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Continued 5α-Reductase Inhibitor Use after Prostate Cancer Diagnosis and the Risk of Reclassification and Adverse Pathological Outcomes in the PASS

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Abstract

Purpose: Outcomes in patients who enroll in active surveillance programs for prostate cancer while receiving 5α-reductase inhibitors have not been well defined. We sought to determine the

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association of 5α-reductase inhibitor use with the risk of reclassification in the PASS (Canary Prostate Active Surveillance Study).

Materials and Methods: Participants in the multicenter PASS were enrolled between 2008 and 2016. Study inclusion criteria were current or never 5α-reductase inhibitors use, Gleason score 3 + 4 or less prostate cancer at diagnosis, less than a 34% core involvement ratio at diagnosis and 1 or more surveillance biopsies. Included in study were 1,009 men, including 107 on 5α-reductase inhibitors and 902 who had never received 5α-reductase inhibitors. Reclassification was defined as increase in the Gleason score and/or an increase to 34% or greater in the ratio of biopsy cores positive for cancer. Adverse pathology at prostatectomy was defined as Gleason 4 + 3 or greater and/or nonorgan confined disease (pT3 or Nl).

Results: On multivariable analysis there was no difference in reclassification between men who had received and those who had never received 5α-reductase inhibitors (HR 0.81, p = 0.31). Patients who had received 5α-reductase inhibitors were less likely to undergo radical prostatectomy (8% vs 18%, p = 0.01) or any definitive treatment (19% vs 24%, p = 0.04). In the 167 participants who underwent radical prostatectomy there was no suggestion of a difference in the rate of adverse pathology findings at prostatectomy between 5α-reductase inhibitor users and nonusers.

Conclusions: Continued 5α-reductase inhibitor use after an initial diagnosis of prostate cancer was not associated with the risk of reclassification on active surveillance in men in the PASS cohort.

Keywords

prostatic neoplasms; 5-alpha reductase inhibitors; watchful waiting; diagnosis; adverse effects

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To treat BPH 5-ARIs are widely used. Since they inhibit the conversion of testosterone to more potent dihydrotestosterone, large, randomized clinical trials have been done to evaluate the efficacy of 5-ARIs for the primary prevention of PCa. In these trials finasteride[1] and dutasteride[2] were associated with a decreased incidence of low grade PCa but a slightly increased incidence of high grade PCa compared to placebo. These findings led to a FDA (Food and Drug Administration) safety advisory regarding the risk of high grade PCa while receiving 5-ARIs.[3]

However, many men continue to receive 5-ARIs, given the effectiveness of 5-ARIs to treat BPH. Evidence also suggests that men on a 5-ARI for BPH who are also annually screened for PCa by digital rectal examination and serum PSA undergo fewer biopsies but the biopsies more frequently show PCa with a similar Gleason score distribution.[4] As PCa AS becomes more popular and recommended[5,6] to manage low and very low risk PCa[7] more of these men will likely elect AS as the initial treatment strategy.

Previous studies of the effect of 5-ARI therapy after enrollment in AS on pathological reclassification have yielded conflicting results.[8,9] It is still unclear whether these agents alter tumor biology to decrease pathological disease progression or whether they lead to decreased treatment which is independent of effects on pathological disease progression.

Furthermore, to our knowledge the effect of 5-ARIs in men on AS to manage cancer and who initiated 5-ARI use prior to a cancer diagnosis is not known.

The goal of this study was to evaluate whether continuing 5-ARIs after a diagnosis of PCa is associated with adverse outcomes while on AS. Specifically we assessed whether 5-ARI therapy was associated with a risk of pathological reclassification on surveillance biopsy and adverse pathology findings (Gleason grade 4 + 3 or greater and/or non-organ confined disease) on radical prostatectomy.

METHODS

Patient Population

Data were obtained from the multicenter PASS (ClinicalTrials.gov NCT000756665), which was approved by the Institutional Review Board at all participating sites (Fred Hutchinson IRB No. 712).[10] Under the PASS protocol serum PSA is recommended every 3 months and the clinic is visited every 6 months. Ultrasound guided biopsies are prescribed between 6 and 12 months after diagnosis, 24 months after diagnosis and every 24 months thereafter. At least 10-core study biopsy regimens were required and 91% of the regimens were 12 cores or more (5-ARI users and nonusers median 12, IQR 12—12). Other tests, including magnetic resonance imaging, may have been performed at clinician discretion. However, since the study started enrollment in 2008, most of the men did not undergo magnetic resonance imaging.

Data on Gleason score, clinical stage, the core ratio and the corresponding PSA values of diagnostic and followup biopsies were extracted from the medical records. Participants were asked to report current 5-ARI use and the 10-year history of 5-ARI use at study enrollment. Current use was assessed at each followup visit. Men who indicated use prior to diagnosis and current use at all followup visits were defined as 5-ARI users in this study.

The 1,069 men included in analysis were enrolled in the PASS by February 2016 and were diagnosed with prostate cancer within 5 years of enrollment. They had Gleason 3 + 4 or less cancer, a less than 34% ratio of biopsy cores containing cancer to total biopsy cores (core ratio) at diagnosis and had undergone at least 1 surveillance biopsy after diagnostic biopsy. We excluded participants who were former 5-ARI users, including 20 with a history of 5-ARI use prior to diagnosis but who discontinued use, 36 in whom 5-ARI was initiated after diagnosis and 4 with unknown 5-ARI use at diagnosis, resulting in 1,009 participants remaining for analysis.

Outcomes

The primary outcome of these analyses was time to reclassification while on AS. Reclassification was defined as 1) an increase in primary or secondary Gleason grade at biopsy only or 2) a composite of an increase in Gleason grade and/or an increase in the ratio of biopsy cores with cancer to total cores (core ratio) to 34% or greater. Participants who were not reclassified were censored at the date of the last study contact, at treatment or 2 years after the last biopsy, whichever was first. A total of 13 deaths occurred in this study population, of which none was due to prostate cancer. In the subset of men who underwent

RP we also examined whether 5-ARI use was associated with a risk of adverse pathology, defined as Gleason grade 4 + 3 or greater and/or nonorgan confined disease (pT3 or Nl).

Statistical Methods

Descriptive statistics were used to characterize the study sample. Differences between 5-ARI users and nonusers were evaluated by the t-test or the Wilcoxon signed rank test for continuous variables and the chi-square or Fisher test for categorical variables.

All time dependent analyses were based on the time between the PCa diagnosis and incident reclassification or a censoring event. Kaplan-Meier curves were plotted to examine how the reclassification-free probability varied by 5-ARI status. Cox proportional hazards models were used to estimate the unadjusted and covariate adjusted HRs of the association between 5-ARI use and the risk of reclassification. Covariate adjusted models were created with certain variables, including diagnostic PSA (natural log transformed, continuous), BMI (continuous), prostate volume (natural log transformed, continuous), age at diagnosis (continuous), self-reported BPH (yes or no), diagnostic T stage (Tla-c or T2a-c), diagnostic Gleason score (3 + 3 or 3 + 4), family history of PCa (yes or no) and the diagnostic core ratio (continuous). The final adjusted model included BMI, the core ratio, PSA and prostate volume. PSA and prostate volume were modeled as separate variables instead of as the composite variable, PSA density. The 61 participants missing the core ratio were dropped out of the multi-variable models. The baseline hazard in all Cox proportional hazards models was stratified by study site. Nonsignificant variables were backward eliminated at a p value cutoff of 0.05.

Sensitivity analyses were performed in the subset of men with Gleason 3 + 3 PCa. Exploratory analyses were done to compare the rate of adverse pathological outcomes between 5-ARI users and nonusers in the subset of 167 men who underwent RP. To address whether our results were biased by an effect of 5-ARI use on biopsy timing we defined biopsies as on time, early or late based on the PASS protocol. Multinomial regression was done to determine whether biopsy timing was associated with 5-ARI use. All analyses were performed with SAS®, version 9.4 and R, version 3.3.0 (https://www.r-project.org/).

RESULTS

A total of 1,009 men were included in this analysis. Median followup was 3.6 years (IQR 2.2—5.4) in censored participants. Table 1 lists demographic data. There were 107 men on a 5-ARI at diagnosis and 902 who had never received a 5-ARI. Men in the 5-ARI group were more likely to have a BPH diagnosis (77% vs 28%) and larger prostate volume (median 51 vs 40 gm), and were older (65 vs 62 years, all p <0.001). Men on a 5-ARI were less likely to undergo RP (8% vs 18%, p = 0.01) or any curative treatment (19% vs 28%, p = 0.04). Men in the 2 groups were statistically similar in racial background, serum PSA, PSA density, clinical stage, Gleason score and the diagnostic positive core ratio.

Overall there was no significant difference in time to grade and/or volume reclassification (p = 0.10) or to grade only reclassification (p = 0.30) between 5-ARI users and nonusers (see figure). Sensitivity analysis limited to men who entered the study with 3 + 3 PCa also did

not reveal any association between 5-ARI use and time to reclassification (data not shown). In an unadjusted Cox proportional hazards model continued use of 5-ARIs while on AS was associated with a decreased risk of reclassification (HR 0.63, 95% CI 0.43—0.94, table 2). However, after adjustment for diagnostic PSA, BMI, prostate size and the diagnostic core ratio 5-ARI use was not associated with a risk of reclassification (HR 0.81, 95% CI 0.55—1.21, p = 0.31). Biopsy timing was not significantly affected by 5-ARI use. Compared to on time biopsy the odds of early or late biopsy were 1.09 (95% CI 0.63–1.89, p = 0.77) and 1.20 (95% CI 0.70–2.08, p = 0.51), respectively.

On exploratory analysis of the 167 participants who underwent RP 158 had never received a 5-ARI while 9 had used 5-ARIs (table 1). There was no suggestion of a difference in the adverse pathology rate based on grade 4 + 3 or greater (p = 0.99) or grade 4 + 3 or greater and/or nonorgan confined disease (p = 0.73). Furthermore, of the men who underwent RP there was no Gleason 8+ disease in those who received 5-ARIs compared to 12 nonusers (8%) with Gleason 8+ disease (data not shown).

DISCUSSION

To our knowledge this is the first study to evaluate the relationship between continued 5-ARI use after the initial PCa diagnosis and the risk of pathological reclassification during subsequent AS. We found that continued 5-ARI use after a cancer diagnosis did not appear to be associated with a higher risk of PCa reclassification on a subsequent biopsy. Although 5-ARI use was associated with decreased pathological reclassification on unadjusted analysis, when controlling for diagnostic PSA, BMI, prostate size and the ratio of cores positive for PCa to total cores sampled on prostate biopsy, continued 5-ARI use did not significantly protect against grade and/or volume reclassification. Furthermore, there was no evidence that men who proceeded to prostatectomy while on a 5-ARI had worse pathological outcomes than men who did not receive a 5-ARI.

Several groups have evaluated the effects of 5-ARI initiation after diagnosis on reclassification during AS but results have been inconsistent. The clinical benefit of 5-ARI use after diagnosis was first evaluated by Finelli[11] and Wong[12] et al, who reported a significantly lower rate of pathological progression (defined as a Gleason score greater than 6, 3 or more cores involved or greater than 50% core involvement) in men who started using 5-ARIs after diagnosis. More recently in a review of the medical records of patients on AS at 1 academic institution Dai et al reported no overall difference in the risk of reclassification (defined as an increase in the Gleason score or the predominant Gleason pattern) between men who started using 5-ARIs within 12 months of diagnosis and those who never used 5-ARIs.[13] In a retrospective analysis of the records of 587 men enrolled in an AS cohort Ross et al found that 5-ARI initiation in 47 men was not associated with a risk of reclassification (defined as any Gleason 4 or greater, more than 3 cores involved with cancer or greater than 50% of any core involved with cancer).[8]

In contrast, in REDEEM, a randomized controlled trial of dutasteride vs placebo in men on AS, men in the dutasteride arm were at significantly lower risk for progression than men in the placebo arm (HR 0.62, 95% CI 0.43—0.89, p <0.001).[9] However, the definition of

progression used in the REDEEM trial included definitive treatment (RP, brachytherapy and hormonal treatment) as well as pathological reclassification. Given the differential rate of definitive treatment in the placebo arm compared to the 5-ARI arm (12.3% vs 7.5%), the primary results reported in this trial were likely biased by the inclusion of treatment as an end point. Moreover, on stratified analyses there was no difference in the risk of pathological progression between the 5-ARI and placebo arms ($p = 0.079$).[9]

Due to previous findings of an increased risk of high grade PCa in 5-ARI users in the PCPT (Prostate Cancer Prevention Trial)[1] and REDUCE (Reduction by Dutasteride of Prostate Cancer Events)[2] trial, there was potential concern for a risk of adverse pathology in an AS population. However, consistent with post hoc analyses of the 2 trials,[14,15] we found no evidence to suggest that the incidence of high grade (Gleason 4 + 3 or greater) cancer in men who proceeded to RP ($p = 0.99$) differed between 5-ARI users and nonusers. The rate of adverse pathology (Gleason 4 + 3 or greater, pT3 or pNl) was also similar between 5-ARI users and nonusers ($p = 0.73$). However, this analysis was limited by the small number of 5-ARI users who elected RP and potential bias in the reasons that men elected RP.

While 5-ARI use did not appear to be associated with time to PCa reclassification in the PASS cohort, 5-ARI users were less likely to elect definitive treatment than nonusers ($p = 0.04$).[10] Avoiding definitive treatment and its associated morbidities[16] may have value to many men who elect AS. While we did not evaluate the reasons why men avoided RP while receiving 5-ARIs, the lower treatment rate may have been related to the well described phenomenon of a decreased PSA rise while on 5-ARIs.[17]

Although groups who evaluated the associations of 5-ARI use with the risk of progression were presumably interested in biological effects, interpreting their results is complicated by the complex relationship between the use of these drugs and factors which influence the outcome. For example, 5-ARI use is associated with an approximate 50% decrease in PSA during year 1 of use and a continued decline thereafter.[17] Since higher PSA is associated with adverse reclassification, 5-ARI use could be expected to decrease the risk of reclassification. However, 5-ARIs are known to decrease prostate size[18,19] and we have found that smaller prostates are associated with a higher risk of reclassification.[10] Thus, these competing influences may substantially affect the timing of biopsy or the ability to detect reclassification to higher grade cancer. However, in the PASS the performance of protocol directed PSA tests and biopsies at prespecified time points allowed for a similar opportunity to detect progression, which helped minimize the potential for bias. Indeed, we found no evidence that 5-ARI use affected the timing of biopsies in the PASS.

Major strengths of our study include the fact that it was a multicenter, prospectively designed study with extensive collection and quality control of clinical data. In addition, including Gleason 3 + 3 and 3 + 4 disease at diagnosis in the PASS cohort made the results of this study more generalizable to community AS protocols.

This study is not without limitations. 1) We determined 5-ARI use by patient self-report at study entry with discrete response options for the duration of use, which could have resulted in an inaccurate assessment of the duration of 5-ARI use. In addition, complete data

on the overall duration or the duration prior to diagnosis were not available. 2) Because few participants reported discontinuing 5-ARIs after diagnosis, we could not examine associations of discontinued use with progression. In addition, data were not available on the type of 5-ARI. 3) The number of men who received 5-ARIs in the RP cohort was small, making it difficult to draw definitive conclusions regarding pathological outcomes.

CONCLUSIONS

Continued 5-ARI treatment in men diagnosed with PCa did not appear to affect the risk of pathological reclassification while on active surveillance in the PASS cohort. Our data suggest that men on 5-ARIs who undergo RP after a period of AS do not show an increased incidence of high grade PCa. Also, 5-ARI users undergo definitive treatment at a lower rate than nonusers.

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Abbreviations and Acronyms

5-ARI	5α-reductase inhibitor
AS	active surveillance
BMI	body mass index
BPH	benign prostatic hyperplasia
PASS	Canary Prostate Active Surveillance Study
PCa	prostate cancer
PSA	prostate specific antigen
REDEEM	Reduction by Dutasteride of Clinical Progression Events in Expectant Management
RP	radical prostatectomy

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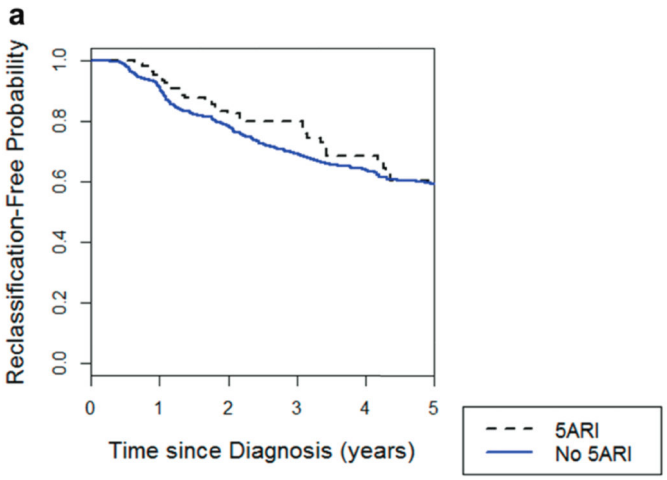
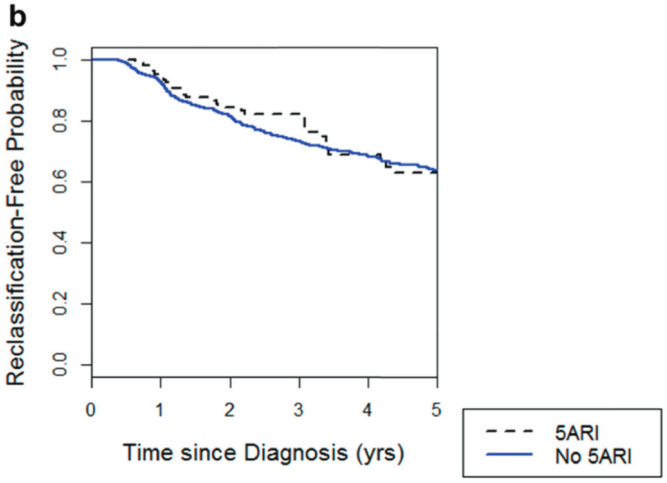


Log-rank test p = 0.10

Number at risk:

	Time since Diagnosis (years)				
	1	2	3	4	5
5-ARI user	100	76	59	41	24
5-ARI non user	784	604	422	297	182



Log-rank test p = 0.30

Number at risk:

	Time since Diagnosis (years)				
	1	2	3	4	5
5-ARI user	100	78	60	41	25
5-ARI non user	792	616	434	305	186

Kaplan-Meier analysis of time to pathological reclassification based on 15-ARI use for any increase in Gleason grade and/or tumor volume to 34% or greater positive core ratio (*a*) and increase in Gleason grade only (*b*).

Table 1.

Demographic and clinical information

	No 5-ARI		5-ARI		p Value*
No. pts	902		107		-
No. reclassified (%):					-
Gleason grade +/or vol	327	(36)	32	(30)	
Gleason grade only	284	(31)	31	(29)	
No. race (%):					0.16
Caucasian American	804	(89)	102	(95)	
African American	59	(7)	3	(3)	
Other	39	(4)	2	(2)	
No. BPH (%)	254	(28)	82	(77)	<0.001
Median cc prostate vol (IQR)	40	(30–54)	51	(34–67)	<0.001
Mean ± SD age	62 ± 7		65 ± 7		<0.001
Median ng/ml PSA (IQR)	4.8	(3.6—6.3)	5.0	(3.6—7.0)	0.25
Median ng/ml/ml PSA density (IQR)	0.11	(0.08–0.16)	0.10	(0.07–0.15)	0.06
No. clinical stage (%):					0.51
T1a-T1c	803	(89)	93	(87)	
T2a-T2c	99	(11)	14	(13)	
No. Gleason score (%):					0.20
3+3	847	(94)	97	(91)	
3+4	55	(6)	10	(9)	
Median core ratio (IQR)	8	(8–17)	8	(8–17)	0.74
No. PCa family history (%)	259	(29)	21	(21)	0.12
Mean ± SD BMI (kg/m^2)	27.9 ± 4.3		27.0 ± 4.0		0.05
Median International Prostate Symptom Score (IQR)	6	(3–11)	9	(6–12)	<0.001
No. any subsequent radiation or prostatectomy (%)	254	(28)	20	(19)	0.04
No. RP (%)	160	(18)	9	(8)	0.01
No. RP adverse pathology outcome (%):	158		9		-
Gleason grade 4 + 3 or greater only	39	(25)	2	(22)	0.99
Gleason grade 4 + 3 or greater +/or nonorgan confined disease	59	(37)	4	(44)	0.73

* Wilcoxon signed rank test or t-test for continuous variables and chi-square or Fisher exact test for categorical variables.

Table 2.

Unadjusted and adjusted time to event Cox proportional hazard models of grade and/or volume reclassification

	HR (95% Cl)	p Value
Unadjusted:		
5-ARI use	0.63 (0.43–0.94)	0.02
Log(PSA) at diagnosis	1.41 (1.17–1.71)	0.0003
BMI	1.03 (1.00–1.06)	0.02
Log(prostate vol)	0.52 (0.41–0.66)	<0.0001
Core ratio at diagnosis	1.06 (1.04–1.07)	<0.0001
Adjusted:		
5-ARI use	0.81 (0.55–1.21)	0.31
Log(PSA) at diagnosis	1.75 (1.44–2.13)	<0.0001
BMI	1.04 (1.02–1.07)	0.001
Log(prostate vol)	0.45 (0.35–0.57)	<0.0001
Core ratio at diagnosis	1.05 (1.03–1.06)	<0.0001