TITLE: The Influence of Patient Heterogeneity on the Harms and Benefits of Prostate Cancer Screening

RUNNING HEAD: Patient Heterogeneity in Prostate Cancer Screening

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Abstract

Background: Several studies suggest that the benefits and harms of PSA-based prostate cancer screening vary with respect to individual factors such as race, family history, and comorbidity. The objective of the study was to evaluate quality-adjusted life years (QALYs) for routine PSA screening compared to no screening for different patient risk groups.

Methods: We developed and validated a simulation model of prostate cancer (PCa) natural history to evaluate the effects of different screening strategies on QALYs for the following patient risk groups: (i) white US men; (ii) African American US men; (iii) white US men with a PCa family history; (iv) white US men with Charlson Comorbidity Index (CCI)=1; and (v) white US men with CCI≥2. To validate the model we compared model-based estimates of number needed to invite (NNI) with published estimates from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Using simulation, QALY gains were estimated for the strategy of annual screening from age 50 to 75 with PSA threshold 2.5 ng/mL.

Results: The PSA screening strategy that minimized NNI was annual screening from age 50 to 75 with PSA threshold 2.5 ng/mL. Estimates of QALYs gained with respect to no screening by group for this screening strategy were: (i) 0.011; (ii) 0.048; (iii) 0.019; (iv) -0.023; and (v) -0.038. Sensitivity analysis suggested this finding is robust with respect to variation in parameters.

Conclusions: The relative gain in QALYs from PSA screening varies significantly among men depending on race, family history, and the presence of comorbidities. These differences suggest clinicians should emphasize the relevance of these risk factors as part of a shared decision making process for patients considering PSA screening.

INTRODUCTION

Several factors have been associated with the risks of PCa incidence and mortality. For example, African American men have higher PCa incidence and mortality than white US men, [1, 2] and men with a family history of PCa have a higher risk of diagnosis than those without a family history. [3] On the other hand, men with competing risks are less likely to experience morbidity and mortality from PCa, [4] and thus the burden of comorbidities may contextually define a lower PCa risk group. Screening for PCa with prostate-specific-antigen (PSA) has been broadly adopted in the United States over the past two decades; [5] however this practice has been a subject of controversy. In 2012 the US Preventive Services Task Force (USPSTF) recommended against PSA screening in the general population, while acknowledging that no firm conclusion can be drawn about African American men or men with a family history of prostate cancer. [6] Groups such as the American Urological Association (AUA) still recommend screening for some men based on shared decision-making that considers individual preferences, life expectancy, and risks factors such as race and family history of PCa. [7]

Differences in incidence and mortality rates, as well as variation in the predictive value of PSA, can affect the balance of harms and benefits of screening within demographic subpopulations of US men. [8] Estimating the public-health implications of screening in these various subgroups is further complicated by both the large number of proposed screening strategies and the difficulty of estimating common performance measures for screening such as the expected number needed to invite (NNI) to avert 1 PCa death. [9, 10]

We used a Markov model of the natural history of PCa to compare PCa screening strategies for five demographic groups based on race (white and African American), family history of PCa, and different levels of comorbid medical conditions. We validated the model by comparing model-based estimates of NNI to published results of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Finally, we estimated QALY gains for each of the patient risk groups.

METHODS

We extended a previously developed Markov model [11] to estimate expected NNI for purposes of model validation and to estimate QALY gains relative to no screening for each of the patient risk groups. Additional details about the model and its validation are provided in the online supplement; and complete details are available in Chapter 3 of Underwood [12].

Model Overview

The health states and transitions between states are depicted in Figure 1. In our model, men have PSA tests according to a given screening strategy that defines the frequency of testing and the threshold at which to recommend biopsy. All simulated patients are initially disease free, starting at age 40, but may later develop PCa according to the Markov transitions over the health states, which is illustrated in Figure 1. Men diagnosed with PCa are treated by radical prostatectomy. Each patient is permitted to undergo no more than a single prostate biopsy. Our model accounts for clinical incidence by incorporating PSA-screening lead time based on data from Savage and others. [13]

Model Parameters

We developed and validated a simulation model of PCa natural history to evaluate the effects of different screening strategies for the following risk groups: (i) white US men without a family history of PCa and without comorbidities; (ii) African American US men without a family history of PCa and without comorbidities; (iii) white US men *with* a family history of PCa but without comorbidities; (iv) white US men with Charlson

Comorbidity Index (CCI)=1 but without a family history of PCa; and (v) white US men with CCI≥2 but without a family history of PCa. We refer to risk groups (i)–(v) in abbreviated fashion as the white, African American, family history, CCI=1, and CCI≥2 risk groups, respectively. The white risk group is the reference subpopulation from which we derived parameters for the other risk groups.

PSA values were sampled using a previously published linear random-effects model.[14] The model uses a linear changepoint formulation for log(PSA) such that the growth rate of log(PSA) accelerates after the onset of PCa. Parameters of the model were based on data from the control arm of the Prostate Cancer Prevention Trial (PCPT).[15] This model was previously validated against data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) Trial.[16] To estimate the PSA samples for African American men without PCa, we used the age-dependent ratio of the mean PSA level for African American men to the mean PSA level for white US men.[17] To estimate the PSA samples for African American men with nonmetastatic PCa, we used the ratio of the mean PSA level for African American men to the mean PSA level for white US men from a Radiation Therapy Oncology Group prospective registration study.[18] These ratios were multiplied by PSA histories sampled used the previously described linear random-effects model in order to approximate PSA levels for African American men with and without PCa.

To estimate the age-specific annual PCa incidence rate for African American men, we multiplied the following quantities: (a) the ratio of the relevant 5-year average annual

incidence rate for African American men to that for the reference subpopulation; and (b) the age-specific annual incidence rate for the reference subpopulation. To account for family history, we used the logistic regression model for PCa risk based on the Prostate Cancer Prevention Trial (PCPT).[8] We used the PCPT model to compute the ratio of the annual PCa incidence rate for a white US male with a family history of PCa divided by the annual PCa incidence rate for a white US male without a family history of PCa. We used the latter ratio to convert the annual PCa incidence rate for the reference subpopulation into an estimate of the annual incidence rate for white US men with a family history of PCa. We computed the relevant ratio for each of the PSA levels in our model.

The annual mortality rate from causes other than PCa was estimated by subtracting the PCa-specific mortality rate based on SEER data[19] from the all-cause mortality rate reported by the CDC.[20] To estimate the probability of metastasis from undetected PCa, we summed the product of the probability of each cancer grade upon detection[21] and the corresponding probability of metastasis for that cancer grade.[22]

The relationship between survival and the CCI was established in a competing-risks analysis.[4] The percentage increase in other-cause mortality rate for patients based on age and CCI was estimated by comparing the reported PCa-specific and all-cause mortality rates for men having CCI=0 with the corresponding rates for men having CCI>0. Using these comparisons, we computed adjusted annual other-cause mortality rates for the selected subpopulations with different comorbid medical conditions and

different age ranges. For white men with CCI=1 in the age groups 66–74 and 75+, the ratios of their annual other-cause mortality rate to the corresponding rate for the reference subpopulation were, respectively, 2.45 and 1.34. The corresponding ratios for white men with CCI ≥ 2 were, respectively, 3.65 and 1.82. The other-cause mortality rates for the age group <66 were unchanged.

To estimate each age-specific annual PCa mortality rate for African American men, we multiplied the following quantities: (a) the ratio of the relevant 5-year average annual PCa-specific mortality rate for African American men to that for the reference population; and (b) the age-specific annual PCa- specific mortality rate for the reference population. To estimate each age-specific annual other-cause mortality rate for African American men, we then subtracted our estimate of the corresponding age- specific annual PCa mortality rate from the annual all-cause mortality rate for African American men as given in US life tables.[23]

The annual probability of PCa-specific death for African American men with metastatic PCa (mPCa) was approximated by the product of the following quantities: (a) the annual probability of PCa-specific death for men from the reference subpopulation with mPCa; and (b) the African American–vs–white hazard ratio of all-cause mortality reported in a study on the outcomes of African American and white men with mPCa.[2]

PSA Screening Strategies

We selected the PSA-threshold-based screening strategies that were used in two

of the largest randomized control trials on PCa screening—namely, the PLCO [9] and the ERSPC [10] trials—as well as strategies considered in other prominent studies.[24, 25] The selected strategies are listed in Table 1.

Estimation of NNI and Model Validation

To estimate NNI to avert 1 PCa death, we simulated a population of men under a given screening strategy. Next, we simulated the *same* population in the absence of any screening. We then estimated NNI by dividing the size of the simulated population by the total reduction in PCa mortality induced by screening with the given strategy relative to no screening. We derived 95% confidence interval (CI) estimators of the expected NNI by the univariate delta method.[26]

We validated our model by comparing model-based estimates to estimates from the literature for the following statistics for the risk groups whites and African Americans: overall PCa diagnosis rate; overall PCa-specific mortality rate; expected lifespan; and survival time for patients with mPCa. Estimates for these statistics for each of the white and African American risk groups were computed based on samples of 50,000 men from the corresponding risk groups who were screened using strategy P5 from Table 1 (we used this strategy because it is most consistent with the strategy used in the PLCO trial).

We further validated our model by comparing model estimates of NNI to published NNI estimates from the ERSPC trial. For purposes of validation we incorporated imperfect adherence to the PSA testing strategy, as observed in the ERSPC trial. We

also relaxed the assumption that patient have at most 1 biopsy. We simulated the trial at each of 7 centers (Netherlands, Belgium, Sweden, Finland, Italy, Spain, and Switzerland) using statistical data on each center's participant population, published in Schröder and Roobol.[27] A complete description of the validation approach and additional results, including a derivation of the expected NNI estimator, can be found in Chapter 3 of Underwood.[12]

Estimation of QALY Gains

Although we used NNI to identify the best strategy from Table 1 and for model validation purposes, QALYs-based measures are more appropriate for obtaining a balanced representation of the benefits and harms of PSA screening since they provide explicit consideration of the impact of PSA screening, biopsy, and treatment. Therefore we focus on results for expected QALY gains relative to no screening for the evaluation of the screening strategy P6 in Table 1, which was the strategy that minimized NNI.

Simulated patients accumulated rewards in QALYs during each period they are alive based on their health state and the clinical decisions made or previously made. For each year that a patient was alive, the patient earned a reward of 1 appropriately reduced by the applicable disutilities. There are disutilities in our model associated with PSA screening, prostate biopsy, the diagnosis of PCa, definitive treatment, posttreatment recovery, and living with metastatic PCa. The disutilities for screening, biopsy, and diagnosis are one-time quality-of-life

decrements that correspond to year of occurrence. The posttreatment recovery disutility is an annual quality-of-life decrement that is applied in any time period during the posttreatment recovery period, other than the first year, immediately following definitive treatment. The metastasis disutility is an annual quality-of-life decrement that is applied in any time period in which the patient has metastatic PCa. All disutility estimates were taken from Heijnsdijk and others.[25]

Synchronized Patient Histories

We used an estimator of expected QALY gains relative to no screening as the performance measure for comparing patient risk groups. The expected value of QALY gains is a relative measure that involves comparisons of paired (synchronized) simulations. This use of *common random numbers* to make significantly reduce the number of samples necessary to compare different screening strategies.

RESULTS

The strategy of screening from age 50 to 75 with a PSA threshold for biopsy of 2.5 ng/ml (strategy P6) resulted in the smallest estimated expected NNI for all of the risk groups. Therefore, this screening strategy was used as the reference strategy for evaluating QALY gains for the patient risk groups. The expected NNI estimates with 95% CIs for screening with strategy P6 by risk group were: (i) 187 ± 17; (ii) 80 ± 5; (iii) 144 ± 11; (iv) 234 ± 24; and (v) 289 ± 33. These estimates are based on samples of 100,000 simulated patients from each risk group.

Model Validation

To validate our model against the ERSPC study using NNI, we aggregated all of the study-center populations and estimated NNI for the aggregate population. The model-based aggregate estimates of NNI for the ERSPC study with 95% CIs were:1025 [767,1283], 674 [540; 808], and 531 [437; 625] at, respectively, 9-, 11-, and 13-years of follow-up. The ERSPC-reported values of NNI with 95% CIs, taken from Schröder and others [27] at 9-, 11-, and 13-years of follow-up were, respectively, 1410 [1142, 1721], 1055 [645, 2894], and 781 [490, 1929]. The aggregate simulated and ERSPC-reported NNI estimates are compared in Figure 2. The overlapping 95% CIs indicate there is no statistically significant difference between the results at the p=0.05 level.

Clinical Statistics for Each Risk Group

Table 2 contains a selection of clinical statistics estimated for each of risk groups (i)–(v) by simulating 100,000 patients from each of the patient risk groups. The number of screens is an estimate of the total lifetime number of PSA tests per 100,000 patients. The number of biopsies and treatments are per 100,000 patients for each risk group Table 2 also provides the number of PCa-specific deaths averted by screening per 100,000 patients, relative to no screening. The number of overdiagnoses is an estimate of the number of patients treated for which neither clinical detection nor metastasis would have occurred in the absence of screening. The mean months saved is an estimate of the mean increase in life expectancy across all of the simulated patients whose life expectancies were increased relative to no screening.

Estimation of QALY Gains

Estimates of expected QALY gains with respect to no screening by risk group for screening strategy P6 were as follows: (i) 0.011 ; (ii) 0.048; (iii) 0.019; (iv) -0.023; and (v) -0.038. The relative differences are illustrated in Figure 3. Negative values for groups (iv) and (v) indicate that screening results in net harm for patients with CCI≥1. Groups (ii) and (iii), the African American and family history risk groups, had significantly greater QALY gains relative to the whites risk group.

Sensitivity Analysis

We performed one-way sensitivity analysis over the following factors: other-cause mortality rate; metastasis rate from undetected PCa; PSA screening lead time; and QALY disutilities. At the low and high levels of each of these factors, we evaluated screening strategy P6 in each of the risk groups. The estimated expected QALY gains from these Sensitivity analysis experiments are shown in Table 3.

The other-cause mortality rate was varied by ±20%. The low and high levels of the metastasis rate from undetected PCa were taken from the lower and upper bounds of the 95% CI on the rate of progression to metastatic PCa reported in the literature [28]. The PCa leadtime was varied by ±5 yrs. For the low and high levels of the QALY disutilities, we simultaneously varied all of the individual QALY-disutility parameters to

their most favorable and unfavorable values, respectively, as reported in Heijnsdijk and others.[25]

DISCUSSION

There are varying recommendations for PCa screening in the United States, including those provided by the USPSTF [6] the ACS [29] the AUA [7] and the National Comprehensive Cancer Network (NCCN) [30] among others. All of these guidelines acknowledge the increased risk associated with race and family history, but to the authors knowledge there are no published estimates of how these risk factors influence the harms and benefits of PCa screening.

In contrast to other simulation studies [31, 25] we compared PCa screening for different well- established risk groups, and we quantified the results in terms of the expected NNI to avert 1 PCa death. Our validation study indicated that there is no statistically significant difference in NNI between the model-based results and the aggregate results from the ERSPC trial.

The greatest QALY gain was for the African American risk group, followed by the family history group, suggesting that screening in these subpopulations has the most benefit with the fewest patients screened. On the other hand, the QALY gains for white US men with CCI=1 or CCI≥2 were negative, suggesting patients with significant competing risks from comorbidities stand to gain less than other risk groups in the absence of risk-based customized PSA screening. Thus, the benefit from PSA screening was not uniformly distributed across risk groups.

There were also significant differences in the number of screens, biopsies, treatments, and overdiagnoses among risk groups. The most significant differences

were between the white and African American risk groups. African American men had fewer PSA screens but a higher rate of biopsy and treatment. This is due to the fact that African American men were generally diagnosed at an earlier age than white men. The rate of overdiagnosis was also higher among African American men compared to white men, which is consistent with the higher observed diagnosis rate. In practice the higher rate of overdiagnosis would likely be mitigated through the use of active surveillance for low risk men.

The sensitivity analysis results indicated that the most influential model parameter was the metastasis rate of undetected PCa. The relative order of the white, African American and family history risk groups remained the same in nearly all cases, and the QALY gains for the CCI=1, and CCI≥2 were negative in all cases except for the most favorable choices of metastasis rate and disutilities of screening, biopsy and treatment. These results support the robustness of the conclusion that there is greater benefit to screening in the African American and family history risk groups, and that there is no such benefit for the comorbidity risk groups.

There are several limitations that must be weighed in considering the results of this study. First, our Markov model focused on a screening population and assumed at most 1 biopsy per lifetime because the decision process for repeat biopsies are complex. However, most patients have a single biopsy, and PCa discovered on a repeat biopsy tends to be less clinically significant [32]. Another limitation is that our model assumed all diagnoses were treated by surgery. However, prostatectomy remains the most common treatment modality for PCa and the effect of this assumption is to overestimate the

disutility of PCa diagnosis; therefore future studies that incorporate active surveillance may reveal higher QALY gains. Although there were no statistically significant differences between model-based results and published outcomes from the ERSPC model, there were differences in the point estimates. There are reasons to anticipate these differences. First, the ERSPC is based on European populations of patients, whereas our reference risk group is largely representative of US men. Second, our simulation of the ERSPC study centers relied upon broad statistical descriptions of each center's population, and therefore can yield at best rough point estimates. Finally, the annual probability of PCa-specific death for African American men was approximated by multiplying the annual probability of PCa-specific death for the reference subpopulation by an all- cause mortality hazard ratio. This was done because there is evidence to suggest that differences in outcomes between African American and white men may be due to inequalities in access to health care and/or difference in comorbidities.[33]

The QALY gains associated with PSA screening vary significantly among men depending on race, family history, and the presence of comorbidities. These differences underscore the need for further study of these risk factors, and for clinicians to emphasize the relevance of these risk factors for patients considering PSA screening.

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Table 1. PSA Screening Strategies Compared in This Study.

Strategy Label	*Strategy Description*			Source
	Range of Ages (yr.)	Screening Interval (yr.)	PSA Thresh-old (ng/mL)	
P1	–	–	–	
P2	40–75	5	4.0	[24]
P3	50–75	2	4.0	[24]
	50–59	1	3.5	
P4	60–69	1	4.5	[24]
	70–75	1	6.5	
P5	50–75	1	4.0	[24, 9]
P6	50–75	1	2.5	[24]
P7	40, 45	–	4.0	[24]
	50–75	2	4.0	
P8	40, 45	–	4.0	[24]
	50–75	1	4.0	
P9	55–69	1	3.0	[25]
P10	55–74	1	3.0	[25]
P11	55–69	4	3.0	[25]
P12	55	–	3.0	[25]
P13	60	–	3.0	[25]
P14	65	–	3.0	[25]

Strategy P1 is no screening. Strategies P2–P8 were taken from a prominent simulation study.[24] Strategy P5 was also used in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.[9] Strategies P9–P14 were used in the European Randomized Study of Screening for Prostate Cancer (ERSPC).[25]

Table 2. Estimates of Clinical Statistics

	(i)	(ii)	(iii)	(iv)	(v)
	Whites	**African Americans**	**Family History**	**CCI=1**	**CCI>=2**
No. of PSA screens	1,860,887	1,518,896	1,831,256	1,793,546	1,747,223
No. of prostate biopsies	30,714	37,737	32,949	29,211	28,158
No. of prostatectomies	15,036	25,043	18,176	12,912	11,609
No. of PCa deaths averted	572	1,325	739	465	373
% overdiagnosis	32	43	33	43	51
Mean months of life saved	128 ± 7	130 ± 5	131 ± 7	110 ± 8	94 ± 7

Clinical statistics for annual PSA screening from age 50 to 75 with a biopsy threshold of 2.5 ng/mL. Results are based on samples of 100,000 simulated patients from the corresponding risk groups. For mean months of life saved, the 95% CIs are reported. CCI means Charlson Comorbidity Index.

Table 3. Sensitivity analysis on expected QALY gains.

OTHER-CAUSE MORTALITY RATE		
	Low level	**High level**
Whites	0.031 ± 0.001	-0.002 ± 0.001
African Americans	0.099 ± 0.002	0.015 ± 0.001
Family History	0.044 ± 0.001	0.002 ± 0.001
CCI=1	-0.009 ± 0.001	-0.031 ± 0.001
CCI≥2	-0.029 ± 0.001	-0.043 ± 0.001
METASTASIS RATE FROM UNDETECTED PCa		
	Low level	**High level**
Whites	-0.067 ± 0.001	0.145 ± 0.001
African Americans	-0.114 ± 0.001	0.322 ± 0.002
Family History	-0.079 ± 0.001	0.185 ± 0.001
CCI=1	-0.076 ± 0.001	0.069 ± 0.001
CCI≥2	-0.077 ± 0.000	0.029 ± 0.001
PCa LEADTIME		
	Low level	**High level**
Whites	-0.003 ± 0.001	0.024 ± 0.001
African Americans	0.020 ± 0.001	0.073 ± 0.001
Family History	0.001 ± 0.001	0.035 ± 0.001
CCI=1	-0.032 ± 0.001	-0.015 ± 0.001
CCI≥2	-0.044 ± 0.001	-0.033 ± 0.001
QALY DISUTILITIES		
	Low level	**High level**
Whites	0.046 ± 0.001	-0.020 ± 0.001
African Americans	0.113 ± 0.001	0.008 ± 0.001
Family History	0.059 ± 0.001	-0.014 ± 0.001
CCI=1	0.017 ± 0.001	-0.057 ± 0.001
CCI≥2	0.003 ± 0.001	-0.073 ± 0.001

One-way sensitivity analysis for each risk group on estimated expected QALY gains when screening annually from ages 50 to 75 with PSA threshold 2.5 ng/mL. Each estimate and the corresponding 95% CI is based on n=10,000,000 simulated patients from the corresponding risk group at the corresponding experimental level.

FIGURE LEGENDS

Figure 1, Natural History Model: Health States and Progression Paths in the Markov Model. Transitions between states are represented by arrows.

Figure 2, Comparison of NNI from the Markov Model and ERSPC Trial: Comparison of published and simulated NNI results at 9, 11, and 13 years of follow-up based on estimates for each of 7 centers (Netherlands, Belgium, Sweden, Finland, Italy, Spain, and Switzerland) using statistical data on each center's participant population for strategy P5 in Table 1. The 95% CI estimators are based on the univariate delta method.

Figure 3, QALY Gain estimates: The estimated expected QALY gains relative to no screening for each risk group based on a sample of 10,000,000 patients from the corresponding risk group. The 95% CIs were less than 1% of the mean for all risk groups.

FIGURE 1

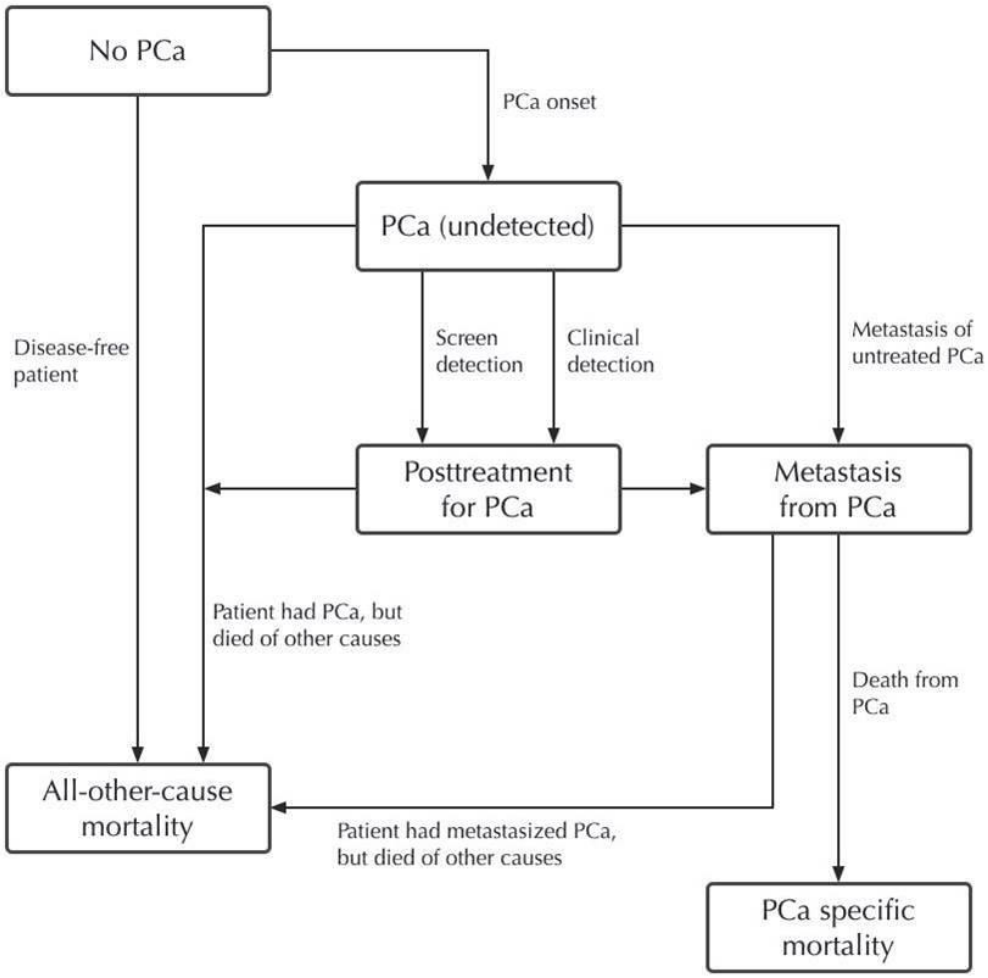

No PCa
PCa onset
PCa (undetected)
Disease-free patient
Screen detection
Clinical detection
Metastasis of untreated PCa
Posttreatment for PCa
Metastasis from PCa
Patient had PCa, but died of other causes
Death from PCa
All-other-cause mortality
Patient had metastasized PCa, but died of other causes
PCa specific mortality

FIGURE 2

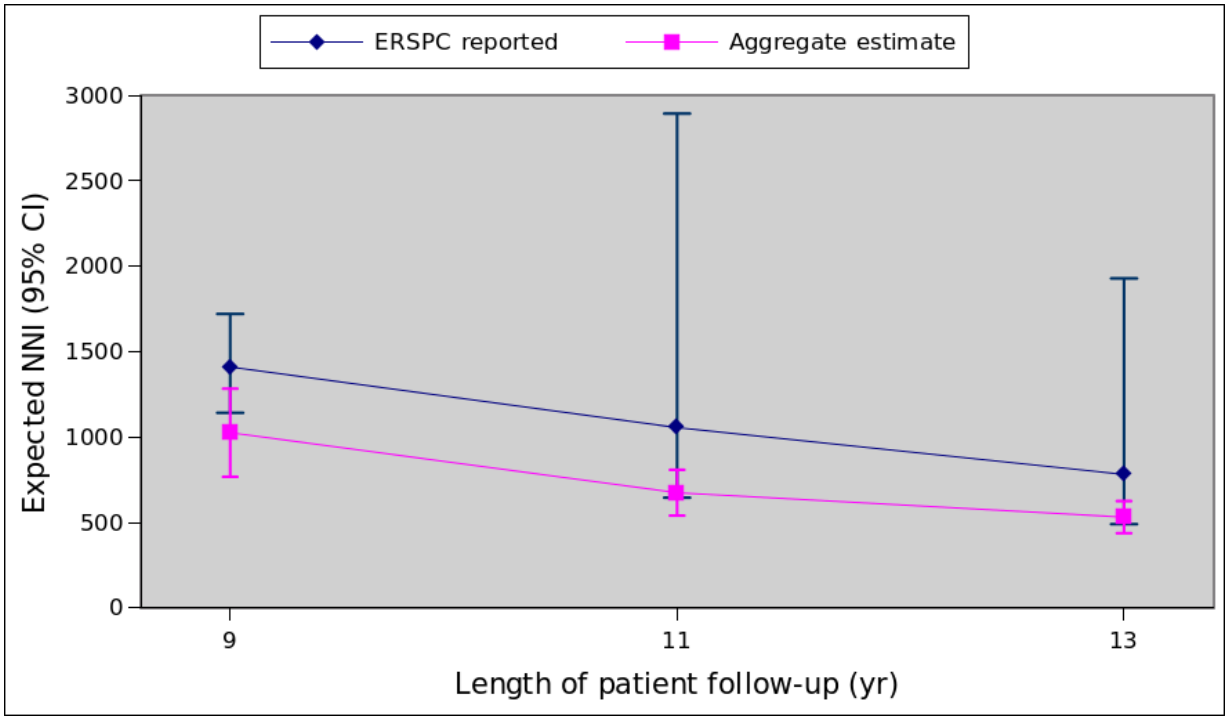
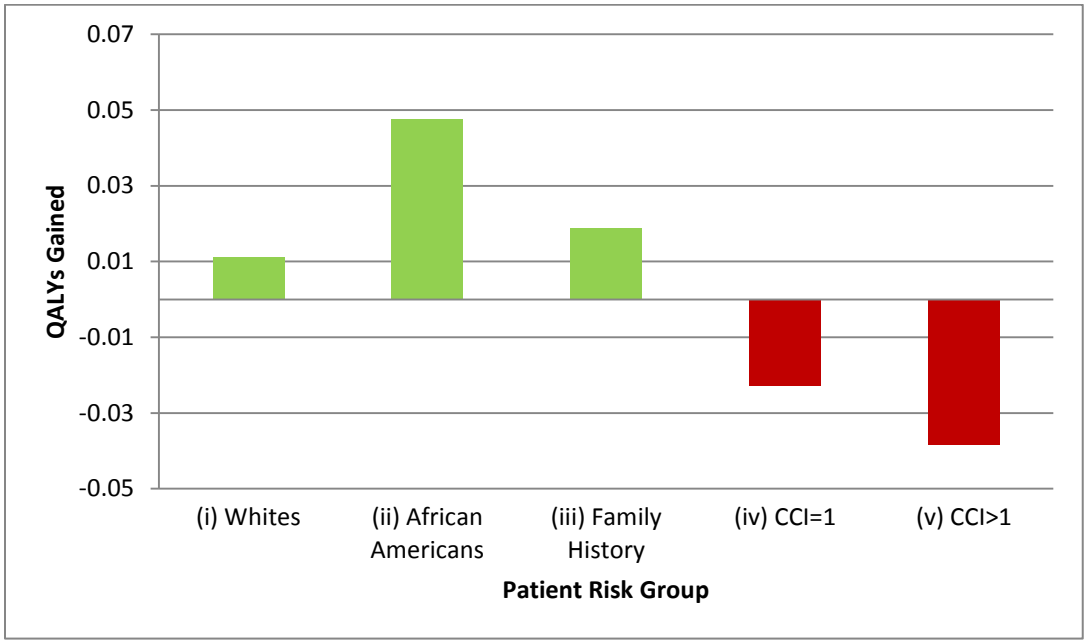

ERSPC reported
Aggregate estimate
Expected NNI (95% CI)
3000
2500
2000
1500
1000
500
0
9
11
13
Length of patient follow-up (yr)

FIGURE 3


0.07
0.05
0.03
0.01
-0.01
-0.03
-0.05
QALYs Gained
(i) Whites
(ii) African Americans
(iii) Family History
(iv) CCI=1
(v) CCI>1
Patient Risk Group