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Projecting Prostate Cancer Mortality in the PCPT and REDUCE Chemoprevention Trials

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Abstract

Introduction—Two recent chemoprevention trials demonstrated significant reductions in overall prostate cancer incidence. However, a possible increase in high-grade disease has raised concerns that the drugs' harms, including mortality due to high-grade disease, may outweigh the benefits. We attempted to estimate the effect on prostate cancer mortality of these drugs in order to be able to better evaluate the cost-benefit tradeoff.

Methods—We analyzed prostate cancer incidence in the Prostate Cancer Prevention Trial (PCPT) and REDUCE trials, which evaluated finasteride and the related compound dutasteride, respectively (both versus placebo). We utilized 13-year prostate cancer survival data from the Prostate, Lung, Colorectal and Ovarian (PLCO) trial to project prostate cancer mortality from incidence patterns; survival rates were applied to incident cancers according to prognostic strata, which were defined by Gleason score, PSA and clinical stage. For PCPT, the analysis was performed using both original trial results and previously published adjusted analyses that attempted to account for artifacts related to the drugs' effect on prostate volume.

Results—For PCPT, the estimated relative risk (RR) for prostate cancer mortality was 1.02 (95% CI 0.85-1.23) using the original trial results and 0.87 (95% CI 0.72-1.06) and 0.91 (95% CI 0.76-1.09) based on the adjusted PCPT analyses. For REDUCE, the mortality RR was 0.93 (95% CI 0.80-1.08).

Conclusions—Projecting a mortality outcome of PCPT and REDUCE as an approach to weighing benefits versus harms suggests at most a small increase in prostate cancer mortality in the treatment arms, and possibly a modest decrease.

Keywords

chemoprevention trial; dutasteride; finasteride; Gleason score; prostate cancer; mortality

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Introduction

Chemoprevention is one approach to lessening the burden of prostate cancer. In 2003, the Prostate Cancer Prevention Trial (PCPT) reported a 25% reduction in prostate cancer period prevalence associated with the 5-alpha reductase inhibitor finasteride compared to placebo in men with baseline prostate-specific antigen (PSA) under 3ng/ml (1). The REDUCE trial, comparing the related 5-alpha reductase inhibitor dutasteride against placebo in men with PSA above 3 ng/ml and a prior negative biopsy, reported in 2009 a 23% reduction in overall prostate cancer period prevalence (2).

The results of PCPT and REDUCE, however, raised concerns about high grade disease; in both trials an increase was observed in the incidence of Gleason 8-10 disease in the active drug arm (1,2). Although the increase was not statistically significant in either study, the numbers of Gleason 8-10 cases were small and there was relatively little power to identify a significant difference. The biological plausibility of the increase in high grade disease has been debated, with some evidence of a possible mechanism (3,4). Recently, an FDA panel voted overwhelmingly against approval of both finasteride and dutasteride for a cancer prevention indication (5). The primary reason for the disapproval was the apparent increase in the incidence of Gleason 8-10 cancers in the active drug arm that was seen in the two trials.

At the FDA panel, and elsewhere, the question arose as how to balance a clear decrease in Gleason 2-6 disease, and possibly Gleason 7 disease, with a possible increase in Gleason 8-10 disease. The absolute number of Gleason 2-6 cancers prevented by the drugs overwhelms the observed absolute number of additional Gleason 8-10 cancers, since Gleason 2-6 is so much more common. However, Gleason 8-10 disease has considerably worse prognosis than Gleason 2-6 (or even 7) disease, so it is not clear how the trade-off would be evaluated. Further, especially in PCPT, where many of the Gleason 2-6 cancers were diagnosed only on mandated end-of-study biopsy in men with low PSA, the clinical significance of these cancers has been questioned (5).

One common metric that could be employed to assess the benefits and harms of an increase in one type of prostate cancer versus a decrease in another is disease-specific mortality. Specifically, one could project from the incidence results, using appropriate survival statistics, the prostate cancer-specific mortality rate over an extended period of follow-up for the drug and placebo arms (note that neither REDUCE nor PCPT planned for an extended mortality follow-up). This approach would effectively weight each cancer according to its risk of disease-related death and use prostate cancer mortality as the common metric to compare the risks and benefits of the drugs. The recently published United States Preventive Services Task Force recommendations statement on screening for prostate cancer, which recommended against such screening, suggested, under research needs and gaps, that “additional research would be useful to ... determine the effect of 5-alpha reductase inhibitors on prostate cancer mortality” (6). This exercise then comprises a modeling-based component of such research.

Several prior analyses have attempted to estimate the survival benefit associated with finasteride by applying prostate survival statistics to observed prostate cancer incidence rates in PCPT (7-9). These analyses all utilized survival rates obtained either from cohorts of men with symptomatically detected disease or from the Surveillance, Epidemiology and End Results (SEER) data base, which represents a mixture of screen-detected and symptomatically detected disease. However, due to frequent PSA screening and routine scheduled (by protocol) biopsies in both PCPT and REDUCE, the cancers diagnosed in these trials were overwhelmingly detected in the absence of symptoms. Because of lead time

and overdiagnosis, which are both substantial in prostate cancer, survival rates would be expected to be substantially higher in screen detected cases than in symptomatically detected cases, even if screening had no effect on prostate cancer mortality (10). Therefore, to estimate the mortality effect in these two chemoprevention trials as accurately as possible, we utilized survival rates obtained from the intervention arm of the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial, where men were receiving annual screening with PSA.

Methods

PCPT

The PCPT randomized 9,423 men to finasteride (5mg/day) and 9459 to placebo (1). Eligibility criteria included a baseline PSA level ≤ 3.0 ng/ml. Subjects were treated and followed over a 7 year period, during which they were monitored for compliance and screened annually with PSA and digital rectal exam (DRE). Subjects with an elevated PSA or suspicious DRE were referred for biopsy. In addition, all subjects without cancer diagnosis at the end of the study were asked to return for an end-of-study biopsy. All biopsies were reviewed centrally by pathologists blinded to study arm. Among men with at least one biopsy, a 25% reduction in prostate cancer period prevalence was reported for men in the finasteride compared to placebo arm.

An issue in PCPT was a possible bias in cancer detection and Gleason grading on biopsy due to the effect of finasteride in shrinking the prostate gland. Several research groups attempted to correct for this bias using various approaches, including extrapolating the Gleason scoring from the subset of cases with radical prostatectomy and correcting for differences across arms in prostate volume (11-13). As described below under Statistical Methods, we performed the mortality projection in multiple ways for PCPT, using both the observed (biopsy) Gleason scoring and adjusted scoring.

REDUCE

The REDUCE trial tested dutasteride 0.5 mg/day against placebo for prostate cancer chemoprevention (2). Eligibility criteria included a baseline PSA of 3.0-10 ng/ml (2.5-10 for men less than 60), and a history of a single negative biopsy. Subjects were treated and followed for four years and received PSA tests every 6 months. Biopsies were performed at year 2 and year 4 or for cause. All positive biopsies were reviewed centrally by a pathologist who was blinded to treatment arm. A total of 8,231 men were enrolled in the trial. Among men who underwent prostate biopsy in years 1-4, an overall reduction of 20% in prostate cancer period prevalence was observed for the dutasteride compared to the placebo arm.

PLCO

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 at baseline (14-16). The methods have been described elsewhere. Briefly, randomization to a screened or control arm took place between 1993 and 2001, with 154,900 persons (and 76,685 men) enrolled at ten centers. Men in the screening arm received PSA and DRE at baseline (year 0) and then annually through year 3, and received PSA only at years 4 and 5. Exclusion criteria included history of a PLCO cancer, removal of the entire prostate, and starting in 1995, having had more than one PSA blood test in the past three years. A PSA result of > 4 ng/ml was considered positive. Prostate cancer cases and deaths were ascertained through routine follow-up of positive screens and through the use of an annual study update questionnaire supplemented with National Death Index searches. Certified tumor registrars at each screening center abstracted, using a

standardized protocol, clinical and pathologic (if available) T, N and M stage characteristics, biopsy Gleason score and Gleason score from radical prostatectomy (if performed). There was no centralized pathology review of Gleason scoring.

The major characteristics of all three trials are summarized in Table 1.

Statistical Methods

To estimate mortality from prostate cancer (PCa) from the chemoprevention trial data we simulated a mortality endpoint trial by "virtually" following up all diagnosed PCa cases. Since there are 13 available years of PLCO survival data, to utilize all that survival information we virtually followed subjects with PCa for 13 years from diagnosis. As subjects were diagnosed at different study times, however, this necessitates that (virtual) follow-up time from enrollment varied across cases. Cases diagnosed at the latest time in PCPT, year 7, were followed for 20 years from enrollment while those diagnosed earlier, at year "n", were followed for only n+13 years, and were effectively "censored" for the last (7-n) years of a virtual 20 year mortality trial.

This virtual censoring should not bias the results, however, because the time of diagnosis was similar across arms in both PCPT and REDUCE. In PCPT, in the finasteride arm, 23% of cancers were diagnosed through year 3 and 46% diagnosed at end of study biopsy; the corresponding percentages for the placebo arm were 23% and 50%. In REDUCE, 66% of dutasteride versus 68% of placebo arm cancers were diagnosed at study years 1-2. Thus, virtual censoring was about equal across arms for both trials.

We divided PCa cases into prognostic strata, and for each stratum computed expected deaths as the number of cases times one minus the appropriate survival rate, where the latter was the 13 year prostate-specific survival rate in the corresponding stratum among intervention arm PLCO cases as computed using the Kaplan-Meier method. For each stratum, the same survival rate applied for each trial arm. We did not account for other-cause mortality, as it would be expected to be similar for each arm. Total expected deaths were calculated by summing up expected deaths over all prognostic categories, with death rates defined as expected deaths over total subjects with incidence endpoint data (i.e., with biopsy). The relative risk (RR) for mortality was computed as the ratio of expected death rates.

For PCPT, as the majority of Gleason 2-6 cancers were diagnosed at end-of-study biopsy (i.e., not for cause) and were generally low risk, we stratified these further according to PSA level (≤4, >4 ng/ml), and T stage (T1a-T1c, T2a-T2c) for clinically localized cancers, and by TNM stage (III, IV) for non-clinically localized cancers. Since finasteride reduces PSA levels, for the drug arm we used the same adjustments to PSA as were used in PCPT to determine for-cause biopsy, i.e., multiplying measured PSA by a factor of 2.0 through year 3 and by a factor of 2.3 afterwards (1). Gleason 7 and 8-10 cancers were stratified according to TNM stage (I/II, III and IV); for stages III and IV, due to small numbers, control and intervention arm PLCO cases combined were used to derive survival rates. Also, for stage IV, Gleason 2-6 and Gleason 7 cases were grouped together.

In addition to the standard ("unadjusted") analysis of PCPT data, we performed two "adjusted" analyses, based on adjustments for the biopsy grading artifact mentioned above. The first adjusted analysis is based on the method of Pinsky et al, which involved extrapolating radical prostatectomy (RP) Gleason results to all cases; the second is based on the analysis of Cohen et al., which modeled Gleason specific risk corrected for differences in volume and numbers of biopsy cores across arms (12,13).

For the first adjusted analysis, the method derived Gleason category-specific mis-classification probabilities of biopsy grading that were differential by arm; applying these produced the adjusted RRs for each Gleason category reported by Pinsky et al (12). For the current analysis, we applied these mis-classification probabilities assuming that they were independent of PSA and clinical stage. This produced adjusted counts of cases in each Gleason category, with the categories stratified similarly as described above by PSA and clinical stage.

For the second adjusted analysis, the reported odds ratios (ORs) from Cohen et al. were converted to revised counts by Gleason category in the placebo arm; counts in the finasteride arm were assumed unchanged (13). This (prostate volume-adjusted) method, unlike the RP extrapolation method, changes not only the Gleason distribution of cases but also the total number of cases, since more cancers are likely to be missed in the placebo arm due to larger volume. As above, conversions of Gleason category were assumed independent of PSA and clinical stage; in addition, all additional placebo arm Gleason 2-6 cancers were assumed to be of the lowest risk (PSA < 4 and T1a-T1c).

For REDUCE, unlike PCPT, we did not have the access to the raw data, so we were only able to use as strata the reported Gleason categories (2-6,7,8-10). Note that the majority of men had PSA > 4 in REDUCE (mean baseline PSA=5.9, SD=1.9) so it is not as critical to stratify by PSA (or T-stage).

A boot-strapping approach was utilized to calculate confidence intervals on the relative risk for mortality. Specifically, we performed bootstrapping with replacement (n=1000 runs) to randomly generate replicate trial data sets and then applied the process described above to each replicate, including necessary modifications for the adjusted PCPT analyses. Variability in the PLCO-derived survival rates was accounted for by sampling from the distribution of survival rate estimates, which were assumed normal with the standard error as computed from the Kaplan-Meier analysis.

Results

Table 2 summarizes the findings of PCPT and REDUCE with respect to prostate cancer period prevalence by arm and Gleason category. For PCPT, the data for the observed (biopsy) Gleason categories are shown as well as the results of the adjusted analyses. For Gleason 7 cases in PCPT, the period prevalence relative risk (RR) was slightly above 1 (1.08) in the unadjusted and below one (RR=0.79 and 0.89) in the adjusted analyses. RRs were below 1 for Gleason 2-6 cases (range 0.47-0.64) and above 1 for Gleason 8-10 cases (range 1.44-1.61) in all the PCPT analyses. In REDUCE, period prevalence RRs were lower than one for Gleason 2-6 (RR=0.73) and Gleason 7 (RR=0.92) cases, and greater than one (RR=1.60) for Gleason 8-10 cases.

Table 3 shows 1-Survival rate estimates (and standard errors) at 13 years derived from the PLCO cohort for different prognostic strata. These rates were utilized to compute the mortality projections for the two trials.

Table 4 displays the results of the projected mortality analysis. For the PCPT unadjusted analysis, expected death rates were similar in each arm, 14.6 (finasteride) and 14.2 (placebo) per 1,000 men, for an RR of 1.02 (95% CI 0.85-1.23). The death rate due to Gleason 2-6 cancers was greater in the placebo arm, whereas the death rate due to Gleason 8-10 cancers was greater in the finasteride arm. The adjusted analyses showed RRs of 0.87 (95% CI: 0.72-1.06) and 0.91 (95% CI: 0.76-1.09) for the RP Gleason and prostate-volume methods, respectively. In the RP Gleason adjusted analysis, the death rate differential (finasteride – placebo) for Gleason 7 disease was -2.0 (8.6 versus 10.6), compared to 0.2 (5.4 versus 5.2)

in the unadjusted analysis; the differential also decreased for Gleason 8-10 cases, from 2.1 to 1.2. In the prostate volume adjusted analysis, the death rate differential also decreased for Gleason 7 disease (compared to the adjusted analysis). In this (volume) analysis, deaths rates for 7-10 disease were essentially equal, reflecting the adjusted RR of 1.03 for 7-10 disease, with minor adjustments for small clinical stage differences between arms; however, the death rate due to Gleason 2-6 disease was lower in the finasteride arm, resulting in the mortality RR of 0.91.

For REDUCE, the death rates were 16.4 (dutasteride) versus 17.7, for an RR of 0.93 (95% CI: 0.80-1.08). The death rate was higher for Gleason 8-10 cases in the dutasteride arm, but lower for the Gleason 2-6 and the Gleason 7 cases.

Discussion

Like most chemoprevention trials, neither PCPT nor REDUCE had a cancer mortality endpoint, but rather an incidence endpoint. For a slow-growing tumor like prostate cancer, the length of follow-up required for a mortality endpoint would be considerable, on the order of 15-20 years, making such trials logistically prohibitive under most circumstances. For PCPT and REDUCE, even if the cohorts were followed for a long period, as this analysis has done in a virtual manner, the sample size was still too small to have adequate power with a reasonable hypothesized mortality reduction. Based on the current analyses, assuming a true mortality reduction of 15% and 15-20 years of follow-up from randomization, the power of the study would only be in the range of 20-30%.

Realistically, thus, mortality endpoint chemoprevention trials are unlikely to be performed for prostate cancer and we are left with using cancer incidence as a surrogate endpoint. With this surrogate endpoint unclear in these trials, however, due to a possible increase in high-grade cancer along with an overall incidence decrease, a modeling exercise that projects future mortality is one approach in attempting to move from the surrogate endpoint (incidence) to the endpoint of arguably greater interest (mortality).

Any attempt to extrapolate a mortality effect from an incidence one, however, must be interpreted cautiously. In our analysis of PCPT, due to widely expressed concerns about the preponderance of cancers, primarily Gleason 2-6, that were not detected for cause and that may have limited clinical significance, we made efforts to carefully stratify by important prognostic variables, T-stage and PSA, in addition to Gleason score, when applying survival rates from PLCO. In PCPT, 78% of finasteride and 77% of placebo arm Gleason 2-6 cancers were T1a-T1c, which was modestly higher than the comparable percentage in PLCO (68%). Due to this stratification, the survival rates we applied should reasonably approximate the true rates for this (PCPT) cohort. Additionally, we are estimating the relative risk of mortality, which is less sensitive to survival rate fluctuations than absolute mortality rates. For REDUCE, since men had generally high (> 4ng/ml) baseline PSA, concerns about clinically insignificant disease were lower, and without stage or PSA data available to us, we only stratified survival on Gleason score. To assess the potential effect of additional stratification by PSA and stage, we repeated the PCPT analysis using only the Gleason categories (2-6,7,8-10) as survival strata. Although absolute mortality rates were 10-20% higher, RRs were very similar, 0.99 (versus 1.02) for the unadjusted analysis and 0.87 and 0.88 (compared to 0.87 and 0.91) for the two adjusted analyses. Thus further stratification for REDUCE would likely have resulted in little change in the estimated mortality RR.

Although, for PCPT, we stratified survival by Gleason score, PSA and stage, there are other prognostic factors that we were unable to account for because they were not collected in PLCO. The CAPRA risk assessment tool, which has been validated as a predictor of prostate

cancer specific mortality, utilizes percent positive cores in addition to Gleason score, PSA, and stage (and age) in determining a ten point prognostic index; specifically, one point is allotted for percent positive cores > 33% (17). Analysis of PCPT shows that for Gleason 2-6 low risk (T1/T2) disease there was roughly a 5% differential by arm in cases meeting this threshold, with higher rates in the placebo arm. Additionally, a one point increase in the CAPRA score in low risk men adds approximately a 2% decrease in 10 year prostate-specific survival (17). Using these numbers, we were able to effectively further stratify the PLCO survival strata for Gleason 2-6 disease by percent positive cores. The result was essentially no change in the mortality RRs; 1.02 and 0.87 as before for the unadjusted and adjusted RP Gleason analysis and 0.90 versus 0.91 for the adjusted volume analysis.

There is a general consensus in the research community that some bias in prostate cancer detection and/or biopsy grading occurred in PCPT, either of which would favor the finasteride arm; however, the magnitude of such bias and the appropriate methods for adjusting for it are less clear. Using two previously published methods for such an adjustment, we obtained RR estimates that were very similar (0.87 and 0.91). Another adjusted analysis, which also utilized the RP Gleason results, produced lower incidence RR estimates for Gleason 7-10 and 8-10 disease, RR=0.73 and 1.25, respectively, than did the RP Gleason method utilized here (RR=0.87 and 1.44, respectively) (9). Applying this analysis to our mortality projections would result in a lower mortality RR than those seen here. A similar artifact with respect to biopsy grading and detecting of prostate cancer may have also occurred in REDUCE. An analysis of the effects of dutasteride on prostate volume estimated that cancer detection rates were increased by 11-17% in men on dutasteride as compared to placebo (18). Adjusting for such artifacts would reduce the projected mortality RR estimate for dutasteride from that computed here.

Several prior analyses utilized prostate cancer survival rates to assess the benefits versus harms of finasteride, with life-years saved as the metric (7-9). Each produced a range of estimates depending on whether Gleason grade differences were deemed artifactual or not and other considerations. Grover et al. demonstrated per person life years gained of between 0.02 to 0.2 years and Lotan et al. showed similar life years gained of between 0.35 to 3 months (0.03 to 0.25 years); the greatest gains were achieved under the assumption that all Gleason grade differences were artifactual while the lowest were achieved assuming the grade differences were as observed and that only cancers detected on for-cause biopsy contributed to mortality (7,8). Zeliadt et al., using SEER survival rates, showed gains of between 0.006 to 0.04 life years per person, with the latter derived assuming grade differences were artifactual (9). As mentioned in the Introduction, however, the survival rates employed in these analyses were not derived from the experience of highly screened cohorts. For example, Lotan et al. used a 15 year cause-specific survival rate for Gleason 5-6 disease of 85% (for men 60-64) based on a case series of clinically detected cancers, whereas in the current analysis (Table 3) the 13 year cause-specific survival for Gleason 2-6 cases (92% of which were Gleason 5-6) was 96.2%. Analysis of PLCO and SEER data shows that for Gleason 5-7 cases the death rate (i.e., 1-cumulatitve survival rate) was about one third lower in PLCO as compared to what would be expected based on SEER survival rates.

One can convert the deaths rates shown in Table 4 to life years saved, at least for the 13 year follow-up period we utilized. For Gleason 2-6, 7 and 8-10 cases, the average life years lost during this period for a man dying from prostate cancer were 4.0, 4.4 and 6.1, respectively, based on the PLCO survival rates. Taking the adjusted RP Gleason analysis results as an example, the differential death rate per 1000 (placebo minus finasteride) of 1.5 (i.e., 4.0-2.5) for Gleason 2-6 disease translates into a relative life years gained for finasteride arm men of 6.0 per 1000 (1.5*4.0). A similar analysis for Gleason 7 and Gleason 8-10 cases gives

relative life years gained for finasteride arm men of 8.8 (2.0*4.4) and -7.3 (-1.2*6.1) per 1000, respectively. This sums to 0.0075 life years gained per person (or 7.5 per 1000), which is 5 to 33 times less than the most optimistic figures from the above three studies. These divergent results are explained by the higher survival rates, especially for Gleason 2-6 disease, used in the current analysis, as well as by differences in how the possible grading artifact is dealt with. While our RP Gleason analysis adjusts for bias by arm in grading, it retains differences in percent incidence reductions by Gleason grade; in contrast, in the above studies percent incidence reductions were assumed constant across Gleason categories when grade differences were assumed artifactual. Differences in the follow-up time periods employed could also lead to some differences in the estimates.

As a thought experiment, consider an actual mortality endpoint trial that demonstrated similar incidence trends as seen in PCPT and REDUCE (i.e., overall decrease but possible increase in high stage disease on drug) but demonstrated either 1) a statistically significant mortality reduction, 2) no significant mortality reduction but a point estimate for the mortality RR below 1 and an upper bound only slightly above 1, or 3) a point estimate modestly above 1.0 (whether statistically significant or not). Under scenario 1, despite harm to some individual men, it is likely that most would conclude that the benefits outweigh the harms, while for scenario 3 the consensus would likely be strongly against using the drugs. In scenario 2 the benefit is essentially confined to reductions in cancer incidence only, which given the frequent and serious side effects of standard prostate cancer treatments is substantial in itself; however, for this to outweigh harms one would need confidence that there was no true mortality increase or that it was at most negligibly small. With the current modeling exercise, we have in effect scenario 2 (assuming one uses the adjusted PCPT analyses), except that there is further uncertainty due to the fact that it is only a “virtual” trial, with all of the caveats of modeling and extrapolation. Nonetheless, the analysis is useful in attempting to quantify the effects on prostate cancer mortality of these drugs, especially since they are currently approved for the treatment of benign prostatic hyperplasia and are used for that purpose by many men.

Conclusion

The PCPT and REDUCE trials of 5-alpha reductase inhibitors each demonstrated a significant overall decrease in prostate cancer incidence for the treatment arm along with a trend for an increase in high-grade disease. Projecting a mortality outcome of these trials as an approach to weighing benefits versus harms demonstrates that there likely would have been at most a small increase in prostate cancer deaths in the treatment arms, and possibly a modest decrease.

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Table 1

Major characteristics of PLCO and the two chemoprevention trials.

	PLCO	PCPT	REDUCE
Number randomized	38,350 [1]	18,882	8,231
Years enrolled	1993-2001	1994-1997	Not reported
Mean age (SD)	62 (5)	63 (6)	63 (6)
Baseline eligibility criteria [2]	Less than 2 prior PSA tests [3]	PSA < 3 ng/ml	Single Negative Biopsy; PSA 2.5 to 10 ng/ml [4]
PSA Testing Schedule	Annual (for 6 years)	Annual (for 7 years)	Every 6 months (for 4 yrs)
Biopsy	For cause	For cause and end-of-study	For cause, year 2 and year 4

[1] Intervention (screening) arm only

[2] All trials excluded men with prior prostate cancer diagnosis

[3] About 10% of men were randomized before the time (April, 1995) that this criterion went into effect

[4] PSA 3.0-10.0 ng/ml for men over age 60

Table 2

Period Prevalence by Gleason score in PCPT and REDUCE.

PCPT			
	Finasteride (N=4,958 w/biopsy)	**Placebo (N=5,223 w/biopsy)**	**RR (95% CI)**
Unadjusted (Biopsy Gleason)	Period Prevalence		
2-6	10.0%	16.9%	0.59(0.50-0.63)
7-10	5.8%	4.7%	1. 23(0.97-1.36)
7	3.9%	3.6%	1.08(0.84-1.25)
8-10	1.9%	1.2%	1.61(1.1-2.1)
Unknown	0.8%	1.2%	0.64
Adjusted based on RP Gleason[1]			
2-6	9.3%	14.6%	0.64 (0.51-0.71)
7-10	7.2%	8.3%	0.87(0.68-1.05)
7	5.8%	7.3%	0.79(0.60-0.99)
8-10	1.4%	1.0%	1.44(0.8-2.5)
Adjusted based on prostate volume [2]			OR (95% CI)
2-6	10.0%	19.0%	0.47 (0.41-0.54) [3]
7-10	5.8%	5.6%	1.03 (0.84-1.26)
7	3.9%	4.4%	0.89 (NR)
8-10	1.9%	1.2%	1.51(1.01-2.26)
Unknown	0.8%	1.2%	0.64 (NR)
REDUCE			RR (95% CI)
Biopsy Gleason	Dutasteride (N=3,299 w/biopsy)	Placebo (N=3,407 w/biopsy)	
2-6	13.2%	18.1%	0.73 (0.65-0.83)
7	5.8%	6.3%	0.92 (0.76-1.1)
8-10	0.88%	0.55%	1.60 (0.9-2.8)

[1]Derived from Pinsky et al. (12)

[2]Derived from Cohen et al. and Theoret et al. (5,13)

[3]95% CI for OR of Gleason 2-6 cancer versus not cancer; approximates 95% CI for OR of Gleason 2-6 cancer versus not Gleason 2-6 cancer.
NR=not reported

Table 3

1-Survival Rates (prostate-cancer specific) at 13 Years from PLCO cohort

	Gleason 2-6	Gleason 7	Gleason 8-10	Unknown Gleason
	Rate (SE)	**Rate (SE)**	**Rate (SE)**	**Rate (SE)**
Sub-stratum	Rates used for PCPT			
PSA≤4, T1a-c	0.018 (0.013)			
PSA>4, T1a-c	0.024 (0.008)			
PSA≤4, T2a-c	0.026 (0.016)			
PSA>4, T2a-c	0.058 (0.023)			
Any PSA, T1/2		0.135 (0.038)	0.298 (0.065)	0.071 (0.04)
T3 (TNM Stage III)	0.128 (0.070)	0.230 (0.131)	0.293 (0.098)	0.128 (0.070) [1]
T4/N1/M1 (TNM Stage IV) [2]	0.547 (0.10)	0.547 (0.10)	0.840 (0.06)	0.547 (0.01) [1]
	Rates used for REDUCE			
All	0.038 (0.009)	0.141 (0.036)	0.360 (0.056)	N/A

Note: Based on PLCO intervention arm cases only except for Stage III/IV, where control arm cases were also used.

[1] Rate for PLCO Gleason 2-6 cases used

[2] PLCO 2-6 and 7 Gleason cases were combined to produce rate

Table 4

Projected Mortality by Arm in PCPT and REDUCE

PCPT	**Finasteride Arm**	**Placebo Arm**	
	Death Rate per 1,000 (%of deaths)[1]	**Death Rate per 1,000 (%of deaths)[1]**	**RR (95 % CI)**
Original Biopsy Gleason			
2-6	2.7 (18)	4.3 (30)	
7	5.4 (37)	5.2 (37)	
8-10	5.9 (40)	3.8 (27)	
Unknown	0.6 (4)	1.0(7)	
Total	14.6	14.2	1.02 (0.85-1.23)
Adjusted (RP Gleason)			
2-6	2.5 (16)	4.0 (23)	
7	8.6(56)	10.6 (60)	
8-10	4.2 (27)	3.0 (17)	
Total	15.3	17.6	0.87 (0.72-1.06)
Adjusted (Prostate Volume)			
2-6	2.7 (18)	4.7 (29)	
7	5.4 (37)	6.5 (40)	
8-10	5.9 (40)	4.0 (25)	
Unknown	0.6 (4)	1.0(6)	
Total	14.6	16.1	0.91 (0.76-1.09)
REDUCE	Dutasteride Arm	Placebo Arm	
Biopsy Gleason	Death Rate per 1,000 (% of deaths)[1]	Death Rate per 1,000 (% of deaths)[1]	RR (95 % CI)
2-6	5.0 (30)	6.9 (39)	
7	8.2 (50)	8.9(50)	
8-10	3.2 (20)	2.0(11)	
Total	16.4	17.7	0.93 (0.80-1.08)

[1]Death rates based on denominator of all biopsied men