort ($N = 16,472$)	No family history ($N = 11,149$)	With family history ($N = 5323$)	p value
Median age at surgery (IQR)	63.0 (58.0, 68.0)	64.0 (58.0, 68.0)	62.0 (56.0, 67.0)	<0.0001
Median BMI at surgery (kg/cm^2) (IQR)	27.6 (25.4, 30.2)	27.7 (25.4, 30.2)	27.6 (25.4, 30.2)	0.72
Median prostate volume (cm^3) (IQR)	33.0 (25.2, 45.4)	33.0 (25.2, 45.4)	33.0 (25.2, 45.1)	0.30
Median preoperative PSA (ng/ml) (IQR)	6.1 (4.3, 9.5)	6.2 (4.3, 9.7)	6.0 (4.2, 9.2)	0.001
Clinical stage				<0.0001
cT1	7679 (46.9 %)	5005 (45.2 %)	2674 (50.6 %)	
cT2	7899 (48.3 %)	5494 (49.6 %)	2405 (45.5 %)	
cT3	782 (4.8 %)	575 (5.2 %)	207 (3.9 %)	
Biopsy Gleason score				<0.0001
≤6	9668 (69.7 %)	6400 (68.7 %)	3268 (71.8 %)	
7	3403 (24.5 %)	2322 (24.9 %)	1081 (23.8 %)	
8–10	796 (5.7 %)	594 (6.4 %)	202 (4.4 %)	
D'Amico risk group				<0.0001
Low risk	6509 (44.5 %)	4243 (43.0 %)	2266 (47.7 %)	
Medium risk	4570 (31.3 %)	3127 (31.7 %)	1443 (30.4 %)	
High risk	3534 (24.2 %)	2491 (25.3 %)	1043 (21.9 %)	
Adjuvant radiation treatment	664 (4.0 %)	468 (4.2 %)	196 (3.7 %)	0.12
Adjuvant hormonal treatment	1729 (10.5 %)	1214 (10.9 %)	515 (9.7 %)	0.02
Salvage radiation treatment	2046 (12.4 %)	1396 (12.5 %)	650 (12.2 %)	0.57
Salvage hormonal treatment	2287 (13.9 %)	1602 (14.4 %)	685 (12.9 %)	0.009
Median follow-up[a] (years) (IQR)	9.9 (5.9, 15.5)	9.6 (5.9, 15.2)	10.5 (6.2, 16.3)	<0.0001

[a] Among those alive at last follow-up

Table 2 Pathologic characteristics stratified by family history

	Overall Cohort ($N = 16,472$)	No family history ($N = 11,149$)	With family history ($N = 5323$)	p value
Pathological Gleason score				0.001
≤6	9697 (60.6 %)	6440 (59.7 %)	3257 (62.5 %)	
3 + 4	3931 (24.6 %)	2634 (24.4 %)	1297 (24.9 %)	
4 + 3	1266 (7.9 %)	885 (8.2 %)	381 (7.3 %)	
8–10	1108 (6.9 %)	831 (7.7 %)	277 (5.3 %)	
Pathologic tumor stage				<0.0001
pT2	12,622 (76.8 %)	8381 (75.3 %)	4241 (79.8 %)	
pT3a	2125 (12.9 %)	1492 (13.4 %)	633 (11.9 %)	
pT3b	1631 (9.9 %)	1209 (10.9 %)	422 (7.9 %)	
pT4	54 (0.3 %)	39 (0.4 %)	15 (0.3 %)	
Median tumor volume (cm^3) (IQR)	1.5 (0.5, 4.0)	1.6 (0.5, 4.2)	1.4 (0.4, 3.9)	0.006
Positive surgical margin (%)	4465 (27.1 %)	3051 (27.4 %)	1414 (26.6 %)	0.28
Median no. nodes removed (IQR)	8.0 (5.0, 11.0)	8.0 (5.0, 12.0)	7.0 (5.0, 11.0)	0.0001
pN+ (%)	701 (4.3 %)	520 (4.7 %)	181 (3.4 %)	0.0006

ACM (HR 0.68; $p < 0.0001$). Addition of FH to this preoperative model increased the c-index from 0.77 to 0.78 for CSM and 0.66 to 0.67 for ACM. In a multivariable model inclusive of pre- and postoperative variables (Table 5), FH remained associated with significantly decreased CSM (HR 0.68; $p = 0.003$) and ACM (HR 0.69; $p < 0.0001$).

Table 3 Multivariate logistic regression assessing likelihood of non-organ-confined disease in total cohort (pT3, pT4, and/or N+)

	OR	95 % CI		*p* value
Year of surgery	0.96	0.95	0.97	<0.0001
Age at surgery	1.03	1.02	1.03	<0.0001
BMI at surgery	1.03	1.02	1.04	<0.0001
Prostate volume	0.99	0.99	1.00	<0.0001
D'Amico risk group	3.02	2.84	3.21	<0.0001
Family history	0.84	0.76	0.93	0.0007

Discussion

We examined here the association of FH with clinicopathologic and oncologic outcomes in a large cohort of men treated with RP in the PSA era with long-term follow-up. We found that men with a FH of prostate cancer were more likely to have smaller, lower-grade tumors, and were less likely to have adverse pathologic features at surgery. Perhaps most notably, FH of prostate cancer was independently associated with reduced CSM and ACM.

Family history has been identified as one of the strongest risk factors for prostate cancer. Indeed, a first-degree relative with PCa doubles an individual's relative risk of diagnosis, and this risk increases with the number, degree, and age of onset of affected family members [4, 5]. Overall, approximately one-third of patients diagnosed with PCa report a positive FH [20, 21]. However, other than an earlier age of diagnosis, the impact of FH on clinicopathologic characteristics and oncologic outcomes remains controversial.

That is, several studies have reported no differences in pathologic features between patients with and without a PCa FH [8, 9, 12], while others have suggested that FH is associated with lower-grade tumors [13, 22–24] and organ-confined disease [25]. In particular, a recent analysis from the Finnish Prostate Cancer Screening Trial found that men with a FH of PCa were more likely to have localized, lower-grade tumors than men without a FH [7]. Moreover, Sacco et al. [16], in a retrospective series of 606 cases, noted a lower frequency of positive margins ($p = 0.01$), perineural infiltration ($p = 0.03$), and positive lymph nodes ($p = 0.005$) among patients with a FH of prostate cancer.

An analysis of data from the prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial found men with a FH of PCa had a both a higher incidence of prostate cancer (16.9 vs. 10.8 %; $p < 0.01$) and prostate cancer-specific mortality (0.56 vs. 0.37 %; $p < 0.01$) compared to men without a family history [6]. However, men with a FH of PCa in the screening arm of the trial had a lower PCa-specific mortality compared to men with a FH of PCa in the usual care arm (0.36 vs. 0.77 %, respectively; $p = 0.06$) [6]. Importantly, as the PLCO is a screening trial, it does not include data about treatment modalities and outcomes among those diagnosed with PCa.

Men who undergo RP for definitive local treatment represent a distinct population from the broader population diagnosed with prostate cancer. Accordingly, the association of FH with oncologic outcomes following RP merits

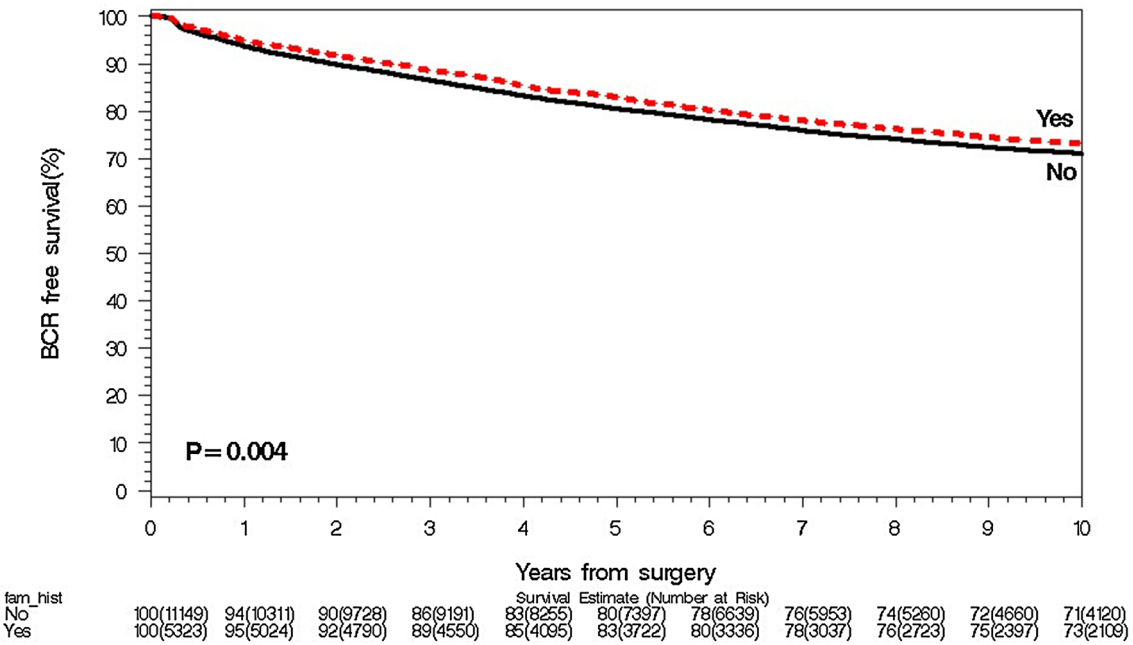

Fig. 1 Ten-year biochemical recurrence-free survival of patients with and without a FH of PCa after RP

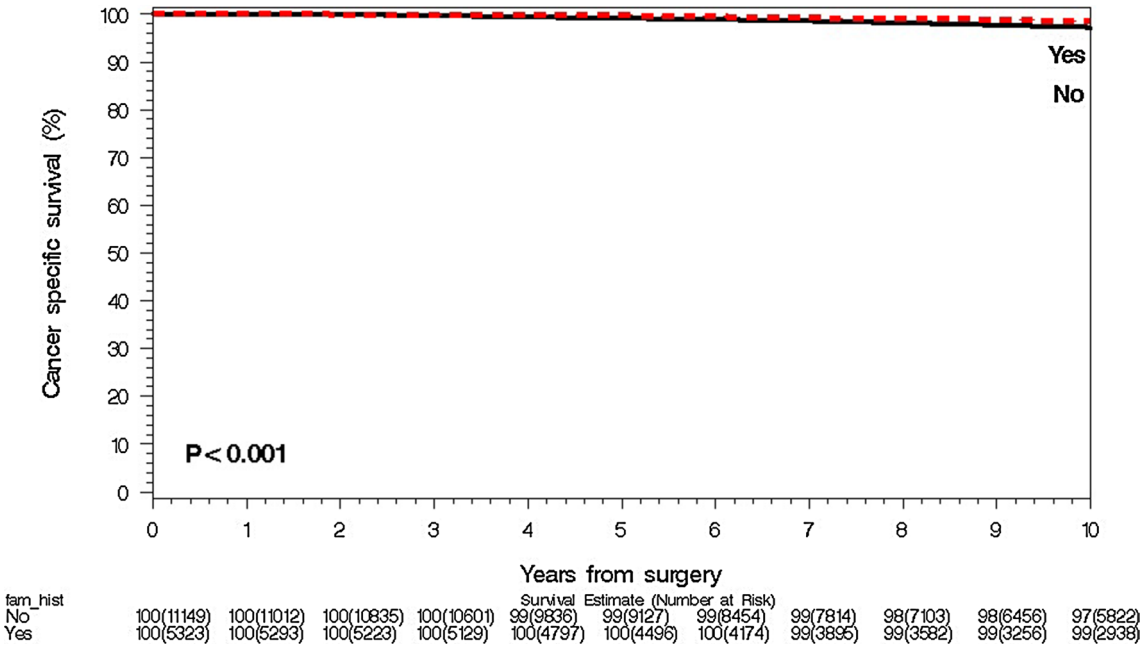

Fig. 2 Ten-year cancer-specific survival of patients with and without a FH of PCa after RP

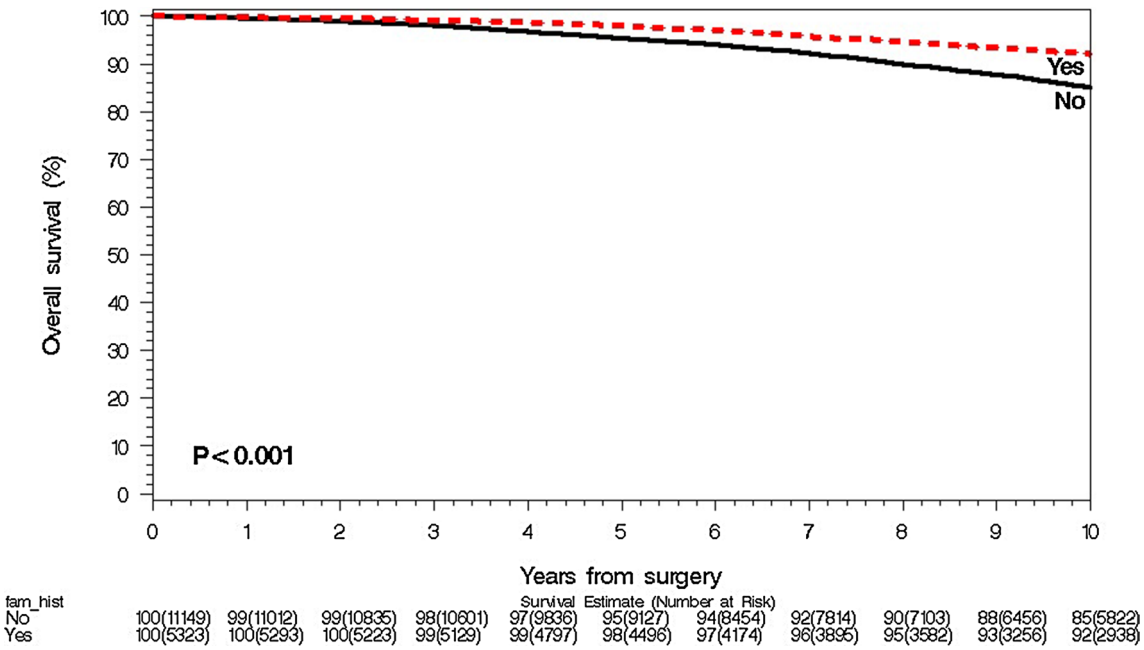

Fig. 3 Ten-year overall survival of patients with and without a FH of PCa after RP

separate investigation. Interestingly, Kupelian et al. [2, 26] reported a worse 5-year BCR rate for patients with a positive FH regardless of treatment modality. On the other hand, subsequent studies have found no evidence of inferior oncologic outcomes among men with a FH of PCa treated with RP [8, 14–16, 27]. In fact, Lee et al. [13] reported improved disease-free survival rates for those with a FH at both 5 and 10 years compared to those without a FH (86 and 80 vs. 73 and 66 %, respectively; $p = 0.01$).

Meanwhile, Siddiqui et al. [10] subdivided 3560 patients treated with RP at Mayo Clinic between 1987 and 1997 into three groups for analysis: those with familial prostate cancer (FPC), defined as at least 1 first-degree relative with PCa; those with hereditary prostate cancer (HPC), defined

Table 4 Cox multivariate model based on preoperative variables

	Systemic progression		Prostate cancer death		All-cause mortality	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Year of surgery	1.05 (1.03–1.07)	<0.0001	0.99 (0.97–1.02)	0.61	1.00 (0.99–1.01)	0.81
Age at surgery	1.01 (0.99–1.02)	0.42	1.03 (1.02–1.05)	0.0003	1.09 (1.08–1.09)	<0.0001
BMI at surgery	1.06 (1.04–1.07)	<0.0001	1.06 (1.03–1.09)	<0.0001	1.03 (1.02–1.04)	<0.0001
Prostate volume (Log_2)	1.06 (0.96–1.19)	0.26	0.99 (0.85–1.15)	0.84	0.93 (0.88–0.98)	0.008
D'Amico risk group	3.23 (2.90–3.60)	<0.0001	2.96 (2.52–3.49)	<0.0001	1.31 (1.24–1.37)	<0.0001
Family history	0.80 (0.68–0.94)	0.008	0.62 (0.48–0.81)	0.0003	0.68 (0.63–0.75)	<0.0001
c-stat (without family history)	0.77		0.77		0.66	
c-stat (with family history)	0.77		0.78		0.67	

Table 5 Cox multivariate model, inclusive of postoperative variables

	Systemic progression		Prostate cancer death		All-cause mortality	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Year of surgery	1.02 (1.00–1.04)	0.05	0.95 (0.93–0.98)	0.0008	1.00 (0.98–1.01)	0.34
Age at surgery	0.99 (0.98–1.00)	0.13	1.02 (1.00–1.03)	0.065	1.09 (1.08–1.10)	<0.0001
BMI at surgery	1.03 (1.01–1.05)	0.003	1.03 (1.01–1.06)	0.02	1.03 (1.02–1.04)	<0.0001
Prostate volume (Log_2)	1.12 (1.00–1.26)	0.06	1.02 (0.86–1.20)	0.86	0.94 (0.89–1.00)	0.03
Preoperative PSA (Log_2)	1.00 (0.93–1.07)	0.93	0.94 (0.85–1.04)	0.20	1.04 (1.00–1.08)	0.08
Family history	0.87 (0.74–1.02)	0.09	0.68 (0.53–0.88)	0.003	0.69 (0.63–0.75)	<0.0001
Pathologic tumor stage (ref = pT2)						
pT3a	1.88 (1.54–2.29)	<0.0001	1.70 (1.26–2.29)	0.0005	1.20 (1.08–1.34)	0.0008
pT3b/T4	2.59 (2.10–3.21)	<0.0001	2.54 (1.87–3.45)	<0.0001	1.25 (1.09–1.42)	0.001
Pathologic Gleason score (ref = 6)						
Gleason 7	4.41 (3.52–5.52)	<0.0001	3.86 (2.80–5.33)	<0.0001	1.20 (1.10–1.32)	<0.0001
Gleason 8–10	9.21 (7.07–11.98)	<0.0001	9.39 (6.47–13.61)	<0.0001	1.67 (1.45–1.93)	<0.0001
Positive surgical margin	1.06 (0.89–1.252)	0.51	1.24 (0.97–1.58)	0.09	1.03 (0.94–1.13)	0.53
Tumor volume (Log_2)	1.25 (1.20–1.32)	<0.0001	1.32 (1.22–1.43)	<0.0001	1.04 (1.02–1.07)	0.0001
pN+	1.37 (1.06–1.79)	0.02	1.78 (1.24–2.55)	0.002	1.27 (1.05–1.54)	0.01
Adjuvant RT	0.99 (0.76–1.28)	0.94	0.59 (0.39–0.90)	0.02	0.93 (0.79–1.11)	0.43
Adjuvant HT	0.67 (0.54–0.84)	0.0005	0.65 (0.47–0.89)	0.008	0.85 (0.74–1.00)	0.03

as nuclear families with 3 cases of prostate cancer, families with prostate cancer in each of 3 generations and families with 2 men diagnosed before age 55 year; and sporadic prostate cancer (SPC). Other than increased preoperative PSA levels in HPC patients ($p = 0.04$), no differences in clinicopathologic or oncologic outcomes were observed following RP [10]. Similarly, Heck et al. [12] stratified 8041 German patients with PCa by D'Amico risk group and similarly found no differences between those with SPC, FPC or HPC with the exception of an earlier age of diagnosis for those with a FH. In a subsequent analysis of 7690 German registry patients, Brath et al. [27] identified a trend toward worse oncologic outcomes after RP for patients without a FH of PCa compared to those with a FH of PCa; however, the study lacked statistical power to detect a significant difference.

To our knowledge, we provide here the largest study to date evaluating survival among men with FH of prostate cancer treated with RP. While the present results differ somewhat from previous data reported from our institution [10], several potential explanations for this discrepancy exist. For one, Siddiqui et al. [10] only included men from 1987 to 1997 and therefore had fewer patients than our current series. Moreover, as described above, the prior study classified patients into three groups; hereditary, familial, and sporadic [10]. Thus it is possible that the subgroups may also have in part masked the ability to discern a significant association with outcomes.

Indeed, our series benefits from the long-term follow-up and large sample size. As such, our study may have determined a statistically significant difference in outcomes where prior studies did not due to the larger sample size here, with greater resulting statistical power [10, 12, 27]. Nevertheless, the absolute differences in 10-year CSS and OS were relatively small and may be of uncertain clinical relevance. The favorable oncologic outcomes (decreased CSM) among men with a FH of PCa may be the result of a more aggressive screening approach in these patients, as a FH of PCa has been recognized as a risk factor for diagnosis, and thus screening is advocated for such patients. Indeed, the improved CSS may thereby be an indirect reflection of the benefit of pCa screening. Meanwhile, the noted decrease in ACM for men with a FH of PCa may be an extension of the decrease in CSM, and/or may be a function of increased overall health awareness among these men, leading to for example earlier screening and treatment of conditions such as cardiovascular disease, diabetes, and colorectal cancer that may decrease the mortality from these conditions. We must acknowledge as well that, given the retrospective nature of our study, the findings may also be due to residual unmeasured confounding.

We recognize that out study was limited by its retrospective design and by the self-reported ascertainment of FH. FH information has multiple challenges, including recall bias, adoption, education, and the number of male family members [28]. We did not have available the number of affected family members, or the age at diagnosis of pCa in family members. In addition, there is inherent selection in a surgical cohort, and it is possible that those selected for surgery may have had more favorable disease features; as such, our findings cannot be generalized to all PCa patients. We did not have information on the number of prior PSAs in the patients here prior to diagnosis. Additionally, we did not separate patients into familial and hereditary PCa; therefore, these findings may not be applicable to patients with hereditary PCa. We also acknowledge potential unmeasured confounding, as we were unable to adjust for features such as lymphovascular invasion and/or the extent of extraprostatic extension in our analysis. Finally, our cohort is predominately Caucasian, and thus the prognostic significance of FH in other races remains to be determined.

In conclusion, in this surgical population, men with a FH of prostate cancer had clinically lower-risk disease at presentation, more favorable pathology at RP, and significantly better cancer-specific and overall survival compared to those without FH of PCa. These results may be utilized for patient risk stratification and counseling.

Authors' contribution Westerman was involved in protocol/project development and manuscript writing/editing. Gershman wrote/edited the manuscript. Karnes and Thompson edited the manuscript. . Rangel was involved in data analysis and data collection or management. Boorjian was involved in protocol/project development and manuscript editing.

Compliance with ethical standards

Ethical standard We have adhered to the rules of good scientific practice and ethics. This manuscript is not under simultaneous consideration and has not been previously published in whole or part. All authors made substantial contributions to the creation of this manuscript as listed above, and all have given consent for manuscript submission.

Conflict of interest The authors declare no conflict of interest.

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