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Study Need and Importance: A family history (FH) of prostate cancer (PC) is a well-established risk factor for the development of PC, but an FH including other malignancies suggestive of a hereditary cancer syndrome (HCS; eg, breast, ovarian, and pancreatic cancer) is increasingly recognized as a risk factor as well. The role of a broader definition of FH as a risk factor for patients on active surveillance (AS) for PC has not been investigated. Here, we evaluate the impact of an expanded definition of FH on AS outcomes under the hypothesis that patients at high genetic risk based on their FH are at increased risk of disease progression.

What We Found: Using a novel scoring metric to capture multigeneration FH data among the 855 evaluable patients in our AS cohort, we found that patients with an FH suggestive of HCS (but not those with FH of PC alone) have an increased hazard of biopsy progression (see Figure) and progression to treatment on AS, compared to patients without such FH. However, the subset of patients with an FH suggestive of HCS who underwent delayed treatment after a period of AS did not experience higher rates of adverse pathology at prostatectomy or biochemical recurrence.

Limitations: Longer follow-up is required to assess late outcomes of AS. Data partially predate the introduction of MRI into our AS program. Our novel FH scoring metric also warrants validation in future studies. Furthermore, FH was not systematically obtained by a genetic counselor; therefore, differences in documenting FH could have resulted in observer bias.

Interpretation for Patient Care: Patients with an FH suggestive of HCS can still be safely offered AS but should be counseled about the higher risk of biopsy progression. These patients warrant closer monitoring compared to patients without a strong FH. Our data support the wider inclusion of an expanded definition of FH in counseling patients considering AS.

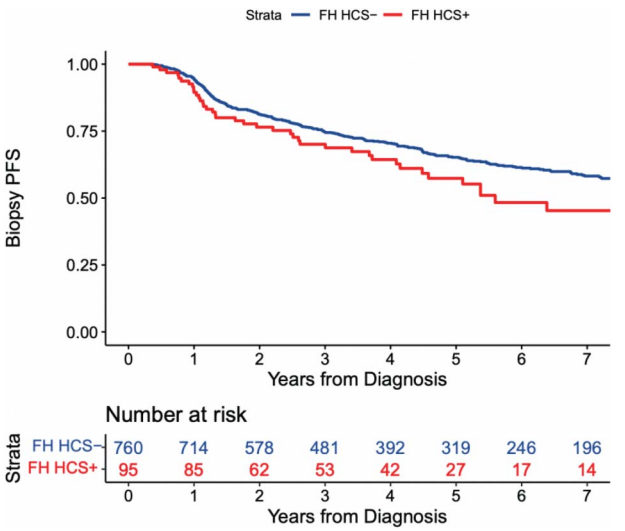

Figure. Kaplan-Meier curve of biopsy progression-free survival (PFS) for patients with vs without a strong family history (FH) suggestive of a hereditary cancer syndrome (HCS).

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Impact of an Expanded Definition of Family History on Outcomes of Active Surveillance for Prostate Cancer

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Purpose: Despite family history being an established risk factor for prostate cancer, the role of a broader definition of family history inclusive of not just prostate cancer but other genetically related malignancies has not been investigated in the active surveillance population. Here, we evaluate the impact of an expanded definition of family history on active surveillance outcomes.

Materials and Methods: Patients undergoing active surveillance for prostate cancer at Massachusetts General Hospital from 1997-2019 with detailed data available on family cancer history were identified. Primary outcome was biopsy progression-free survival, and secondary outcomes were treatment-free survival, adverse pathological features at prostatectomy, and biochemical recurrence after treatment. Statistical analyses were conducted using the Kaplan-Meier method and Cox regression.

Results: Among 855 evaluable patients, 300 (35.1%) patients had any family history of prostate cancer, and 95 (11.1%) had a family history of related malignancies suggestive of a hereditary cancer syndrome. Family history of prostate cancer alone was not associated with biopsy progression, whereas family history suggestive of a hereditary cancer syndrome was associated with a significantly

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Conflict of Interest: Jason A. Efstathiou: Advisory/Consulting: Blue Earth Diagnostics, Boston Scientific, AstraZeneca; Honorarium: Genentech; Advisory boards: Merck, Roviant Pharma, Myovant Sciences, Janssen, Bayer Healthcare. Eliezer M. Van Allen: Advisory/Consulting: Tango Therapeutics, Genome Medical, Genomic Life, Enara Bio, Janssen, Manifold Bio, Monte Rosa; Research support: Novartis, BMS; Equity: Tango Therapeutics, Genome Medical, Genomic Life, Syapse, Enara Bio, Manifold Bio, Microsoft, Monte Rosa; Patents: Institutional patents filed on chromatin mutations and immunotherapy response, and methods for clinical interpretation; intermittent legal consulting on patents for Foaley & Hoag; Editorial Boards: *JCO Precision Oncology*, *Science Advances*. Adam S. Feldman: Advisory/Consulting: Olympus, Vessi Medical; Research Funding: Convergent Genomics. Keyan Salari: Research Funding: Convergent Genomics.

Ethics Statement: This study received Institutional Review Board approval (IRB No. 2021P002912).

Publication History: This study was presented in part at the Society of Urologic Oncology Annual Meeting, December 3-5, 2020; Genitourinary Cancers Symposium, February 11-13, 2021; and the AUA Annual Meeting, September 10-13, 2021.

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increased risk of biopsy progression (HR 1.43, 95%CI 1.01-2.02), independent of other known clinicopathological risk factors in multivariable analysis. Similarly, family history suggestive of a hereditary cancer syndrome was associated with significantly lower treatment-free survival (HR 1.58, 95%CI 1.14-2.18) in multivariable analysis. No significant association was found between family history and adverse features on surgical pathology or biochemical recurrence.

Conclusions: An expanded family history suggestive of a hereditary cancer syndrome is an independent predictor of biopsy progression during active surveillance. Men with such a family history may still be offered active surveillance but should be counseled regarding the higher risk of disease progression.

Key Words: prostatic neoplasms; watchful waiting; prostate cancer, familial; neoplastic syndromes, hereditary

A family history (FH) of prostate cancer (PC) is a well-established risk factor for the development of PC.[1,2] There has been increasing recognition that FH of certain malignancies, such as breast, ovarian, and pancreatic cancer, also increases the risk of being diagnosed with PC, pointing to a shared genetic predisposition.[2-6] Indeed, inherited DNA repair-gene mutations (eg, *BRCA1/2*) result in a hereditary cancer syndrome (HCS) typified by an increased risk of forming breast, ovarian, prostate, and pancreatic cancers. The AUA and National Comprehensive Cancer Network (NCCN) guidelines now recommend germline genetic testing for patients with high-risk or metastatic PC and those with a strong FH suggestive of an HCS.[7,8] However, in clinical practice genetic testing for most patients yields negative results, as <5% of men with localized PC are estimated to harbor a pathogenic germline mutation in a known PC risk gene.[9] Nonetheless, such patients and their families often remain at elevated risk for PC and other associated malignancies, suggesting the presence of additional, yet to be identified genetic risk factors and/or shared environmental risk factors.[10] Thus, FH remains a potentially important tool that encompasses both shared genetic and environmental factors underlying PC risk.

While several germline DNA repair-gene mutations increase the risk of aggressive PC,[11,12] the extent to which a strong FH suggestive of an HCS may similarly increase the risk of high-grade PC is unknown. This information would be important to inform counseling of patients considering active surveillance (AS) for otherwise seemingly indolent PC. While multiple studies have shown an absence of association between FH of PC and disease progression on AS,[13-17] these prior studies focused on a narrower definition of FH of PC alone. We sought to investigate how a broader definition of FH that incorporates genetically related cancer types (ie, breast, ovarian, and pancreatic cancers) impacts the risk of progression in a large institutional AS cohort. Here, we describe the association between an expanded definition of FH and outcomes of AS for PC under the hypothesis that patients at high genetic risk based on their FH are at increased risk of disease progression on AS.

MATERIALS AND METHODS

Study Population

With institutional review board approval, we retrospectively identified patients with PC managed by AS between 1997 and 2019.[18,19] Selection guidelines for AS at our institution include cT1-T2a, grade group (GG) 1 (and select low-volume GG2) disease with ≤50% positive cores, and PSA <10 ng/mL. Prostate MRI began to be used in our cohort in 2007, but 93% were obtained from 2012 or later. Triggers for intervention include biopsy progression by grade or volume, PSA progression, and digital rectal exam progression.

FH Score

Detailed FH data on prostate, breast, ovarian and pancreatic cancer were obtained by retrospective review of clinical notes. We excluded patients missing data on FH of PC in the medical record. No documented FH of breast, ovarian, or pancreatic cancer was treated as a negative FH for these malignancies. We sought to develop a quantitative score that captures multigeneration FH data, accounts for degree of genetic relatedness and is intuitive to calculate. Therefore, we employed the kinship coefficient, a simple measure of relatedness used in genetics and genealogy, for weighting FH data (similar in concept to a recent breast cancer study[20]).

Our framework integrates into a composite score the weighted sum of the number of first- (FDR), second- (SDR), and third-degree relatives (TDR) from the same side of the family with each relevant cancer type (ie, prostate, breast, ovarian, and pancreatic):

$$S = w_{FDR} * \Sigma(n_{FDR}) + w_{SDR} * \Sigma(n_{SDR}) + w_{TDR} * \Sigma(n_{TDR})$$

Weights were set to be proportional to the kinship coefficient, such that $w_{FDR}=1$, $w_{SDR}=0.5$, and $w_{TDR}=0.25$. To avoid inflating evidence of an HCS by summing unrelated family members, S was separately computed for maternal and paternal lineage, and the maximum score was used for subsequent analysis. An FH suggestive of HCS (FH HCS) was defined as $S>1$, which corresponds to approximately the >90th percentile of S-scores in our cohort (Figure 1) and can be translated clinically to >1 FDR or FDR-equivalent (ie, 1 FDR=2 SDRs=4 TDRs) with relevant cancer history. For example, a father (FDR)

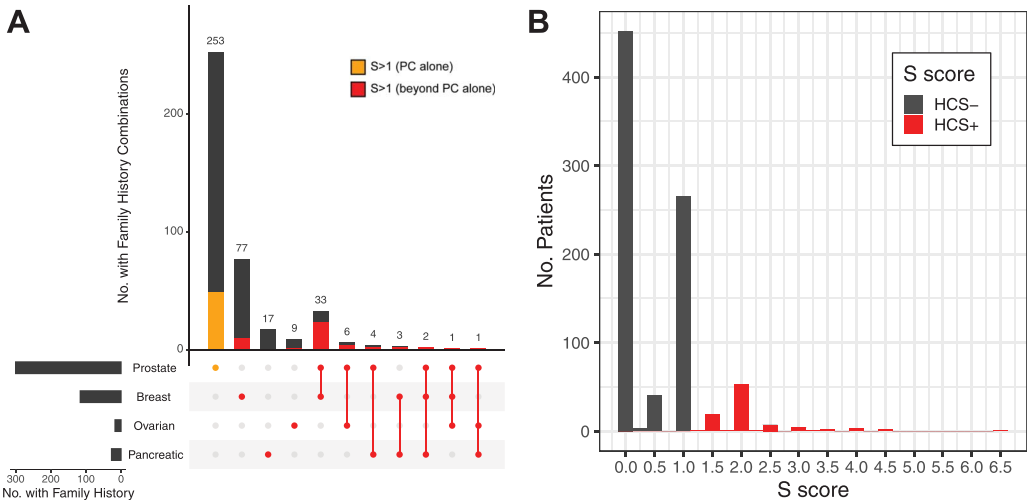

Figure 1. A, Overlap of family history of hereditary cancer syndrome (HCS)–related cancer types. Gray bars indicate the total number of patients in the active surveillance cohort with each family history combination specified in the dot matrix. Orange bar indicates HCS+ subset of patients (ie, family history score $S>1$) based on family history of prostate cancer (PC) alone. Red bars indicate HCS+ subset of patients based on family history beyond PC. B, Distribution of S scores across entire cohort and patients with $S>1$ indicated in red.

with PC and 2 paternal aunts (SDR) with breast cancer would yield $S=w_{FDR}*1+w_{SDR}*2=2$.

Outcomes

The primary outcome of the study was biopsy progression-free survival (BPFS). Biopsy progression was defined by either grade (GG1 to ≥GG2 or GG2 to ≥GG3) or volume (≤50% cores positive and ≤50% maximum core involvement on diagnostic biopsy, progressing to either >50% cores positive or >50% maximum core involvement). Secondary outcomes were adverse pathological features at radical prostatectomy (RP; ≥GG3, pT3-4, or lymph node involvement), treatment-free survival (TFS), and biochemical recurrence (BCR) among patients who underwent delayed definitive treatment after a period of AS.

Statistical Analysis

Baseline clinicopathological characteristics were compared by FH category using the Mann-Whitney *U*-test for continuous and Fisher's exact test for categorical variables. Unadjusted Kaplan-Meier estimates of BPFS and TFS by FH category were generated. To estimate the hazard of FH of PC or FH suggestive of an HCS on each time-to-event outcome (BPFS, TFS, BCR), multivariable Cox proportional-hazard models were utilized, adjusting for known clinically associated factors: age, GG, PSA, percent cores positive and maximum percent core involvement on diagnostic biopsy. Follow-up started on the date of diagnosis for BPFS and TFS, and on the date of definitive treatment with surgery or radiation for BCR. Follow-up continued until the relevant event date for each outcome: biopsy demonstrating progression (BPFS), date of treatment (TFS), or date of confirmed PSA recurrence (BCR). Patients were censored on the date of last follow-up if no event had occurred. For sensitivity analysis, the multivariable Cox model of BPFS was repeated restricted to NCCN very low-risk and low-risk patients, adjusted for the same covariates. The same covariates were also adjusted for in a multivariable logistic regression to estimate the odds ratio for adverse pathological features at RP. P value for statistical significance was $<.05$. All statistical analyses were performed using R.

RESULTS

Among the 1,268 patients in our institutional AS cohort, we excluded patients with <2 biopsies or <1 year follow-up time (n=243), high-volume disease on diagnostic biopsy (>50% cores positive or >50% maximum core involvement; n=103), or missing FH data (n=67). Of the 855 evaluable patients, 300 (35%) had an FH of PC and 95 (11.1%) had FH HCS (ie, $S>1$; Figure 1). Patient baseline clinicopathological characteristics are presented in Table 1. At least 1 prostate MRI was obtained in 482 (56%) patients, and there were no significant differences between FH categories in the proportion of patients who underwent MRI on AS or number of surveillance biopsies.

There were 330 patients who experienced biopsy progression while on AS. The median follow-up time for patients who did not progress was 6.3 years. There were 165 patients who underwent RP at a median of 2.3 years (IQR 1.6-3.8 years) after diagnosis, 38 of whom had adverse pathological features on final surgical pathology. A total of 360 patients progressed to treatment with either surgery or radiation, with biopsy progression being the most common reason for treatment irrespective of FH. Only 12 (1.4%) patients in our AS cohort have undergone germline genetic testing and 2 had a pathogenic variant identified in a PC risk gene (1 *BRCA2* and 1 *MSH6*); neither experienced disease progression during the follow-up of this study.

Table 1. *Baseline Clinicopathological Characteristics by Family History Status*

Variable	Overall N=855	Positive FH PC N=300	Negative FH PC N=555	*P* value[a]	Positive FH HCS N=95	Negative FH HCS N=760	*P* value[a]
Age, median (IQR), y	64 (59-69)	63 (58-69)	66 (60-69)	< .001	64 (59-70)	64 (59-69)	.9
Initial PSA, median (IQR), ng/mL	5.0 (3.8-6.4)	4.6 (3.3-5.9)	5.1 (4.1-6.8)	< .001	4.3 (3.1-5.7)	5.0 (4.0-6.6)	.001
Prostate volume, median (IQR), mL	42.5 (32.0-58.1)	41.0 (30.0-56.0)	43.2 (33.4-60.0)	.046	37.6 (27.8-51.2)	43.5 (33.0-59.0)	.008
PSA density, median (IQR), ng/mL^2	0.11 (0.08-0.15)	0.11 (0.07-0.15)	0.11 (0.08-0.15)	.12	0.11 (0.08-0.16)	0.11 (0.08-0.15)	.8
Initial biopsy grade group, No. (%)							
1 (Gleason 3+3)	837 (97.9)	298 (99.3)	539 (97.1)	.043	94 (98.9)	743 (97.8)	.7
2 (Gleason 3+4)	18 (2.1)	2 (0.7)	16 (2.9)		1 (1.1)	17 (2.2)	
Clinical T stage, No. (%)							
cT1	795 (93.0)	276 (92.0)	519 (93.5)	.4	86 (90.5)	709 (93.3)	.3
cT2	60 (7.0)	24 (8.0)	36 (6.5)		9 (9.5)	51 (6.7)	
Prostate MRI on AS, No. (%)							
Yes	482 (56.4)	178 (59.3)	304 (54.8)	.11	59 (62.1)	423 (55.7)	1.0
Positive MRI (PI-RADS ≥3)	218 (25.5)	72 (24.0)	146 (26.3)		27 (28.4)	191 (21.5)	
Negative MRI (PI-RADS <3)	264 (30.9)	106 (35.3)	158 (28.5)		32 (33.7)	232 (34.2)	
No/Missing	373 (43.6)	122 (40.7)	251 (45.2)		36 (37.9)	337 (44.3)	
No. biopsies on AS, median (IQR)	2 (2-3)	2 (2-3)	2 (2-3)	.9	2 (2-3)	2 (2-3)	.7

Abbreviations: AS, active surveillance; FH, family history; HCS, hereditary cancer syndrome; IQR, interquartile range (25th-75th); MRI, magnetic resonance imaging; PC, prostate cancer; PI-RADS, Prostate Imaging-Reporting and Data System; PSA, prostate-specific antigen.
[a] *P* values were calculated using Mann-Whitney *U*-test for continuous and Fisher's exact test for categorical variables.

One additional patient who had an FH of a germline *BRCA2* mutation but had not personally undergone genetic testing did experience disease progression.

Each FH category was evaluated for association with disease progression on AS. No significant association was found between FH of PC alone and BPFS in multivariable Cox regression (HR 1.13, 95%CI 0.90-1.42, $P = .3$; Table 2), and Kaplan-Meier estimates were similar between patients with vs without FH PC (Figure 2). However, FH HCS was associated with a significantly increased hazard of biopsy progression; in multivariable analysis, FH HCS was a statistically significant predictor of biopsy progression, after adjusting for known clinically associated factors (HR 1.43, 95%CI 1.01-2.02, $P = .046$; Table 2 and Figure 3). We found no significant difference in biopsy progression based on whether patients underwent a prostate MRI while on AS ($P = .66$) and no significant difference between FH categories with respect to MRI utilization or number of biopsies on AS (Table 1).

We next examined the impact of FH on progression to treatment (Table 2). Similar to BPFS, no significant difference was observed in TFS between patients with vs without FH PC, whereas FH HCS was significantly associated with worse TFS. In multivariable analysis, FH HCS was a statistically significant predictor of TFS (HR 1.58, 95%CI 1.14-2.18, $P = .006$; Table 2). Regarding adverse pathology at RP, no significant association was found with FH PC ($P = .8$) or FH HCS ($P = .7$). Similarly, there were no statistically significant differences in the hazards of BCR between FH categories among the subset of patients (n=337) who underwent delayed treatment after a period of AS (all $P > .4$; 5-year BCR rates: 84% FH PC− vs 93% FH PC+ and 87% FH HCS− vs 90% FH HCS+), though this analysis was likely underpowered due to few BCR events (n=27).

Finally, our sensitivity analysis restricted to NCCN very-low-risk (n=405) and low-risk (n=381) PC demonstrated FH HCS (but not FH PC alone) was associated with an increased hazard for biopsy progression (HR 1.37, 95%CI 0.96-1.96, $P = .087$), consistent with the overall cohort results but not reaching nominal statistical significance in this subgroup analysis.

DISCUSSION

We found that patients with a strong FH suggestive of an HCS (but not those with FH PC alone) have an increased hazard of biopsy progression and coming to treatment on AS compared to patients without such FH. However, the subset of FH HCS patients who underwent delayed definitive treatment after a period of AS did not appear to experience higher rates of adverse pathology at RP or BCR. Our study represents one of the largest cohorts in which the impact of FH on AS outcomes has been investigated.[13-17] Unique to our study is the broader definition of FH considered to be clinically relevant to men on AS, including an FH of not only PC, but also other malignancies with shared genetic underpinnings (ie, breast, ovarian, and pancreatic cancers). Further, we present a novel FH scoring metric that aggregates affected relatives across multiple generations while accounting for degree of relatedness.

Over the past decade, the relationship between FH of PC and disease progression on AS has been investigated in 5 studies to our knowledge,[13-17,21] all

Table 2. *Multivariable Cox Proportional Hazards Models of Biopsy Progression-free Survival and Treatment-free Survival*

	Biopsy progression-free survival		Treatment-free survival	
Variable	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
PC				
No FH	-	-	-	-
FH PC	1.13 (0.90-1.42)	.3	1.20 (0.96-1.49)	.10
HCS				
No FH ($S=0$)	-	-	-	-
FH ($0<S\leq1$)	1.12 (0.89-1.42)	.3	1.09 (0.86-1.36)	.5
FH HCS ($S>1$)	1.43 (1.01-2.02)	.046	1.58 (1.14-2.18)	.006

Abbreviations: CI, confidence interval; FH, family history; HCS, hereditary cancer syndrome; PC, prostate cancer; *S*, family history score.
Multivariable models adjusted for age, Gleason grade, prostate-specific antigen, percent cores positive, and maximum percent core involvement at diagnosis.

generally concluding that FH of PC is not associated with disease progression on AS. Notable differences between our study and prior studies that might account for the discordant findings include smaller sample size of previously examined AS cohorts (n=200-471); varying definitions for disease progression (biopsy-detected vs biomarker-detected) among prior studies; lack of a standardized definition of positive FH; and perhaps most importantly, the prior studies focused on FH of PC alone and did not include related malignancies that raise suspicion for an HCS. Our results are consistent with previous studies, where FH of PC alone was not associated with a higher risk of biopsy progression. Only when an expanded definition of FH that includes related malignancies was employed did we observe FH to be associated with an increased risk of progression on AS.

Most recently, Jibara et al examined the association between FH of prostate and other cancer types with clinicopathological outcomes in their institutional AS cohort.[22] Their analysis of 3,211 patients (with median follow-up of 3.7 years) demonstrated an increased risk of biopsy grade progression on AS among patients with strong FH of PC but not among those with strong FH of other cancers. Notably, in their study FH HCS was defined based on NCCN Guidelines criteria as ≥3 relatives from the same side of the family with any of a dozen different cancer types.[23] We believe this definition is likely too broad to enrich for a shared genetic predisposition for PC and may in part explain the discordant results. Nonetheless, our studies reach similar conclusions in that strong FH does not appear to increase risk of adverse pathology at RP and thus AS can still be safely offered to such patients.

In our AS cohort, while all 95 patients with FH HCS meet germline genetic testing criteria per NCCN Guidelines,[23,24] the vast majority of patients have not undergone testing. Determining the germline mutation status of our AS patients will be a focus of future work, but we expect the carrier rates of DNA repair-gene mutations to be quite low (<5%) in localized PC (vs ~12% in metastatic PC[9,25]). Indeed, in a combined analysis of 2 independent AS cohorts,[26] pathogenic mutations in a three-gene panel (*BRCA1*, *BRCA2*, *ATM*) were found in only 26 of 1211 patients (2.1%). However, patients harboring a mutation in any of these genes (particularly *BRCA2*) carried a significantly higher risk of grade reclassification. Even among highly pre-selected patients, 1 study of a prospective genetic testing database found germline mutations in

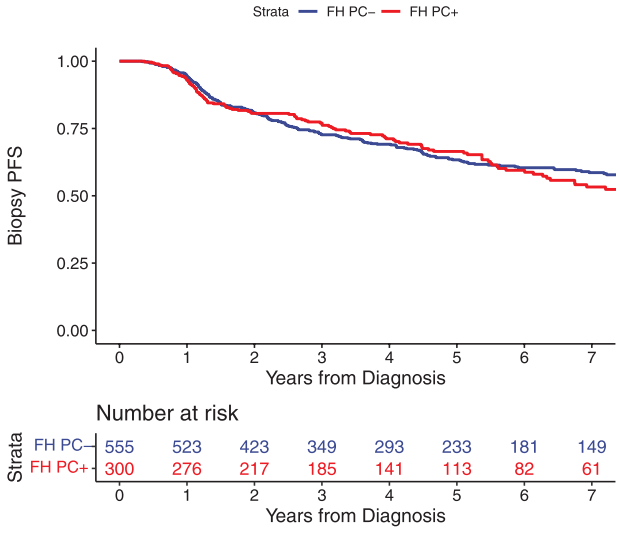

Figure 2. Kaplan-Meier curve of biopsy progression-free survival (PFS) for patients with vs without any family history (FH) of prostate cancer (PC).

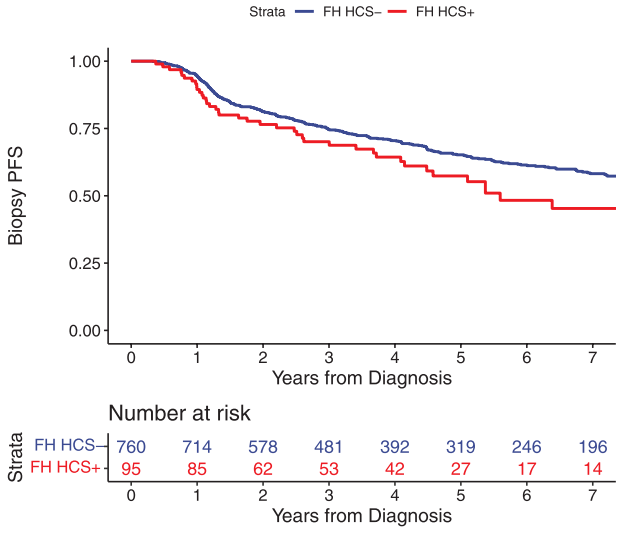

Figure 3. Kaplan-Meier curve of biopsy progression-free survival (PFS) for patients with vs without a strong family history (FH) suggestive of a hereditary cancer syndrome (HCS).

only 19.5% of 169 probands with FH suggestive of HCS that includes PC.[10] Together, these studies suggest that germline DNA repair-gene mutations likely account for a small minority of AS patients with strong FH or those experiencing biopsy progression. Our results underscore the added value of a detailed FH as an inexpensive tool for assessing the independent risk conferred by FH on biopsy progression.

While patients in our study with FH HCS experienced a higher risk of disease progression, no association was found with adverse pathology at RP or BCR after treatment, suggesting that with timely intervention curative treatment is likely not compromised. It is likely that our observed association between FH and biopsy progression results from a combination of occult, undersampled high-grade cancer present at diagnosis and progression from low- to high-grade disease over time. This is consistent with a recent study identifying an increased risk of high-grade PC among patients referred for prostate biopsy with FH of both prostate and breast cancers.[27] Overall, we believe such patients can still be safely offered AS but should be counseled about the higher risk of biopsy progression.

Our study has several important limitations. First, while our median follow-up time of 6.3 years is longer than previous studies investigating FH in AS, it limits our evaluation to short- to intermediate-term outcomes of AS. Longer follow-up will be required to assess late outcomes of AS (BCR, metastasis and PC-specific mortality). Second, only 18 patients in our analysis had GG2 disease, and therefore our results may not be generalizable to this subset of men on AS. Third, our data partially predate the introduction of MRI into our AS program, and it is possible that patients with strong FH might be more likely to have a positive MRI and be excluded from AS. However, our data suggest no differences in the proportion of patients with positive MRIs between FH categories. Fourth, we introduce a novel FH scoring metric, which warrants validation in future studies. Finally, because FH was not systematically obtained by a genetic counselor, differences in documenting FH data could lead to observer bias. For example, if patients with higher risk disease were asked in more depth about extended family history, this could bias our results towards a higher risk estimate. Ascertainment bias may also be possible if retrospectively reviewed cases where FH was negative were recorded as missing. However, this would have biased our results towards a lower risk estimate. Additionally, given in clinical practice patients undergoing AS are not routinely evaluated by genetic counselors, our results are likely more generalizable to standard clinical practice.

CONCLUSIONS

We demonstrate that a strong FH suggestive of an HCS is associated with a significantly increased hazard of biopsy progression and progression to treatment for men on AS for PC. However, no association was identified between FH and the probability of adverse pathological features at RP or BCR among patients who ultimately underwent definitive treatment. Therefore, such patients can still be safely offered AS but should be counseled about the higher risk of biopsy progression and warrant closer monitoring compared to patients without a strong FH. These data support the wider inclusion of an expanded definition of FH in patient counseling and clinical decision-making for patients considering AS. Further research is warranted to investigate the underlying genetic factors that increase the risk of disease progression on AS.

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