Prostate cancer, family history, and eligibility for active surveillance: A systematic review of the literature.

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Abstract:

Background: Active surveillance is an increasingly prevalent treatment choice for low-grade prostate cancer. The eligibility criteria for active surveillance are varied and it is unclear if family history of prostate cancer should be used as an exclusion criterion when considering men for active surveillance treatment.

Objective: To determine whether family history plays a significant role in the progression of prostate cancer for men undergoing active surveillance.

Methods: PubMed searches of "family history and prostate cancer", "family history and prostate cancer progression" and "factors of prostate cancer progression" were used to identify research publications about the relationship between family history and prostate cancer progression. These searches generated 536 papers that were screened and reviewed. Six publications were ultimately included in this analysis.

Results: Review of six publications suggests that family history does not increase the risk of prostate cancer progression. Six studies found that family history does not increase the risk of prostate cancer progression, while one study found that family history increases the risk of prostate cancer progression only in African Americans.

Conclusion: A family history of prostate cancer does not appear to increase a patient's risk of having more aggressive prostate cancer and is therefore unlikely to be an important factor in determining eligibility for active surveillance. Further studies are needed to better understand the relationship between race, family history, and eligibility for active surveillance.

Introduction:

Prostate cancer is the second most common cancer in American men[1]. One in seven men will be diagnosed with prostate cancer during his lifetime[1]; however, the aggressiveness of the disease can vary between patients allowing for different treatment options. Men with highly aggressive prostate cancer typically receive treatment while active surveillance is an option for patients with lower-risk, less-aggressive cancer. Different centers have proposed different criteria to guide clinicians in determining the eligibility of a patient for active surveillance. Commonly used criteria include low grade and low volume tumor on biopsy and low PSA[2].

There are multiple studies suggesting that a family history of prostate cancer increases an individual's risk of developing prostate cancer; however, it is unclear if family history should be included as an eligibility criterion for active surveillance. Herein, we performed a systematic review of all available literature regarding the possible relationship between family history and prostate cancer progression and eligibility for active surveillance. These results will have implications for providers and policy makers as they consider the impact that family history could have on the implementation of active surveillance.

Objective and Methods:

Our objective was to review relevant literature to assess whether a family history of prostate cancer was associated with prostate cancer progression and therefore should be included in the criteria for selecting patients for consideration of active surveillance. No review protocol exists for the topic, so we searched PubMed using terms of "family history and prostate cancer", "family history and prostate cancer progression", and "factors of prostate cancer progression" to identify published English-language studies that evaluated the relationship between prostate cancer progression or aggressiveness of disease and family history. We aimed to identify publications that evaluated family history among patients eligible for or on active surveillance protocols.

The searches were performed in March 2016 and generated 536 publications. These were screened first by titles and then by reviewing abstracts. Of the 536 publications, 464 publications were excluded because they were not focused on prostate cancer progression or eligibility for active surveillance. Sixty-six publications were then excluded because they were commentaries rather than primary research publications. This resulted in six candidate publications. References of these six publications were reviewed to identify additional publications and none were found. Therefore, a total of six publications were included in this systematic review (Figure 1). Two independent assessors (JMT and JMD) evaluated the papers. The principle summary measure was the p-value that evaluated the clinical risk for aggressive prostate cancer in participants with and without a family history of prostate cancer. There was a risk of bias from the limited number of studies and participants, so results were not pooled. Institutional Review Board approval was not required since this was an analysis of previously reported, publically available literature.

Results:

We identified six publications reporting on the relationship between family history and prostate cancer progression in patients eligible for or on active surveillance (Table 1).

All six observational studies of men found no relationship between family history and prostate cancer progression. Four studies used pathologic features to determine progression and progression was defined by a change to adverse, more aggressive pathology. Two studies used biomarkers such as prostate cancer antigen three (PCA3), transmembrane protease, serine 2 (TMPRSS2-ERG), and prostate specific antigen (PSA) to determine prostate cancer aggressiveness.

Impact of family history on pathologic findings

In a study by Selkirk and colleagues, 200 patients were categorized as having no family history of prostate cancer, one family member with prostate cancer, and two or more family members with prostate cancer[3]. The authors found that men with and without family history were re-categorized with higher grade cancer on follow up biopsy at similar frequencies (30.9% and 32.8%, respectively; $p = 0.776$). When comparing patients who had one, two and three family members with prostate cancer, there did not appear to be a significant difference in men that were re-categorized with higher grade cancer ($p = 0.641$).

Similarly, Goh and colleagues examined 471 prostate cancer patients on active surveillance protocols[4]. Of these patients, 55 had adverse pathology on repeat biopsies. The authors found no significant relationship between family history of prostate cancer and adverse pathology ($p = 0.154$) and found no significant relationship between family history of prostate cancer and time to treatment. The researchers further analyzed the DNA of 386 of the 471 prostate cancer patients for 39 prostate cancer risk single nucleotide polymorphisms (SNPs) and calculated genetic risk scores of aggressive prostate cancer. Analysis of genetic risk scores showed that there was no significant relationship between genetic risk scores and adverse pathology or time to treatment ($p = 0.573$ and $p = 0.965$, respectively).

Iremashvili and colleagues found that family history was not a predictor of prostate cancer progression by following 249 patients with prostate cancer on active surveillance protocols[5]. Of the 249 patients, 64 patients showed a change to adverse pathology on surveillance biopsies and univariate analysis showed that family history was not a significant predictor of prostate cancer progression ($p = 0.91$). Prostate cancer progression risk was, however, significantly higher in African American patients, regardless of family history ($p < 0.001$). Pietzak and colleagues examined 468 patients with D'Amico low-risk disease who would have been eligible for active surveillance, but had immediate prostatectomy. The authors examined the pathologic specimens in accordance with six different active surveillance criteria protocols[6]. The authors found that African Americans were more likely to have adverse pathology if they met Prostate Cancer Research International: Active Surveillance Study (PRIAS) active surveillance criteria or met criteria for all six studied protocols. Family history was only a significant predictor of prostate cancer progression among African American patients ($p = 0.04$).

Impact of family history on serum biomarker findings

Two observational studies used biomarkers, including PSA, to evaluate the relationship between family history of prostate cancer and cancer aggressiveness or progression in patients on active surveillance. Lin and colleagues

followed 387 prostate cancer patients on active surveillance using PCA3 and TMPRSS2-ERG fusion biomarkers[7]. The authors found that family history of prostate cancer had no significant correlation with PCA3 and TMPRSS2-ERG fusion biomarkers; therefore, family history was not an effective determinant of having aggressive cancer ($p = 0.28$ and $p = 0.37$, respectively). Randazzo and colleagues sought to evaluate whether family history of prostate cancer was a risk factor for prostate cancer incidence, grade, and development of interval disease among men undergoing PSA screening for prostate cancer[8]. Of the 610 patients who were found to have prostate cancer identified by PSA screening, a higher percent of men had a positive family history than had a negative family history (18.0% vs 12.0%, $p < 0.01$). However, family history was not a significant predictor of finding aggressive cancer ($p = 0.3$) or of interval development of prostate cancer ($p = 0.20$).

Discussion:

We identified six peer-reviewed publications that evaluated the relationship between family history of prostate cancer and prostate cancer progression or aggressiveness. Results from all six studies suggest that patients with and without a family history of prostate cancer have no detectable differences in the probability of cancer progression while on active surveillance, with the exception of one study that found an increased risk of adverse pathologic features among African American men. Despite extensive investigations, most authors have been unable to demonstrate a relationship between family history and aggressiveness of disease.

This review has several limitations. First, we were only able to identify six relevant articles, although we believe that this is the totality of what has been published in English in PubMed. The six articles also used two different definitions of disease progression, either biopsy-detected pathologic progression or serum biomarker-detected progression. Because of the limited number of studies, we were unable to create a unified definition of disease progression. Finally, there was some suggestion in these publications that there may be a relationship between race, family history, and prostate cancer, but we were not able to fully examine this possible relationship because of the limited number of publications on this specific topic. Additional research on the subject of race, family history, and eligibility for active surveillance is needed. The relationship of family history to specific genetic markers for prostate cancer is also a subject of further inquiry[11, 12].

Notwithstanding these limitations, we think these findings have important implications for clinicians, patients and policymakers. For clinicians, there does not appear to be enough evidence to support the use of family history as an exclusion criterion when considering men for active surveillance. Physicians may need to make extra efforts to explain to patients and families that a positive family history does not require that patients be excluded from active surveillance. However, for African American men, a positive family history may suggest an increased risk for more aggressive disease. For policy makers, the limitations of these data and the possible relationship between family history and prostate cancer aggressiveness in African American men suggests a need to support additional prospective, large cohort studies of this subject.

Conclusion:

According to our systematic review of relevant literature, a family history of prostate cancer does not appear to increase a patient's risk of having more aggressive prostate cancer and should not be utilized as an absolute exclusion criterion for active surveillance treatment. As always, individual decisions about the appropriateness of active surveillance treatments should be guided by shared decision-making between patients and their well-informed health care providers.

Conflicts of Interest

Jaya Telang and Dr. Dupree report grants from Blue Cross Blue Shield of Michigan; Dr. Miller reports grants from Blue Cross Blue Shield of Michigan and RO1-CA-174768; Dr. Lane and Dr. Cher have nothing to disclose.

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Table 1: Summary of Family History and Prostate Cancer Progression Publications

Study	Total number of patients	% patients with + family history	% patients with + family history and PC progression	% patients without + family history and PC progression	P-value
Studies that utilized pathologic findings to evaluate disease progression or risk					
Selkirk[3]	200	40.5	31.0	33.0	0.78
Goh[4]	471	16.5	7.9	14.2	0.15
Iremashvili[5]	249	17.7	25.0	25.8	0.91
Pietzak[6]	468	31.2	na*	na*	>0.05
Pietzak[6] **Subset of African American patients**	66	28.8	47.8	22.2	0.04
Studies that utilized biomarker findings to evaluate disease progression or risk					
Lin[7]	387	27.2	na^	na^	0.28
Randazzo[8]	610	9.8	4.2+	3.1+	0.20

PC = Prostate cancer* = These specific values were not published for the combined set of African American and White American patients

^ = Results were published as median PCA3 and TMPRSS2:ERG scores

+ = Development of interval prostate cancer

3 = development of internal prostate cancer

Table

PRISMA 2009 Flow Diagram