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Mortality and Complications Following Prostate Biopsy in the PLCO Cancer Screening Trial

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Abstract

Objective—To examine mortality and morbidity following prostate biopsy in the intervention arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) trial.

Subjects and methods—PLCO abstractors recorded the types and dates of diagnostic follow-up procedures following positive screens and documented the types and dates of resultant complications. PLCO tracked participant cancers and deaths. The mortality rate in the 120-day period following prostate biopsy was compared to a control rate of deaths in the 120-day period following a negative screen in men without biopsy. Multivariate analysis was performed to control for potential confounders, including age, comorbidities and smoking. Rates of any, infectious and non-infectious complications were computed among men with negative biopsy; multivariate analysis examined risk factors for complications.

Results—Of 37,345 men enrolled in PLCO (intervention arm), 4861 had at least one biopsy following a positive screen and 28661 had a negative screen and no biopsy. The 120-day post-biopsy mortality rate was 0.95 (per 1,000), compared to the control group rate of 1.8; the multivariate RR was 0.49 (95% CI:0.2–1.1).

Among 3706 negative biopsies, rates (per 1,000) of any, infectious and non-infections complications were 20.2, 7.8 and 13.0, respectively. History of prostate enlargement or inflammation was significantly associated with increased rates of both infectious (OR=3.7) and non-infectious (OR=2.2) complications. Blacks had a higher infectious complications rate (OR=7.1); repeat biopsy was associated with lower rates of non-infectious complications (OR=0.3).

Conclusion—There was no increased mortality following prostate biopsy in PLCO. Complications were relatively infrequent, with several risk factors identified.

Keywords

prostate biopsy; complications; mortality; prostate-specific antigen

Introduction

Due to the high incidence of prostate cancer and the frequent use of prostate-specific antigen (PSA) to screen for prostate cancer, biopsy of the prostate is a very common procedure in

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Conflicts of Interest
None declared

the U.S., with well over 1 million performed annually [1]. Several recent reports have suggested high complication rates following prostate biopsy, and increasing rates over time of infectious complications [2–5]. Additionally, at least one study has suggested significant mortality associated with prostate biopsy, leading a modeling group to conclude that PSA screening would actually result in excess overall mortality due to the deaths from prostate biopsy [6,7].

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial was a randomized controlled trial that examined screening with PSA and digital rectal exam (DRE) in its prostate component [8,9]. PLCO provides an excellent opportunity to examine morbidity and mortality related to prostate biopsy. It was a large, clearly defined, multi-center cohort of men undergoing annual PSA and digital rectal exam (DRE) screening; further, biopsies following positive screens were common and were tracked by the trial, along with resulting complications. Mortality was also tracked by the trial. Finally the trial administered a baseline questionnaire that contains demographic and medical history data that can be used to assess the relationship of various patient-level factors with post-biopsy outcomes.

In this analysis, we examine mortality following prostate biopsy, and compare rates with that of men with negative prostate screens. We also analyze complication rates, and examine factors associated with complications.

Subjects and Methods

PLCO Study Design

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is a multi-center, randomized controlled trial designed to test the efficacy of screening for four types of cancer in persons aged 55–74. The methods have been described previously [10]. Briefly, randomization to an intervention or control arm took place between 1993 and 2001, with almost 155,000 persons randomized at ten screening centers. Exclusion criteria included history of a PLCO cancer, surgical removal of the entire prostate, finasteride use within the past 6 months, and starting in 1995, having had more than one PSA blood test in the past three years. At the time of randomization, subjects filled out a self-administered baseline questionnaire, which assessed demographics, screening and medical history.

Intervention arm men underwent annual PSA and DRE screening for four years, and then additionally two years of PSA-only screening. A PSA result of > 4 ng/ml or a DRE suspicious for cancer was considered a positive screen. Diagnostic follow-up of positive screens was directed by subjects' personal health care providers; PLCO did not specify a diagnostic algorithm, nor oversee the diagnostic process.

Ascertainment of Biopsies, Complications and Mortality

PLCO medical record abstractors recorded the types and dates of all diagnostic follow-up and staging procedures occurring in the year following a positive screen. They were also instructed to document any complications that were a result of a diagnostic or staging procedure and that required medical intervention. Abstractors examined the discharge summary, as well as physicians and nurses notes in the medical record, to determine whether complications had occurred. Complications were coded into about 30 categories, including several categories each for infection, non-infectious urinary complications and bleeding; the date of the complication was also recorded. For hospitalizations, abstractors were instructed to only record the hospitalization if the reason for the hospitalization was not another selected medical complication; for example, in case of fever requiring antibiotics and hospitalization, only the fever requiring antibiotics would be recorded. Specific

complications were not linked to individual diagnostic or staging procedures; thus, when multiple procedures were performed on a given man in the same study year, the procedure that caused the complication cannot be definitively determined.

Prostate cancers were ascertained through medical record abstracting of positive screens and through an annual study update (ASU) form sent to all PLCO subjects that inquired about cancer diagnoses. Deaths were ascertained primarily by means of the ASU; additionally, to obtain more complete mortality data, ASU follow-up was supplemented by periodic linkage to the National Death Index (NDI). Subjects were followed through 12/31/2009 or through 13 years of follow-up, whichever came first.

Each PLCO institution obtained IRB approval for the trial and all subjects provided informed written consent.

Statistical Methods

We examined mortality and complications in various periods following a prostate biopsy. Only those biopsies prompted by a positive PLCO prostate screen were included in the analysis, since PLCO did not consistently track prostate biopsies occurring outside of this window. Men could undergo biopsies in more than one study year (e.g., following a positive baseline screen and following a positive year 1 screen); in a single study year (i.e., after a given positive screen) men generally had only one biopsy.

We calculated the percentage of biopsies for which the subject died within 120 days, and also within 180 days as a sensitivity analysis. Deaths from prostate cancer were excluded. For a control mortality rate, we examined deaths in the 120 day (also 180) period following a negative screen in subjects without any prostate biopsy during the trial. This control group was used because they attended another medical event, prostate screening, as compared to prostate biopsy in the biopsy group, for which a person who was terminally ill or in very poor health would be unlikely to attend.

In addition to comparing raw mortality rates in the biopsy versus control groups, we also developed a logistic regression model. The model covariates included age (5 year age groups), black race, education, marital status, smoking status, study year, and a modified Charlson co-morbidity index, which was derived from baseline questionnaire responses [9]. Because repeated outcomes were used for the same subject, we utilized PROC GENMOD (SAS Version 9.2) with the repeated measures option to derive the logistic model parameters and confidence limits.

We computed the rates of any complication, infectious complications and non-infectious complications following prostate biopsy. Note that, as described above, complications were only reported at the study year level and not at the individual procedure level. To isolate the effect of prostate biopsies alone, we excluded any subject with a prostate cancer diagnosis during the same study year, as staging procedures, which included radical prostatectomy (RP) for this purpose, may have contributed to the reported complications. For ease of interpretation, we limited the analysis to the 94% of positive screens with a single follow-up biopsy in the study year. Note if there were multiple complications and multiple biopsies in the same study year, one cannot determine whether all of the complications were resulting from a single biopsy. As noted above, hospitalization as an outcome of complications was only recorded if the specific reason for hospitalization (e.g., fever requiring antibiotics) was not recorded; therefore, with these data, it is not possible to get an accurate estimate of complications requiring hospitalization. We also developed, again using PROC GENMOD with repeated measures, a multivariate logistic regression model for complications, with

covariates of age, calendar year, black race, history of prostate inflammation or enlargement (as reported on the baseline questionnaire), biopsy number, and Charlson comorbidity score.

Results

A total of 35,870 men underwent at least one PLCO prostate screen. Of these, 28,661 had at least one negative screen and no reported prostate biopsy during PLCO; altogether these men had a total of 139,931 negative screens. A total of 4836 men had at least one positive screen with a follow-up prostate biopsy (out of a total of 10,798 men with any positive screens). For these men there were a total of 5945 positive screens with a follow-up biopsy and a total of 6295 individual biopsies following positive screens (mean 1.06 biopsies per study year with at least one biopsy, with 329 men undergoing multiple biopsies in a study year).

Table 1 shows the characteristics of the above two groups of men, i.e., those with prostate biopsy and those with a negative screen and no prostate biopsy. Men with biopsy were slightly older (mean age 63.7 versus 62.4) but had slightly lower co-morbidity rates. They were generally similar in other characteristics, such as race, smoking status, marital status and education.

Table 2 displays the mortality results. For the men who underwent prostate biopsy, the mortality rate in the 120 day period post biopsy was 0.095%, with 6 deaths out of 6295 biopsies. For the control group, the mortality rate in the 120 day period following a negative screen was 0.18% (255 deaths out of 139,931 negative screens), giving a relative risk of 0.52 (95% CI: 0.2–1.2). The multivariate model gave similar results, with a relative risk of 0.49 (95% CI: 0.2–1.1). Of the 6 deaths in the biopsy group, 3 were due to ischemic heart disease, one to other heart disease, one to chronic airway obstruction, and one to pancreatic cancer (diagnosed after the biopsy).

Of the 6295 biopsies, 32.3% were followed by a prostate cancer diagnosis within 120 days, and 13.3% were followed by a RP within 120 days (median 51 days post-biopsy). None of the 6 deaths occurred in the men with RP within 120 days.

For the 180 day period post biopsy (or post negative screen), the relative risk was 0.76 (95% CI: 0.4–1.3) for the univariate and 0.70 (95% CI: 0.4–1.2) in the multivariate analysis.

Table 3 displays complication rates following prostate biopsy. There were 3706 positive screens with a (single) follow-up biopsy and no accompanying prostate cancer diagnosis during that study year; these screens were in 2,969 distinct men. A total of 75 biopsies had reported complications, 63 (84%) of which occurred within 30 days of biopsy. The rates (per 1,000) of any complication, infectious and non-infectious complications were 20.2 (95% CI: 15.6–24.9), 7.8 (95% CI: 4.9–10.7) and 13.0 (95% CI: 9.2–16.7), respectively (note two subjects had both infectious and non-infectious complications). Of the 48 biopsies with non-infectious complications, 19 had urinary-related complications and 14 had bleeding-related complications.

Multivariate results for complications are displayed in Table 4. A history of prostate inflammation or enlargement was significantly associated with increased rates of any complication (OR=2.6), infectious complications (OR=3.7) and non-infectious complications (OR=2.2). Black race was associated with significantly increased rates of any complication (OR=2.6) and infectious complications (OR=7.1), but not non-infectious complications. A later calendar year (OR=0.5) and repeat biopsy (OR=0.3) were significantly associated with decreased rates of non-infectious complications; later calendar

year did not show a significant association with infectious complications (RR=1.2, 95% CI 0.6–2.5).

None of the six subjects who died (from other than prostate cancer) in the 120 day period post-biopsy had a complication from diagnostic or staging (including RP) procedures. Three men died of prostate cancer within 120 days of a biopsy that followed a positive screen. In two of these, both of which were stage IV cases, there were no complications of diagnostic or staging procedures. The 3rd patient experienced a pulmonary embolus, deep venous thrombosis and blood loss requiring a transfusion on the same day that a prostatectomy and lymphadenectomy were performed, 106 days post-biopsy; the subject died three days later.

Discussion

In this study of men in the PLCO intervention arm, who underwent receiving annual PSA and DRE screening, we found no evidence of excess mortality following prostate biopsy. In both univariate and multivariate analyses, the mortality rate in the 120 (or 180) day period following biopsy was actually less than that seen in a comparable control group, though not statistically significantly so.

Our results with respect to mortality are similar to those from the ERSPC, another randomized trial of prostate screening. Among 12,959 men with a positive PSA screen compared to 37,235 with a negative screen, mortality rates in the 120 day period following the screen were similar, 0.24%, for each group; further, 90% of positive screen men had biopsy, with 59% undergoing it within a month of the screen and 94% within 3 months [11]. The 0.24% mortality rate following a negative screen in ERSPC is similar to the rate found in PLCO in the negative screen group, 0.18%.

In PLCO, because the biopsy rate within one year of a positive screen was rather low, around 30% (although with longer follow-up biopsy rates were considerably higher), comparing 120 day mortality in the positive versus negative screen group, as was done in ERPSC, would not be a valid method of assessing the risk due to biopsy since the positive screen group in PLCO is heavily diluted with men not actually undergoing biopsy in the time period. Therefore, we compared the mortality rate among men who did undergo biopsy following a positive screen with that among men with negative screens, using the 120 day period following biopsy in the former and the 120 day period following the negative screen in the latter. It may also be of interest to compare the mortality rate of the biopsy group with that of men who had a positive screen and did not undergo biopsy, as both of these groups had a positive screen in common. Among 9161 instances of a positive screen and no subsequent biopsy, the mortality rate in the 120 day period following the screen was 0.34%, compared to a rate of 0.095% among biopsied men and 0.18% among men with a negative screen. However, there is a built-in bias with this group, in that one reason these men may have not undergone biopsy is that they died or became terminally ill before they would have had time to schedule and undergo a biopsy. Still, it is reassuring that biopsied men had a substantially lower observed mortality rate than did men with positive screens and no biopsy, so that even with the bias taken into account there was probably no excess risk among the biopsied men.

In contrast, a population-based Canadian study of over 22,000 men undergoing prostate biopsy (mean age 69.3) showed a significantly elevated mortality rate in the 120 day period following biopsy, 1.3%, as compared to a comparison group rate of 0.3% ($p < 0.001$) [6]. This 1.3% rate is substantially higher than that observed in either PLCO (0.095%) or ERSPC, although the mean age was higher in the Canadian cohort. Limiting the PLCO analysis to biopsied men 63 and over at baseline results in a similar mean age of 69.3, but

the mortality rate was still only 0.11%, or less than a tenth of that found in the Canadian cohort. A healthy volunteer effect has been documented in PLCO; however, the observed standardized mortality ratio (SMR) of 40–45% is considerably smaller than the ten-fold difference seen here [12]. Moreover, men undergoing prostate biopsy would be expected to have a reasonable life expectancy and to not be in very poor health, so the Canadian cohort would also likely have an SMR below 100%.

A study using the SEER-Medicare data base of over 17,000 men undergoing prostate biopsy showed, in multivariate analysis, a mortality relative risk in the 30 days following biopsy of 0.29 (95% CI 0.22–0.38) compared to a control population [1]. However, as the control population was essentially a sample of all Medicare enrollees, it likely included a higher proportion of very sick patients than would be present in a group undergoing prostate biopsy.

We observed in the PLCO cohort a relatively low rate of complications of about 2%, with a rate of infectious complications of about 0.8%. A Canadian (Ontario) study of over 40,000 men without prostate cancer showed a 30-day post-biopsy hospitalization rate for the indications of infection, bleeding or urinary obstruction of 1.9%; of these, 72% were for infections, giving a hospitalization rate due to infections of around 1.4% [2]. Thus the rate of infectious complications in PLCO, with or without hospitalization, was only about half the rate (with hospitalization) seen in the Canadian study. Rates of complications in other studies were also generally higher than in PLCO. In a study of the Rotterdam site of ERSPC, fever was reported after 4.2% of biopsies, and hospitalization after 0.8% [5]. A study of 1147 men with biopsy, nested within the U.K. ProtecT study, showed that 1.3% required hospital admission for complications and a further 10.4% initiated a biopsy related consultation with a physician, nurse or other source of medical advice [4]. A U.S. study of 1,000 consecutive biopsies at a single institution showed a rate of hospitalization or emergency room visits due to complications from prostate biopsy of 2.5%, with about half (48%) of the complications being infection-related [3]. The SEER-Medicare study showed a 30-day hospitalization rate of 6.9%, as compared to 2.7% for a control group [1].

In the Canadian study cited above, the hospitalization rate increased significantly with calendar year, rising from 1.0% in 1996 to 4.1% in 2005 [2]. The Rotterdam ERSPC analysis also showed that the hospitalization rate increased significantly over the study period (1993–2011) [10]. In both studies, the majority of hospitalizations were due to infection, and the increase has been suggested to be associated with increasing antimicrobial resistance. In contrast, in PLCO, we failed to reject the null hypothesis of no time trend for infectious complications. A retrospective power analysis, however, showed that the study only had about 35% power to detect a two-fold increase in the infectious complication rate from the earlier (1994–1998) to later (1999–2006) period. The rate of non-infectious complications decreased significantly over time in PLCO.

The Rotterdam ERSPC analysis showed, in a multivariate model, elevated relative risks for post-biopsy hospitalization associated with prior prostatitis (RR=1.58) and prostatic enlargement (RR=1.65), though neither reached statistical significance [5]. The study nested in ProtecT showed similar suggestive but not statistically significant associations of an increased rate of health care contact with prostatitis and prostatic enlargement [4]. We found in PLCO significantly elevated risks for complications (both infectious and non-infectious) associated with prior prostate problems, which included both enlargement and inflammation.

We also found that black race was significantly associated with an increased infectious complication rate, but not an increased rate of non-infectious complications. The SEER-Medicare study found that non-whites (compared to whites) had a significantly increased

risk (RR=2.1) for infectious complications, but no increased risk (RR=0.92) for non-infectious complications [1].

A limitation of the study was that details of the prostate biopsy, such as the number of cores, was not recorded. In addition, by the nature of the medical record abstracting process, which did not record hospitalizations in most instances, we could not estimate a post-biopsy hospitalization rate. Another limitation is that all biopsies included in this analysis were initiated following positive PSA and/or DRE screening tests; therefore, these results may not apply to biopsies conducted for work-ups of suspicious prostate-related symptoms.

In conclusion, there was no increased mortality following prostate biopsy in PLCO. Complications were relatively infrequent, with several risk factors identified.

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Table 1

Characteristics of men with and without prostate biopsy

	Negative Screen, no Prostate Biopsy (n=28661)	Positive Screen with Follow-up Prostate Biopsy (n=4836)
Mean (SD) age at baseline	62.4 (5.3)	63.7 (5.2)
Mean (SD) age at start of mortality follow-up period [1]	64.4 (5.4)	65.5 (5.3)
	%	%
Black Race	4.2	5.2
Married	82.1	83.6
College graduate	40.8	41.0
Current Smoker	11.5	10.3
Former Smoker	51.8	49.4
Modified Charlson co-morbidity score ≥ 1[2]	29.5	26.3
Prostate inflammation or enlargement[3]	23.2	34.0
Calendar year at start of mortality follow-up period [1]		
1994–1998	39.6	51.8
1999–2002	48.8	41.4
2003–2006	11.6	6.8

[1] Start of mortality follow-up was time of negative screen for no biopsy group and time of biopsy for biopsy group. Note subjects could have multiple mortality follow-up periods; each is counted in table.

[2] Includes history of stroke, coronary heart disease/heart attack, cancer, diabetes, COPD, and liver disease. Assessed at baseline.

[3] Assessed at baseline.

Table 2

Post-biopsy mortality

		Time Period	
		120 Days	**180 Days**
Biopsy Group			
	# Biopsies	6295	6295
	# Deaths	6[2]	14[2]
	Rate per 1000 Biopsies	0.95	2.2
No Biopsy (Negative Screen) Group			
	# Negative Screens	139,931	139,931
	# Deaths	255	411
	Rate per 1000 Negative Screens	1.8	2.9
Relative Risk (Biopsy Group versus no Biopsy Group)	Univariate	0.52 (0.2–1.2)	0.76 (0.4–1.3)
	Multivariate [1]	0.49 (0.2–1.1)	0.70 (0.4–1.2)

[1]Model included age (5 year), marital status, black race, college education, smoking status, modified Charlson comorbidity score, and study year.

[2]The six deaths within 120 days were due to pancreatic cancer, ischemic heart disease (3), other heart disease and chronic airway obstruction. Eight additional deaths in the 120–180 day period were due to other heart disease, other respiratory disease, lung cancers, pneumonia, and accidents/injury (4). Note deaths from prostate cancer excluded.

Table 3

Complication rates following biopsy in men without prostate cancer

		All Complications (N=75)	Infectious Complications (N=29)	Non-infectious Complications (N=48)_
	Total biopsies[1]	**Rate (per 1000)**	**N (Rate per 1000)**	**N (Rate per 1000)**
All	3,706	20.2	7.8	13.0
Covariate				
Under Age 70[2]	2,821	17.7	6.4	11.7
Age 70+ [2]	885	28.2	12.4	16.9
P-value		0.06	0.09	0.23
Year 1994–1998[2]	1965	25.4	7.6	18.3
Year 1999–2006[2]	1741	13.5	8.0	6.9
P-value		0.02	0.88	0.003
Non-Black Race	3564	19.1	6.5	13.2
Black Race	142	49.3	42.3	7.0
P-value		0.02	<0.001	0.53
Charlson Score = 0[3]	2753	17.8	7.6	10.9
Charlson Score ≥ 1[3]	953	27.3	8.4	18.9
P-value		0.08	0.82	0.06
No Prostate Inflammation or Enlargement [4]	2325	12.5	3.9	8.6
Prostate Inflammation or Enlargement [4]	1381	33.3	14.5	20.3
P-value		<0.001	0.001	0.003
First Biopsy	2969	22.6	7.7	15.2
Repeat Biopsy	737	10.9	8.1	4.1
P-value		0.07	0.91	0.03

[1] Restricted to subjects with a single biopsy in the study year and no corresponding prostate cancer diagnosis in that study year.

[2] Age/year at time of biopsy

[3] Modified Charlson Score, see Table 1. Assessed at baseline.

[4] Assessed at baseline.

Note: P-Value is for null hypotheses of equal rates across covariate categories.

Table 4

Multivariate logistic regression model of complications following biopsy in men without prostate cancer

	All Complications	Infectious Complications	Non-infectious Complications
	Multivariate OR (95% CI)	Multivariate OR (95% CI)	Multivariate OR (95% CI)
Covariate			
Age 70+ (versus age under 70) [1]	1.4 (0.9–2.4)	1.8 (0.8–4.0)	1.3 (0.7–2.4)
Year 1999–2006 (versus year 1994–1998) [1]	0.7 (0.4–1.1)	1.2 (0.6–2.5)	0.5 (0.2–0.9)
Black Race (versus non-black race)	2.6 (1.2–5.9)	7.1 (2.7–18)	0.5 (0.1–3.6)
Charlson Score ≥1 (versus Charlson Score=0) [2]	1.4 (0.9–2.3)	0.9 (0.4–2.1)	1.7 (0.9–3.0)
Prostate Inflammation or Enlargement (versus no inflammation or enlargement)[3]	2.6 (1.6–4.3)	3.7 (1.6–8.8)	2.2 (1.2–4.1)
Repeat Biopsy (versus first biopsy)	0.5 (0.2–1.1)	0.98 (0.4–2.8)	0.3 (0.1–0.9)

[1] Age/year at time of biopsy

[2] Modified Charlson Score, see Table 1. Assessed at baseline.

[3] Assessed at baseline.

Note: Restricted to subjects with a single biopsy in the study year and no corresponding prostate cancer diagnosis in that study year.