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Does Family History Of Prostate Cancer Affect Outcomes Following Radiotherapy?

Hilary Bagshaw, MD¹, Karen Ruth, MS², Eric M. Horwitz, MD¹, David Y.T. Chen, MD³, and Mark K. Buyyounouski, MD, MS⁴

¹Radiation Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania

²Biostatistics, Fox Chase Cancer Center, Philadelphia, Pennsylvania

³Surgical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania

⁴Radiation Oncology, Stanford University, Stanford, California

Abstract

Objective—To examine family history (FH) as a prognostic factor following radiotherapy (RT).

Materials and Methods—Between 1989 and 2007, 1,711 men with clinically localized prostate cancer and complete family history who had received RT (median RT dose = 74 Gy) without androgen deprivation therapy were analyzed. FH was defined as any prostate cancer in a first degree relative. For the biochemical failure (BF) outcome, this sample size has 85% power to detect a hazard ratio of 1.56 for positive versus negative FH.

Results—With a median follow-up of 71 months, there was no significant difference in the distribution of Gleason score (GS) or prostate specific antigen (PSA) based on FH. A positive FH was not an independent predictor of BF, distant metastasis (DM), prostate cancer specific mortality (PCSM), or overall mortality (OM) in Cox proportional multivariable analysis. On further analysis in a Cox proportional multivariable analysis, men with two or more first degree relatives with prostate cancer had a significantly higher likelihood of BF and DM than those with no FH, although there was no difference in PCSM or OM. Men with a positive FH (23%) were more likely to be younger, have a lower PSA, and non-palpable disease. There was no interaction between a positive FH and neither race nor treatment era (pre-PSA vs. PSA era).

Conclusions—A positive FH is not a prognostic factor following RT and should not alter standard treatment recommendations. Patients with two or more first degree relatives with prostate cancer had a higher likelihood of BF and DM, but there was no effect on survival. There was no interaction between a positive FH and African American race or treatment era. A positive FH was

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Corresponding Author: Mark K Buyyounouski, MD, MS, Associate Professor, Director, Genitourinary Cancers, Stanford University, Department of Radiation Oncology, 875 Blake Wilbur Dr, MC 5847, Stanford, CA. 94305-5847, Phone: 650-725-2736, Fax: 650-725-8231, mark.buyyounouski@stanford.edu, Administrative Assistant: Michelle Jin qjin27@stanford.edu.

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however, associated with more favorable PSA values and T-stage that may be the result of earlier screening.

Keywords

Prostate Cancer; Radiotherapy; Family History

INTRODUCTION

A positive family history (FH) of prostate cancer is feared to portend a poorer outcome following treatment. The traditional pretreatment risk factor used to establish prognosis is serum prostate specific antigen (PSA), Gleason score (GS), and tumor stage (T-stage). Combinations of these factors, as used in the American Joint Commission on Cancer (AJCC)¹ and National Comprehensive Cancer Network (NCCN)², group patients according to the risk of the recurrence, which in turn aids in providing treatment recommendations. A positive FH, however, may represent one or more unidentified negative prognostic factors not represented by PSA, GS, and T-stage.

There are few studies that examine the impact of a positive FH on prognosis following radiotherapy for prostate cancer and the results are conflicted.³⁻⁶ The Cleveland Clinic was the first to report a the detrimental effect of a positive family history of prostate cancer on recurrence following either surgery or RT.³ These results however, were unconfirmed in other series.⁴⁻⁶ Kupelian et al. later reported that the era of treatment might explain the conflicting results where a positive FH may have been important in the pre-PSA but these results have not be confirmed. Furthermore, there is a question as to whether African American race and positive family history might predict for worse outcome after definitive radiation therapy for prostate cancer.⁷ Investigators from the University of Michigan observed combined African American race and positive family history was found to be a significant predictor of worse freedom from relapse rates.⁶

More clinical data are needed to confirm or refute these conflicting findings. The importance of a family history on prognosis may impact an estimated 36,133 men with a familial inheritance pattern of prostate cancer in the United States during 2011 assuming a prevalence of 15%.^{8,9} These men are at risk of receiving more aggressive therapy, such as combination radiotherapy and hormonal therapy, with the belief that a positive family history is detrimental without clear evidence that the prognosis is worse.

The purpose of this study was to determine if a positive family history is a negative prognostic factor independent of PSA, GS and T-stage in the largest and most mature series of men treated with definitive RT. We also seek to determine the influence of treatment era (i.e. pre-PSA era vs. PSA era) and race (i.e. African American) on the prognostic importance of FH.

MATERIALS AND METHODS

Between 1989 and 2007, 1,711 men with clinically localized prostate cancer with a complete family history received RT alone (no androgen deprivation therapy) at Fox Chase Cancer

Center (Philadelphia, PA). Four hundred twenty-six men had been excluded due to missing family history data. All patients had information available regarding GS, T-stage, initial PSA (iPSA), RT dose, and family history. A positive first-degree FH was defined as prostate cancer in one or more first-degree relatives, consistent with prior studies.³⁻⁶ To assess prostate cancer FH burden, FH was further defined as zero, one, or two or more first-degree relatives on the maternal or paternal side of the family. An expanded definition of FH, defined as prostate cancer in one or more first or second degree relatives was also considered. Race was defined as white, black/African American, and other/unknown. The impact of the pre PSA era was evaluated by adjustment for treatment from 1989-1992 compared to 1993-2007.

Radiotherapy

The techniques used for 3D-CRT and IMRT have been previously described.^{10,11} Briefly, patients were immobilized supine in a thermoplastic cast and daily prostate localization was performed in all patients using either the B-type acquisition ultrasound, fiducial markers with electronic portal, computed tomography imaging, or radiofrequency beacons. The planning target volume included the prostate and 1 cm margin for 3D-CRT and 8 mm for IMRT, except posteriorly where the margin was less to enable better rectal sparing. The RT dose was prescribed such that 95% of the planning target volume received 100% of the prescribed dose. The median dose for patients treated with RT was 74 Gy (range: 70-80 Gy).

Patient evaluation and staging

All patients had a history and physical exam including digital rectal exam, pretreatment iPSA, and histologic confirmation of adenocarcinoma with a GS. Sixty eight percent of patients had computed tomography of the abdomen or pelvis while 81% had a bone scan to exclude metastasis. T-stage was established by palpation findings only, without upstaging using pathologic or radiographic information.

Statistical Analysis

The Kaplan-Meier product limit method was used to estimate survival functions for each endpoint by FH (positive vs negative), and differences in the curves were assessed using the log rank test. Cox proportional hazards methods were used for inferences about the relationship of time to endpoint with potential risk factors including FH, GS (2-6 vs 7 vs 8-10), T-stage (T1 vs T2 vs T3), iPSA (continuous), and RT dose (continuous). FH was modeled in three ways: positive vs negative based on FDRs, positive vs negative based on FDRs and SDRs, and to assess increased FH burden, as a categorical variable (0, 1 or 2+ FDRs). Endpoints included biochemical failure (BF, PSA nadir +2 ng/mL), distant metastasis (DM), prostate cancer specific mortality (PCSM), and overall mortality (OM). Men who did not have the endpoint were censored at their last PSA measurement (for BF) or their last available follow-up date. Potential risk factors were considered separately and in a multivariable model for each endpoint. The interaction of race and FH, and PSA era and FH were examined in separate analyses. A p-value <0.05 was considered significant. For the BF outcome, this sample size has 85% power to detect a hazard ratio of 1.56 for a positive FH versus negative FH. All analyses were carried out with SAS 9.2.

RESULTS

Three hundred and eighty six men (23%) had a positive family history for prostate cancer in a first-degree relative. Various patient and treatment-related characteristics are shown in Table 1 based on FH status. Men with a positive FH were more likely to be younger (median age: 67.4 vs. 68.5, Wilcoxon $p = 0.05$), have a lower iPSA (median iPSA: 6.0 vs. 6.4 ng/mL, Wilcoxon $p = 0.04$), have non-palpable disease (T1: 67% vs. 58%, T2 32% vs. 38%, T3: 2% vs. 4%; Chi Square $p = 0.004$), and have received IMRT (54.4% vs 409%, $p = 0.0002$).

With a median follow-up of 71 months (range: 1 to 215), there were 264 (15.5%) events of BF, 63 (3.7%) DM, 28 (1.6 %) PCSM, and 205 (12.0%) OM.

Table 2 shows the univariate analysis. A positive FH was not associated with an increased risk of BF, DM, PCSM, or OM. Figures 1-4 illustrate estimates of freedom from BF (Figure 1), DM (Figure 2), PCSM (Figure 3) and OM (Figure 4), based on FH status.

Table 3 shows multivariable analysis results. A positive FH was not an independent predictor of BF, DM, PCSM, or OM. To assess the importance of treatment era, the same model was examined separately in the pre-PSA and PSA eras. Treatment era did not impact the results and a positive FH remained non-significant in both analyses (data not shown). Of patients with a positive FH, 84% had 1 first degree relative with prostate cancer, and 16% had 2 or more relatives with the disease. Those patients with two or more FDR affected had a higher likelihood of developing BF, with a hazard ratio estimate of 1.87 (95% CI 1.09-3.23, $p=0.024$) on multivariable analysis (results for covariates not shown as they are similar to Table 2 results). This group of patients with two or more FDR affected also had a higher likelihood of developing DM, with a hazard ratio estimate of 2.71 (95% CI 0.97-7.62, $p=0.058$). The number of affected relatives had no impact on PCSM or OM.

The proportion of patients with a positive FH differed based on race, and was 32% for African American, 21% for white and, 34% for other ($p < 0.0006$). However, there was no interaction between a positive FH and race. Race was not an independent predictor of BF ($p = 0.96$) or OM ($p = 0.83$; DM and PCSM not evaluated due to small patient numbers). Within the African American group, the HR for FH was 1.24 ($p = 0.58$) for BF. For white men, the HR for FH is 1.08 ($p = 0.64$) for BF.

An additional analysis was performed to examine the effect of FH in second degree relatives on outcomes. When FH was defined as a first or second degree relative on either the maternal or paternal side with history of prostate cancer, the percent of patients with FH rose from 23% (first-degree relatives only) to 26% with the new definition. On univariate and multivariable analyses positive FH was not associated with an increased risk of BF, DM, PCSM, or OM (data not shown).

DISCUSSION

The data presented above suggest that a positive family history is not a reliable prognostic factor for outcomes following radiotherapy for prostate cancer. A greater number of affected first degree relatives may portend an increased risk of BF or DM, although there is no effect

on survival outcomes. The significance of these results is that patients should not be advised to seek more intensive or aggressive therapies based solely on a family history of prostate cancer.

This study is one of the largest examining the prognostic significance of family history in men with prostate cancer. Twenty-three percent of patients had a positive family history based on FDRs. These patients tended to be younger, have a lower iPSA, and non-palpable disease compared to those patients without a family history. The association of a positive family history to more favorable iPSA values and T-stage is likely the result of more aggressive screening. It is not difficult to imagine that a patient with a family history of prostate cancer would promptly have a prostate biopsy if his PSA or DRE raised any suspicion for cancer.

In 1997, Kupelian et al., from the Cleveland Clinic, were the first to report that the presence of a family history of prostate cancer correlates with treatment outcome.³ In that study of 1,038 men treatment with surgery or radiation, where a positive family history ($n = 110$, 11%) was defined as any first-degree relative with prostate cancer, the 5-yr FFBF (BF defined as two consecutive PSA rises after PSA nadir) rate was 52% for men with a negative family history and 29% for a positive family history. This association was independent of iPSA, biopsy GS, clinical T-stage, treatment modality, and age. The authors concluded that familial prostate cancer might have a more aggressive nature not adequately described by traditional clinical and pathologic factors.

Hanlon and Hanks attempted to confirm these initial results at Fox Chase in 920 men treated with RT between 1987 and 1997.⁴ A positive family history ($n = 97$, 11%) was similarly defined as one or more first-degree relatives with prostate cancers. However, there was no difference in 5-yr FFBF (BF defined as two consecutive PSA rises to a level > 1.5 ng/mL) based on family history status (65% for negative vs. 61% for positive, $p = 0.3$). Adjusting for RT dose, T-stage, iPSA, and GS did not alter the results. Differences in the patient population, follow-up duration, treatment method, and sample size were potential explanations for these discordant results.

Hanus, et al. later studied 1,164 men treated with RT between 1987 and 1996 at MD Anderson Cancer Center.⁵ A positive family history was similarly defined ($n = 148$, 13%) and there was no difference in 6-yr FFBF (BF defined as two or more consecutive rises) between men with a negative (58%) or positive family history (52%). Metastasis-free survival was also examined as an endpoint but, no association with family history was found.

Ray et al. from the University of Michigan also examined this controversy in 538 men treated with radiotherapy between 1983 and 2001, to find no difference in 5-yr FFBF (BF defined as two consecutive PSA rises to a level > 1.5 ng/mL) rates between negative and positive family history ($n = 97$, 18%).⁶ Furthermore, adjusting for age, T-stage, GS, iPSA, race, androgen deprivation therapy use, and RT dose did not alter the results. However, combined African American race and positive family history was found to be a significant predictor of worse freedom from relapse rates. The authors speculated that outcomes

between the two groups are equivalent because the final genetic pathways to oncogenesis may be similar. And regarding the influence of race, further study will be needed to determine if African American race and positive family history might predict for worse outcome after definitive radiation therapy for prostate cancer.

In 2006, Kupelian et al. re-examined the Cleveland Clinic experience to learn that the importance of family history was era-dependent.⁷ Two eras were defined: pre-PSA era (1986-1992) and the PSA era (1993-2002). A positive family history (n = 659, 16%) was associated with poorer 10-yr FFBR in the pre-PSA era (45 % vs. 34 %, $p = 0.2$) but not in the PSA era (61% vs. 67%). A positive family history was independently prognostic for BF (PSA > 0.2 ng/mL for surgery; three consecutive rises for RT) in the pre-PSA persisted in multivariable analysis, which corrected for year of therapy, age, clinical T-stage, iPSA, biopsy GS, treatment modality, and androgen deprivation therapy use, but not in the PSA era. The authors went one step further and validate the importance of a positive family history in the pre-PSA era in multivariable analysis using clinical disease free survival as the endpoint, defined as survival free of any local and/or distant disease detected either by physical exam, radiographic evaluation, or biopsy. A positive family history did not predict for clinical disease free survival in the PSA era.

The limitations of this study include its retrospective nature, which may not adequately account for unknown confounders of a positive FH. However, all the factors that the literature suggests are important were examined and no significant differences were found. Also, this study did not include brachytherapy but the Mount Sinai experience suggests that a positive FH is no more important after brachytherapy than external beam RT¹².

In conclusion, this study confirms that a positive FH is not associated with a higher risk of BF, DM, PCSM, or OM. This result was consistent in the pre-PSA and post-PSA era. Although this data shows that number of FDR with prostate cancer may affect BF and DM, there was no effect on survival outcomes. We were unable to identify an interaction between a positive FH and African American race. Standard treatment recommendations based on National Comprehensive Cancer Network or American Joint Committee on Cancer risk groupings, which utilize iPSA, GS, and T-stage, should not be modified based on a positive FH of prostate cancer.

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CLINICAL PRACTICE POINTS (Original Studies, Case Reports)

There have been conflicting reports as to the prognostic importance of a positive family history (FH) of prostate cancer in men treated with radiotherapy (RT). While the majority of studies have shown no effect of a positive family history, the experience from the Cleveland Clinic suggests that the era of treatment (i.e. pre-PSA vs. PSA era) may be the explanation. In this current study, we confirmed that a positive FH was not prognostic and there was no interaction with treatment era. The University of Michigan experience called to question a possible interaction between a positive FH and African American race however, this was unconfirmed in the current study. This study confirms what the majority of the literature has suggested, which is that a positive FH for prostate cancer is not prognostic following RT. A positive FH should not alter standard treatment recommendations based on National Comprehensive Cancer Network or American Joint Committee on Cancer risk groupings that utilize PSA level, Gleason score, T-stage for assign prognosis.

Figure 1.
Freedom from Biochemical Failure by Family History of Prostate Cancer, log rank p -value = 0.8

Figure 2.
Freedom from Distant Metastasis by Family History of Prostate Cancer, log rank p -value = 0.6

Figure 3.
Cause Specific Survival by Family History of Prostate Cancer, log rank p -value = 0.5

Figure 4.
Overall Survival by Family History of Prostate Cancer, log rank p -value = 0.14

Table 1
Demographic and treatment characteristics by Family History of Prostate Cancer

Characteristic	All (n = 1,711)		Positive FH (n=386)		Negative FH (n=1,325)		p- value *
	N	Percent	N	Percent	N	Percent	
Age							
Median (range)	68.2	(40.7-87.3)	67.4	(46.9-87.3)	68.5	(40.7-86.7)	0.050
Race							
White	1483	86.7	312	80.8	1171	88.4	0.0006
Black	190	11.1	61	15.8	129	9.7	
Unknown or Other	38	2.2	13	3.4	25	1.9	
Gleason Score							
2-6	1199	70.1	267	69.2	932	70.3	0.81
7	470	27.5	108	28.0	362	27.3	
8-10	42	2.5	11	2.9	31	2.3	
iPSA (ng/mL)							
Median (range)	6.3	(0.1-136)	6.0	(0.2-136)	6.4	(0.1-107)	0.041
<10 ng/mL	1315	76.9	305	79.0	1010	76.2	0.19
10-20 ng/mL	325	19.0	71	18.4	254	19.2	
>20 ng/mL	71	4.1	10	2.6	61	4.6	
T stage							
T1	1023	59.8	257	66.6	766	57.8	0.0035
T2	629	36.8	122	31.6	507	38.3	
T3/TX	59	3.4	7	1.8	52	3.9	
Technique							
Conformal	959	56.0	176	45.6	783	59.1	<0.0001
IMRT	752	44.0	210	54.4	542	40.9	
RT dose (cGy)							
Median (range)	7400	(7000-8000)	7600	(7000-8000)	7400	(7000-8000)	0.0002
Number of FDR with Prostate Cancer							
1			325	84.2			
2+			61	15.8			

Abbreviations: FH = family history; iPSA = initial pretreatment prostate specific antigen; IMRT = intensity modulated radiotherapy; RT = radiotherapy; FDR = first-degree relatives

* p-value from test comparing Positive FH and No FH groups. Medians were compared using Wilcoxon rank sum tests, and Chi-square tests were used to compare categorical variables.

Table 2
Univariate Analysis

Biochemical Failure					
Variable	Baseline	Group	HR	95% CI	p-value
Family History	Negative	Pos FH	1.04	0.78-1.38	0.81
Number FDR	0 FDR	1 FDR	0.93	0.67-1.28	0.65
		2+ FDR	1.68	0.98-2.89	0.06
Gleason Score	2-6	7	2.35	1.83-3.00	<0.0001
		8-10	2.11	1.03-4.30	0.041
T-Stage	T1	T2	1.71	1.33-2.21	<0.0001
		T3/TX	3.77	2.44-5.83	<0.0001
iPSA	Continuous		1.02	1.02-1.03	<0.0001
RT Dose	Continuous		1.00	0.95-1.04	0.8471
Distant Metastasis					
Variable	Baseline	Group	HR	95% CI	p-value
Family History	Negative	Pos FH	1.17	0.65-2.09	0.60
Number FDR	0 FDR	1 FDR	1.01	0.53-1.95	0.97
		2+ FDR	2.02	0.73-5.60	0.18
Gleason Score	2-6	7	3.55	2.15-5.87	<0.0001
		8-10	1.25	0.17-9.20	0.83
T-Stage	T1	T2	2.29	1.31-4.01	0.0037
		T3/TX	7.43	3.54-15.60	<0.0001
iPSA	Continuous		1.02	1.01-1.03	<0.0001
RT Dose	Continuous		1.05	0.95-1.15	0.34
Cause Specific Mortality					
Variable	Baseline	Group	HR	95% CI	p-value
Family History	Negative	Pos FH	1.34	0.57-3.17	0.50
Number FDR	0 FDR	1 FDR	1.37	0.55-3.41	0.50
		2+ FDR	1.19	0.16-8.88	0.86
Gleason Score	2-6	7-10	2.66	1.26-5.60	0.0099
T-Stage	T1	T2	1.68	0.74-3.99	0.24
		T3/TX	7.68	2.82-20.93	<0.0001
iPSA	Continuous		1.03	1.01-1.04	<0.0001
RT Dose	Continuous		0.97	0.84-1.12	0.68
Overall Mortality					
Variable	Baseline	Group	HR	95% CI	p-value
Family History	Negative	Pos FH	0.76	0.52-1.10	0.14
Number FDR	0 FDR	1 FDR	0.79	0.53-1.17	0.24
		2+ FDR	0.58	0.21-1.55	0.28
Gleason Score	2-6	7	1.44	1.07-1.93	0.015
		8-10	1.90	0.89-4.07	0.098
T-Stage	T1	T2	1.36	1.02-1.82	0.037

Biochemical Failure					
Variable	Baseline	Group	HR	95% CI	p-value
		T3/TX	2.15	1.30-3.55	0.0029
iPSA	Continuous		1.01	1.00-1.02	0.029
RT Dose	Continuous		0.93	0.88-0.99	0.016

Abbreviations: HR = hazard ratio; CI = confidence interval; OR = odds ratio; iPSA = initial pretreatment prostate-specific antigen; RT = radiation therapy; FH = family history; FDR = first-degree relative.

Table 3
Four Cox Proportional Hazards Multivariable Regression Models (one model for each endpoint) for positive versus negative FH

Variable	Comparison	Biochemical Failure			Distant Mets			Cause Specific Mortality			Overall Mortality		
		HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Family History	Positive vs Negative	1.09	0.81-1.45	0.58	1.33	0.73-2.41	0.35	1.67	0.68-4.11	0.26	0.81	0.55-1.18	0.26
Gleason Score	7 vs 2-6	2.57	1.97-3.40	<0.0001	3.26	1.90-5.60	<0.0001	2.94	1.33-6.50	0.0075	1.62	1.18-2.22	0.0027
T-Stage	8-10 vs 2-6	2.11	1.03-4.32	0.04	1.08	0.15-8.04	0.94	--			1.97	0.92-4.24	0.082
	T2 vs T1	1.4	1.08-1.82	0.013	1.82	1.02-3.22	0.041	1.36	0.56-3.31	0.50	1.22	0.90-1.64	0.20
PSA (ng/ml)	T3/T× vs T1	2.49	1.54-4.04	0.0002	5.36	2.43-11.83	<0.0001	5.63	1.86-17.01	0.0022	1.66	0.98-2.82	0.062
	Continuous	1.02	1.01-1.03	<0.0001	1.02	1.01-1.03	0.0012	1.02	1.01-1.04	0.0066	1.01	1.00-1.02	0.19
RT Dose (Gy)	Continuous	0.95	0.90-0.99	0.027	1.00	0.91-1.10	0.92	0.95	0.82-1.10	0.48	0.92	0.87-0.97	0.0032

Abbreviations: HR = hazard ratio; CI = confidence interval; OR = odds ratio; iPSA = initial pretreatment prostate-specific antigen; RT = radiation therapy; FH = family history; FDR = first-degree relative.
Notes: (1) For BF analyses, 1700 patients were included, and 11 patients without follow-up PSA values were excluded (2) For Cause Specific Mortality, Gleason Score was included as Gleason 7-10 vs Gleason 2-6, due to small cell sizes.