Research Article

Factors Associated with Adherence to an End-of-Study Biopsy: Lessons from the Prostate Cancer Prevention Trial (SWOG-Coordinated Intergroup Study S9217)

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Abstract

Background: The Prostate Cancer Prevention Trial (PCPT) was a 7-year randomized, double-blind, placebo-controlled trial of the efficacy of finasteride for the prevention of prostate cancer with a primary outcome of histologically determined prevalence of prostate cancer at the end of 7 years.

Methods: A systematic modeling process using logistic regression identified factors available at year 6 that are associated with end-of-study (EOS) biopsy adherence at year 7, stratified by whether participants were ever prompted for a prostate biopsy by year 6. Final models were evaluated for discrimination. At year 6, 13,590 men were available for analysis.

Results: Participants were more likely to have the EOS biopsy if they were adherent to study visit schedules and procedures and/or were in good health ($P < 0.01$). Participants at larger sites and/or sites that received retention and adherence grants were also more likely to have the EOS biopsy ($P < 0.05$).

Conclusions: Our results show good adherence to study requirements 1 year before the EOS biopsy was associated with greater odds that a participant would comply with the invasive EOS requirement.

Impact: Monitoring adherence behaviors may identify participants at risk of nonadherence to more demanding study end points. Such information could help frame adherence intervention strategies in future trials. *Cancer Epidemiol Biomarkers Prev; 23(8); 1638–48. ©2014 AACR.*

Introduction

Medical professionals and researchers recognize that nonadherence to medical treatment remains a challenge and have devoted significant resources to the development of intervention strategies to improve adherence rates. Despite these efforts, half of the strategies that are developed and tested fail (1). The preponderance of the literature is devoted to medication adherence, particularly in patients with chronic illnesses, such as diabetes, cardiovascular disease, or HIV, but there is a small literature examining adherence to clinical procedures.

The end-of-study biopsy

The Prostate Cancer Prevention Trial (PCPT) was unusual in that its primary outcome (prevalence of prostate cancer during the 7-year trial) was based on a non-clinically indicated biopsy at the end of the trial (2). A few studies have addressed adherence to a prostate biopsy recommendation and factors associated with agreeing to have the procedure. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) offers an opportunity to examine adherence to prostate biopsy screening recommendations. In this trial, across cancer disease sites, adherent participants were younger, had higher levels of education, and did not have a first-degree relative with cancer (3). Pinsky and colleagues examined factors associated with undergoing a prostate biopsy after a positive PLCO screen (4). Participants were more likely to undergo a biopsy after a prostate-specific antigen (PSA) value of >7 ng/mL and after a positive digital rectal exam (DRE); a

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history of prostate problems and Asian ethnicity were also important correlates with adherence (4). Men over the age of 70 were less likely to obtain a prostate biopsy when presented with a positive screening test in this study (4). Moul noted that 55% of men with a positive PSA (>4 ng/mL) had a biopsy within 3 years of the screening information; even with the highest risk category of PSA levels (PSA level >10 ng/mL), only 75% obtained a biopsy by 3 years (5). In a Veterans Administration clinic–based screening program for prostate cancer, Krongrad and colleagues reported that 57% of men with abnormal PSAs and/or DREs obtained a prostate biopsy (6). These reports suggest that presentation of high-risk status is not sufficient to guarantee that a man will obtain a prostate biopsy.

This analysis expands the potential factors associated with adherence to an invasive end-of-study (EOS) procedure that were previously identified using PCPT data (7, 8) by examining psychosocial outcomes, participant health status, participant adherence, and site characteristics. These factors were drawn from well-known health behavior models such as the Theory of Planned Behavior and the Health Belief model (9, 10). Identifying factors associated with potential nonadherence in a timely manner allows clinical trial researchers to select the population of participants most in need of an intervention to increase adherence. One year before the EOS biopsy coincides with a time when participants are close to the time of the EOS biopsy, yet far enough out that an intervention strategy can be delivered and have sufficient time to work. This approach mimics the real-world experiences of study staff working on clinical trials by only using information site staff have access to at the time the intervention strategy is applied.

This study has two aims. The first is to investigate novel factors associated with adherence through multivariate logistic regression; the second is to use receiver operating characteristic (ROC) curves to compare the specificity and sensitivity of our model among men who were and were not prompted for a biopsy.

Materials and Methods

PCPT description

The PCPT was a 7-year randomized, double-blind, placebo-controlled trial of the efficacy of finasteride for the prevention of prostate cancer (11, 12). The primary outcome for the trial was prevalence of prostate cancer as measured by a transrectal ultrasonographic–guided biopsy of the prostate (minimum of six cores) at the end of 7 years or an interim diagnosis of prostate cancer. Men randomized to finasteride had a 24.8% reduction in the prevalence of prostate cancer compared with those who were randomized to placebo. Details of the trial design and eligibility criteria have been presented elsewhere (2, 13).

Criteria for inclusion in the biopsy adherence sample

This analysis examines factors associated with EOS biopsy adherence using information obtainable as of year 6, 1 year before the EOS biopsy. Participants who died or

became lost to follow-up between years 6 and 7 ($n = 431$) were included in the primary model and counted as having no EOS biopsy.

Eligibility and exclusion criteria are shown in Fig. 1. Participants were eligible if none of the following events happened as of year 6: prostate cancer diagnosis; prostatectomy or cystoprostatectomy; death; and loss to follow up. Participants randomized after March 26, 1996, were excluded because of early study closure on June 24, 2003; these participants did not complete their EOS windows (7-year anniversary of their randomization + 90 days) and their adherence could have been influenced by the early publication of study results. Missing demographic data on 14 participants led to their exclusion from these analyses.

The analysis is stratified by biopsy prompt history: Those participants who had ever been prompted for a prostate biopsy before year 6 (via elevated PSA or DRE suspicious for cancer) and those who had not, as these groups have potentially different motivations for adherence with the EOS biopsy.

Potential covariates

The covariates considered for inclusion in the models are: age at year 6; demographics measured at randomization; comorbidities over the course of the trial; health-related quality of life (HRQL) at year 6; measures of participant adherence at year 6; prior negative biopsy; and site characteristics. See Table 1 for a complete listing of covariates examined in this analysis.

HRQL covariates were assessed using the Short Form-36 (SF-36) Health Survey. SF-36 scales (14–16) are scored on a 0 to 100 scale with higher values reflecting better HRQL. Table 1 lists the four scales selected from the full SF-36 for this analysis, which cover key domains of HRQL. Participants who were off treatment were no longer required to submit HRQL forms. PCPT outcome and covariate measures for the HRQL component of the PCPT are described in Moinpour and colleagues (17) Participants with missing forms and participants with below average scores had similar ORs and were grouped and compared with participants with average or better scores. An "average or better" score is defined as a score that is equal to or greater than the population mean minus half an SD (a moderate-sized effect; ref. 18) for that particular score, based on the SF-36 scales for the U.S. general population for men 55 and older (17); these age-specific norms were provided for the PCPT by Dr. John Ware (personal communication, 1994), based on the normative database for the SF-36 published in the SF-36 manual (19).

General adherence covariates measured how well a participant followed the study protocol. Study drug administration was once daily; participants who stopped taking the study drug were considered off treatment. Adherence to this regimen was measured using pill counts and calculated as a percentage of required pills taken over time; at least 80% was considered adherent. Study contacts were quarterly, with visits every 6 months

and phone calls at 3 months between visits. A participant who missed a regularly scheduled visit or call was counted as ever missing a visit. PSA tests and DREs were required annually with abnormal results prompting a biopsy. Participant refusal of a prompted biopsy by year 6 was considered a measure of nonadherence.

PCPT was conducted at 219 sites, with enrollment ranging from 1 to 1,444 randomized participants. Site characteristics included being an NCI-funded Community Clinical Oncology Program (CCOP) site (20), site performance, and receipt of a retention and adherence (R&A) grant. Site performance was measured by submission rate of study forms, with low submission rates indicating poor site performance. R&A grants were intended to support overall site R&A activities. Additional adherence interventions are described in Table 2. Most of these activities were initiated midway through the trial, particularly after the conduct of a series of focus groups in which we examined barriers and reinforcements for complying with all trial requirements.

Statistical analysis

The probability of participants having an EOS biopsy versus nonadherence was modeled using logistic regression. Analyses used PROC SURVEYLOGISTIC in SAS 9.2 (SAS Institute Inc.) and accounted for participants clustered within sites.

Differences in descriptive study covariates were tested with the t test and the χ^2 test for continuous and categorical measures, respectively. Collinearity diagnostics for multivariate models were performed on all candidate covariates, looking at variance inflation factor. Finally, potential interactions between site characteristics, general adherence, and age were tested; statistically significant interactions were included in the final model. Multivariate models were conducted separately for men who received a biopsy prompt and men who did not.

Study covariates were chosen based on prior literature (7–10); the final multivariate models included factors with significant bivariate relationships (Tables 1 and 3). In selecting these variables, we were aware of the interrelated nature of the many variables involved in encouraging study adherence (21). For this analysis, therefore, we examined a full range of potential interactions between study participants, study staff, and investigators that might reinforce study bonding and enhance participant adherence to study requirements. Predictive power was measured using the area under
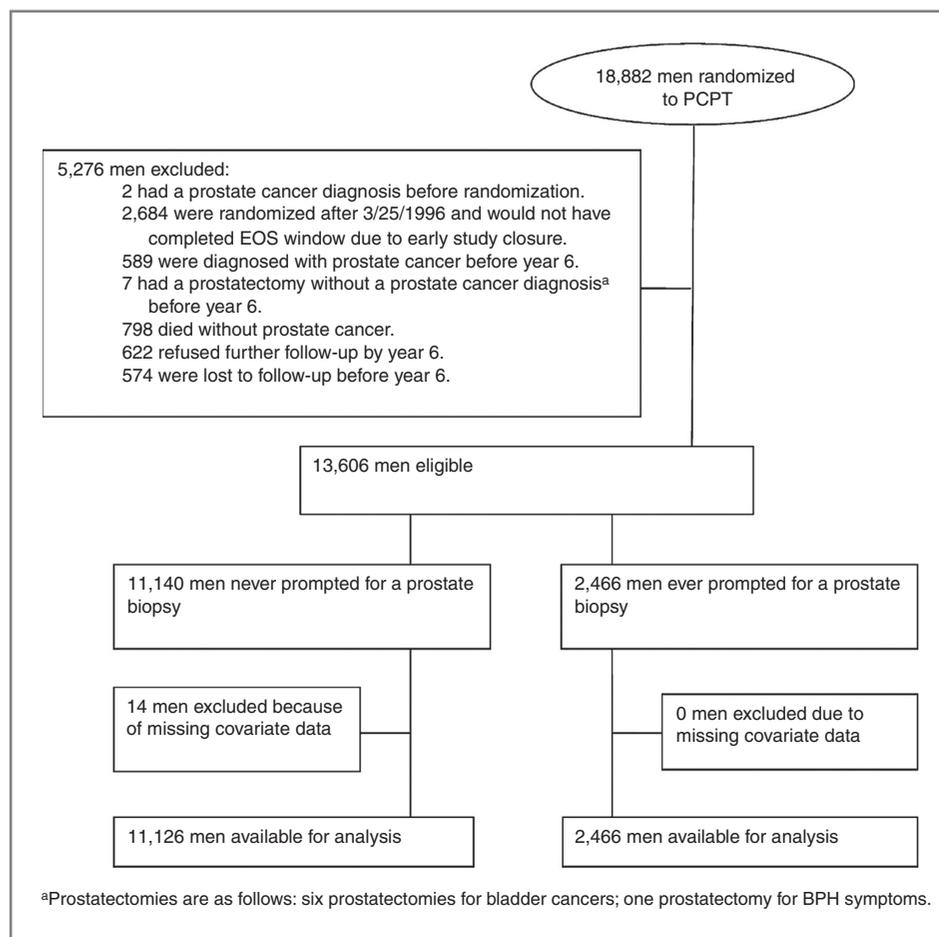

Figure 1. CONSORT diagram for PCPT analysis of factors associated with adherence to the EOS biopsy.

Table 1. Factors potentially associated with adherence to the EOS biopsy at year 7

Covariate description	Covariate description
Demographic	Comorbidities (staff interview)
Age at year 6	BMI (most recent available)
Race	Ever reported BPH
Education[a]	Ever reported a cardiovascular event
Married[a]	Ever reported diabetes
Prostate cancer/clinical history	Ever reported hypertension
Family history of prostate cancer[a]	HRQL[d] from SF-36 (participant-reported)
Ever[b] had a negative prostate cancer biopsy[c]	General Health/Health Perception score
Ever refused a biopsy[c]	Physical Function score
PSA test and/or DRE done at year 6	Mental Health score
Had a biopsy prompt at year 6[c]	Vitality score
Refused a biopsy at year 6[c]	Site characteristics
General adherence	CCOP site
Study drug adherence at year 6	Randomized fewer than 200 participants
Ever missed a contact in the past year (between years 5 and 6)	Poor performance
Ever missed a contact between randomization and year 5	Ever received an R&A grant
Ever off treatment	

Abbreviations: BMI, body mass index; BPH, benign prostatic hyperplasia.
[a]At randomization.
[b]"Ever" indicates "ever before year 6" unless otherwise specified.
[c]Considered only for men who were ever prompted for a biopsy.
[d]At year 6.

the ROC curve, with a value of ≥0.7 considered adequate discrimination (22). All data were used to calculate ROC curves (Fig. 2).

Results

Descriptive findings

Excluded participants were less likely to be white (88% vs. 93%) or be from a larger site (33% vs. 41%). Differences were greater for participants lost to follow-up than participants excluded because of early study closure. Participants who had ever received a biopsy prompt by year 6 were more likely to have an EOS biopsy than those who had not received a prompt [unadjusted OR, 1.28; 95% confidence interval (CI), 1.17–1.41]. The EOS biopsy rate among men ever and never prompted for a biopsy was 67.4% and 61.7%, respectively. The combined EOS biopsy rate for all participants included in this analysis was 62.8%.

Table 3 provides descriptive information for participants by EOS biopsy adherence status. Participants who had an EOS biopsy were different from participants who did not have the procedure. Participants who obtained biopsies were more likely to be adherent to study drug at year 6 (84.2% vs. 46.9%) or have a DRE or PSA test at year 6 (98.5% vs. 75.2%). They were more likely to come from sites that were larger, received R&A grants, or were performing well. Differences for most characteristics presented in Table 3 are not very sizeable, despite the small P values.

Models

Table 4 presents the final model and ORs for having an EOS biopsy for the subset of men who ever had a biopsy prompt by year 6. Main effects show that participants were more likely to adhere to the EOS biopsy if they were adherent to study visit schedules and procedures (adherent to study drug, had DRE/PSA test, and no missed contacts) and/or were in good health (younger age, high/better SF-36 Physical Functioning scores). The SF-36 Mental Health score was identified as being collinear with the other HRQL measures and was excluded from the analyses presented in Tables 4 and 5. Interaction results showed participants at larger sites that received R&A grants were more likely to have an EOS biopsy.

As shown in Table 5, the subset of participants never prompted for a biopsy by year 6 also were more likely to adhere to the EOS biopsy if they were adherent to study visit schedules and procedures and/or were in good health (high/better SF-36 General Health/Health Perceptions scores). Interaction results showed participants at larger sites that received R&A grants also were more likely to have an EOS biopsy.

ROC curves for each model are shown in Fig. 2. The models have adequate discrimination between men who will and will not receive an EOS biopsy; the area under the ROC curve for men ever and never prompted for a biopsy is 0.74 (95% CI, 0.72–0.76) and 0.77 (95% CI, 0.76–0.78), respectively.

Table 2. PCPT biopsy adherence activities

Strategy	Description
Biopsy video: Your prostate biopsy: The final piece of the puzzle	The PCPT Study Coordinator (Ian M. Thompson Jr) introduced video, emphasizing how procedures will differ by the PCPT site; a PCPT Urologist performed two for cause biopsies on patients (not study participants). The Study Coordinator describes the surgery as it is being performed (three components: DRE, probe and ultrasound, and the biopsy); explains what happens to the patient's prostate tissue samples; describes what the patient should do after the biopsy (e.g., take prescribed antibiotic); two study participants comment on for cause biopsies they have experienced during the trial and the importance of the biopsy information for the trial.
Focus Group Project	Four groups held (San Antonio, TX and Winston-Salem, NC) Showed video Identified participant barriers to complying with the endpoint biopsy Suggestions: • Show video as soon as possible • Consider group educational sessions • Provide additional information regarding potential interactions of vitamins, herbs, and medications regarding biopsy procedure • Plan for dissemination of information regarding study findings and next steps for participants after biopsy
Participant feedback after viewing of video	A list was posted at each PCPT site for participants to note comments about the prostate biopsy video.
Site grants	Available for holding sessions to show the biopsy video, for Q&A sessions about the biopsy with study urologist.
Study site staff meetings and workshops	Reinforced the importance of the biopsy requirement and suggested strategies for preparing study participants (End-of-Study Biopsy Packet was distributed). Throughout the trial, site staff received current information on the progress of the study through the PCPT newsletter, the PCPT Update.
EOS biopsy manual	This manual was designed to help study staff educate study participants and site urologists about the importance of the EOS biopsy. It addressed the following planning issues: logistics (e.g., communicating with site urologists); holding a biopsy information session; biopsy information for study participants (e.g., the brochure); pathology issues; plans for after the biopsy; payment information for the biopsy; information on the site grant program; and tips for finding participants lost to follow-up. Site staff was encouraged to customize the folder to make it useful for the specific site but time tables and strategies were suggested.
Articles in the PCPT participant (The Vanguard) and staff newsletters (PCPT Update)	1. Thoughts for the undecided PCPT participant (The Vanguard) 2. Will EOS biopsies tell the whole story? (PCPT Update)
Endpoint biopsy brochure and information sheets	Your Prostate Biopsy: The Final Piece of The Puzzle Brochure allowed participants to have information about the EOS biopsy that they could take with them and share with family members and medical providers: How to prepare for the procedure; the three steps involved in the biopsy; what to expect after the biopsy; follow-up with physicians; receiving the biopsy results.
Pilot study at 1 site	Held endpoint biopsy informational sessions for participants with study urologist and clinical research associates. Successful and not so successful strategies used in this pilot study were summarized for use in training workshops for all PCPT site staff. A procedural manual based on the pilot study was distributed to site staff.
Adherence Coordinator at Coordinating Center	This person (Shannon Hill) supported a comprehensive set of adherence activities that included the endpoint biopsy requirement.

Table 3. Characteristics of the subset of participants eligible for an EOS biopsy at year 6, stratified by whether or not they had the EOS biopsy

	Biopsied at year 7 (*n* = 8,529)	Not biopsied (*n* = 5,061)	*P*[a]
Demographics			
Age at year 6			
Mean (SD)	68.8 (5.4)	69.6 (5.9)	<0.0001
<65 (*n*, %)	2,212 (25.9)	1,191 (23.5)	<0.0001
65–69 (*n*, %)	2,733 (32.0)	1,504 (29.7)	
70–75 (*n*, %)	2,203 (25.8)	1,292 (25.5)	
≥75 (*n*, %)	1,381 (16.2)	1,074 (21.2)	
Race (*n*, %)			
White	7,972 (93.5)	4,695 (92.8)	0.0273
Black	258 (3.0)	196 (3.9)	
Other	299 (3.5)	170 (3.4)	
Married as of randomization (*n*, %)	7,632 (89.5)	4,313 (85.2)	<0.0001
Education as of randomization (*n*, %)			
High school diploma or less	1,517 (17.8)	946 (18.7)	0.3157
Some college/vocational school	2,442 (28.6)	1,465 (28.9)	
College degree	1,441 (16.9)	804 (15.9)	
Post-graduate degree	3,128 (36.7)	1,846 (36.5)	
Missing	1 (0.0)	0 (0.0)	
Family history of prostate cancer as of randomization (*n*, %)	1,387 (16.3)	715 (14.1)	0.0009
General adherence			
Adherent to study drug at year 6 (*n*, %)	7,181 (84.2)	2,374 (46.9)	<0.0001
DRE or PSA test done at year 6 (*n*, %)	8,397 (98.5)	3,804 (75.2)	<0.0001
No missed contacts before year 5 (*n*, %)	5,107 (59.9)	1,918 (37.9)	<0.0001
No missed contacts during the previous year (*n*, %)	6,839 (80.2)	3,231 (63.8)	<0.0001
Ever prompted for a biopsy (*n*, %)	1,661 (19.5)	803 (15.9)	<0.0001
Ever refused a biopsy (*n*, %)	927 (10.9)	500 (9.9)	0.0689
Ever had a negative biopsy (*n*, %)	1,034 (12.1)	431 (8.5)	<0.0001
Comorbidities			
No history of cardiovascular events (*n*, %)	6,084 (71.3)	3,410 (67.4)	<0.0001
No history of diabetes (*n*, %)	7,822 (91.7)	4,609 (91.1)	0.1954
Last available BMI			
Mean (SD)	27.4 (4.2)	27.4 (4.5)	0.5811
Normal (<25; *n*, %)	2,156 (25.3)	1,324 (26.2)	0.6709
Overweight (25–29; *n*, %)	4,155 (48.7)	2,418 (47.8)	
Obese (≥30; *n*, %)	2,142 (25.1)	1,274 (25.2)	
Missing (*n*, %)	76 (0.9)	45 (0.9)	
Smoking status as of randomization (*n*, %)			
Never	2,925 (34.3)	1,592 (31.5)	0.0001
Current	576 (6.8)	414 (8.2)	
Former	5,028 (59.0)	3,054 (60.3)	
Missing	0 (0.0)	1 (0.0)	
HRQL at year 6			
Vitality score			
Mean (SD)	69.5 (17.2)	65.8 (19.9)	<0.0001
Average or better (*n*, %)	6,783 (79.5)	2,404 (47.5)	<0.0001
Below average (*n*, %)	832 (9.8)	516 (10.2)	
Missing form (*n*, %)	914 (10.7)	2,141 (42.3)	
Physical Functioning score			
Mean (SD)	83.3 (19.5)	78.2 (23.9)	<0.0001

(Continued on the following page)

Table 3. Characteristics of the subset of participants eligible for an EOS biopsy at year 6, stratified by whether or not they had the EOS biopsy (Cont'd)

	Biopsied at year 7 ($n = 8,529$)	Not biopsied ($n = 5,061$)	P^{a}
Average or better (n, %)	6,779 (79.5)	2,382 (47.1)	<0.0001
Below average (n, %)	857 (10.0)	545 (10.8)	
Missing form (n, %)	893 (10.5)	2,134 (42.2)	
General Health score			
Mean (SD)	77.2 (16.2)	73.2 (18.8)	<0.0001
Average or better (n, %)	7,118 (83.5)	2,535 (50.1)	<0.0001
Below average (n, %)	515 (6.0)	394 (7.8)	
Missing form (n, %)	896 (10.5)	2,132 (42.1)	
Mental Health score			
Mean (SD)	84.8 (12.3)	82.0 (14.4)	<0.0001
Average or better (n, %)	6,722 (78.8)	2,394 (47.3)	<0.0001
Below average (n, %)	891 (10.4)	528 (10.4)	
Missing form (n, %)	916 (10.7)	2,139 (42.3)	
Site characteristics			
Ever received a recruitment and adherence grant (n, %)	6,318 (74.1)	3,049 (60.2)	<0.0001
Number of participants randomized at site (n, %)			
≤200	4,581 (53.7)	3,434 (67.9)	<0.0001
>200	3,948 (46.3)	1,627 (32.1)	
Poorly performing site (n, %)	734 (8.6)	835 (16.5)	<0.0001
CCOP (n, %)	2,835 (33.2)	1,570 (31.0)	0.0076

Abbreviation: BMI, body mass index.
[a]P values are from t tests (comparison of means) and χ^{2} tests (comparison of categorical distributions).

Site size has a modest impact on the variability of EOS biopsy adherence. The intraclass correlation coefficient (ICC) for site size and EOS biopsy adherence among men ever prompted for a biopsy is 0.11 (0.11 for small sites; 0.07 for large sites). Among men never prompted for a biopsy ICC = 0.08 (0.08 for small sites; 0.05 for large sites).
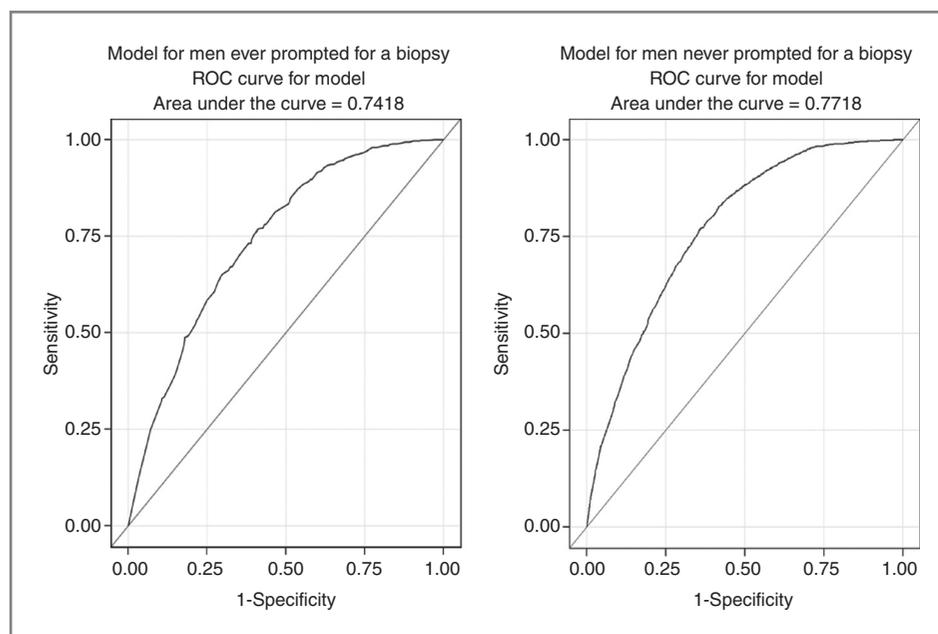
Figure 2. ROC curves for the multivariate logistic regression model stratified by biopsy prompt status.

Table 4. ORs for EOS biopsy adherence for men ever prompted for a biopsy

n = 2,466 at risk, *n* = 1,662 events		
	OR (95% CI)	*P*
Model 1		
Demographics		
Age ≤ 70[a] at year 6	1.39 (1.15–1.67)	0.0008
General adherence		
Adherent to study drug at year 6	2.29 (1.80–2.91)	<0.0001
DRE or PSA test done at year 6	5.28 (2.88–9.65)	<0.0001
No missed contacts before year 5	1.35 (1.09–1.66)	0.0053
No missed contacts during the previous year	1.47 (1.08–2.00)	0.0146
HRQL at year 6		
Physical Functioning score average or better	1.67 (1.33–2.09)	<0.0001
Site characteristics		
Ever received an R&A grant	1.80 (1.27–2.55)	0.0009
≤200 participants randomized at site	0.71 (0.50–1.01)	0.0601
Model 2		
Site size[b] and receipt of R&A grant		
Smaller site, received an R&A grant	2.36 (0.83–6.67)	0.1057
Smaller site, no R&A grant	1.50 (0.53–4.21)	0.4417
Larger site, received an R&A grant	3.81 (1.35–10.70)	0.0113
Larger site, no R&A grant	1.00 (ref.)	
Model 3		
Site size[b] and PSA/DRE test at year 6		
Smaller site, participant had DRE/PSA	5.42 (2.10–14.03)	0.0005
Smaller site, participant had no DRE/PSA	1.42 (0.49–4.14)	0.5234
Larger site, participant had DRE/PSA	7.88 (3.18–19.55)	<0.0001
Larger site, participant had no DRE/PSA	1.00 (ref.)	

NOTE: Interactions obtained by adding each one separately to the main effects model. Model 1, only the main effects; Model 2, the main effects and the site size/R&A grant interaction; and Model 3, the main effects and the site size/DRE and PSA tests interaction.
[a]Median age at year 6 for this group.
[b]Site size is defined as smaller (≤200 participants registered) or larger (>200 participants registered).

Discussion

The goal of this research was to identify factors prospectively associated with the EOS biopsy in the PCPT. More specifically, we sought to determine which factors identifiable at year 6 were associated with the willingness of a participant to undergo an invasive procedure 1 year later. The PCPT is unique because it was a prevention, rather than a treatment, trial: The biopsy procedure was critical for evaluating the intervention, but not clinically indicated for most participants. A recent study examining the use of research biopsies in therapeutic clinical trials shows that participants may not have a clear understanding of the risks and benefits of these procedures, suggesting that researchers need to improve study protocols and informed consents to ensure that participants fully understand the study procedures and requirements (23). This is particularly important in trials like the PCPT in which the EOS biopsy happens 7 years after participant enrollment.

Interpretation of results

Our results show that a variety of participant and site characteristics are associated with participant adherence to the invasive EOS requirement. At the participant level, adherence with study schedule and procedures and general good health is associated with higher EOS biopsy rates; participants at sites that were larger and/or procured R&A grants also had higher EOS biopsy rates.

Probstfield and colleagues have identified failing to adhere to the study agent regimen, missing a study visit, and going off study treatment as "red flags" (24, 25) that should be addressed during the course of the trial to keep participants fully engaged in trial activities and outcomes ascertainment.

These "red flags" coincide with the general adherence factors identified in this analysis as being associated with EOS biopsy adherence. Although the analysis does not indicate that improving adherence to study requirements will improve adherence to the EOS biopsy, it does lend support to their status as "red flags."

Table 5. ORs for EOS biopsy adherence for men never prompted for a biopsy

$n = 11,126$ at risk, $n = 6,868$ events

	OR (95% CI)	*P*
Model 1		
Demographics		
Age ≤ 68[a] at year 6	1.19 (1.08–1.31)	0.0005
Married	1.32 (1.14–1.53)	0.0002
General adherence		
Adherent to study drug at year 6	2.75 (2.38–3.18)	<0.0001
DRE or PSA test done at year 6	5.61 (4.18–7.53)	<0.0001
No missed contacts before year 5	1.37 (1.19–1.58)	<0.0001
No missed contacts during the previous year	1.25 (1.03–1.53)	0.0234
Comorbidities		
No history of cardiovascular events before year 6	1.35 (1.19–1.52)	<0.0001
HRQL at year 6		
General Health/Health Perception score average or better	1.62 (1.40–1.87)	<0.0001
Site characteristics		
Ever received an R&A grant	1.29 (0.98–1.71)	0.0730
$\leq$200 participants randomized at site	0.63 (0.47–0.84)	0.0016
Poorly performing site	0.66 (0.46–0.96)	0.0300
Model 2		
Site size[b] and receipt of R&A grant		
Smaller site, received an R&A grant	1.49 (1.15–1.94)	0.0030
Smaller site, no R&A grant	1.32 (1.03–1.69)	0.0288
Larger site, received an R&A grant	2.69 (2.10–3.45)	<0.0001
Larger site, no R&A grant	1.00 (ref.)	
Model 3		
Age at year 6[c] and site performance		
Younger participant, poor site performance	0.70 (0.46–1.06)	0.0941
Younger participant, acceptable site performance	1.24 (1.12–1.37)	<0.0001
Older participant, poor site performance	0.79 (0.57–1.10)	0.1679
Older participant, acceptable site performance	1.00 (ref.)	
Model 4		
Age and adherence to study drug, at year 6		
Younger participant, adherent	3.34 (2.77–4.03)	<0.0001
Younger participant, not adherent	1.28 (1.09–1.51)	0.0028
Older participant, adherent	2.91 (2.43–3.50)	<0.0001
Older participant, not adherent	1.00 (ref.)	

NOTE: Interactions obtained by adding each one separately to the main effects model. Model 1, only the main effects; Model 2, the main effects and the site size/R&A grant interaction; Model 3, the main effects and the age/site performance interaction; and Model 4, the main effects and the age per study drug adherence interaction.
[a]Median age at year 6 for this group.
[b]Site size is defined as smaller ($\leq$200 participants registered) or larger (>200 participants registered).
[c]Age is defined as younger ($\leq$68) and older (>68).

Our study found that older men were less adherent, as did the PLCO for any diagnostic procedure (4). In the PCPT, the lower EOS biopsy adherence rate for older participants could be related to the perceived physical demands of the procedure or age-related medical contraindications. For example, one of the reasons physicians recommended that participants not obtain the EOS biopsy was the need to stop anticoagulation medication for this study-specific procedure. It is important to note

that these physicians were not associated with the study, so their primary concern was the well-being of their patients.

We expect larger sites to perform better in nearly all aspects of the study, including having higher rates of EOS biopsies, primarily due to economy of scale. Successful large sites require better management practices to be efficient. Smaller sites can tolerate inefficiencies better and, due to small volume, may lack the motivation to

streamline study practices. For example, the top accruing PCPT site had 1,444 participants, nearly three times the next largest site, and was considered one of the best sites of PCPT for data quality. The finding about R&A grants is ambiguous. We cannot determine from this analysis whether site use of R&A grants specifically affected EOS biopsy rates, or whether there is something different about the sites that applied for and received the R&A grants.

The primary concern of this analysis is correctly identifying participants at risk of not completing final study requirements. Identifying these participants shortly before the final study outcome assessment and targeting them with intervention strategies to increase adherence with final study requirements may be a better use of limited staff time than strategies directed at all participants throughout the trial. The cost of any strategies and the cost of identifying the appropriate participants, however, must be weighed against the benefit to the study. If the study design assumptions are not being met and the ability of the study to achieve its objectives is at risk, an intervention strategy may be worthwhile to salvage the study. In the case of the PCPT, we conducted a number of adherence activities to help site staff and participants recognize the importance of the EOS biopsy. These initiatives were not formally evaluated, although we solicited and received feedback from site staff and study participants on their reaction to most of these activities; this feedback was helpful each time and helped inform the next set of activities.

PCPT met its study specified biopsy rate of 60%, which implies reasonable adherence because the study design required a 60% rate ascertainment of prostate cancer status. Interventions were suggested to all PCPT sites for enhancing adherence with the EOS biopsy because this was an invasive trial outcome. As noted in Table 2, we held EOS informational/educational sessions with participants (often funded with an R&A grant), asked sites to show the EOS biopsy video distributed to all PCPT sites at the educational session and making it accessible to participants whenever they were at the site, distributed the EOS Biopsy brochure to all participants, and provided the EOS biopsy manual to be used by site staff to ready each site and its participants for this challenging outcome.

Limitations

The study population was mostly white, highly educated, and healthy; the results may not be applicable to more diverse and underserved populations. To obtain the PCPT prostate biopsy endpoint, the study required a participant commitment of 7 years, and the models apply only to participants who remained in the study for at least 6 years.

Conclusions

A variety of factors are prospectively associated with complying with the EOS biopsy: adherence to basic requirements for research study participation, good participant health, and certain site characteristics. This model is perhaps best used as a starting point for other studies to consider when trying to increase adherence to invasive, nonclinically indicated procedures. These factors can be used to identify a subgroup of trial participants who are not likely to have a nonclinically indicated procedure. The study can then apply an appropriate intervention strategy to increase adherence to that procedure.

We conclude with a quotation from a PCPT participant who agreed to be in one of the focus groups held midway through the 7-year study period. The question was raised about the impact of any problems experienced with the study drug. One participant who indicated some problems with the drug said, "...but dropping out would be like jumping ship. All that time would be wasted." The facilitator asked him, "For you or the study?" and the participant responded, "Well, for me and the study because I am the study." Our ability to carry out successful long-term prevention trials is certainly enhanced if we can create a study environment that generates this level of participant commitment.

Disclosure of Potential Conflicts of Interest

Disclaimer

Authors' Contributions

Acknowledgments

Carolyn Harvey, PHD; M. Shannon Hill, BM; Lori Minasian, MD; Carol M. Moinpour, PhD; Rose Mary Padberg, RN, MA; Jeanne Parzuchowski, RN, MS; Jeffrey Probstfield, MD; Anne Ryan, RN; Connie Szczepanek, RN, BSN; Sarah Moody Thomas, PhD; Ian Thompson, MD; and Clarence Vaughn, MD.

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