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A joint model of PSA growth and prostate cancer natural history and outcomes (PSAPC): Model Profile

Fred Hutchinson Cancer Center

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Version Table

Version	Date	Notes
1.0.00	2025-09-30	Major update
HI.001.08062009.43308	2009-08-06	Historical release

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Readers Guide

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Reader's Guide

Core Profile Documentation

These topics will provide an overview of the model without the burden of detail. Each can be read in about 5-10 minutes. Each contains links to more detailed information if required.

Model Purpose
This document describes the primary purpose of the model.

Model Overview
This document describes the primary aims and general purposes of this modeling effort.

Assumption Overview
An overview of the basic assumptions inherent in this model.

Parameter Overview
Describes the basic parameter set used to inform the model, more detailed information is available for each specific parameter.

Component Overview
A description of the basic computational building blocks (components) of the model.

Output Overview
Definitions and methodologies for the basic model outputs.

Results Overview
A guide to the results obtained from the model.

Validations Overview
A discussion of the major calibration and validation exercises performed throughout model development.

Key References
A list of references used in the development of the model.

Model Purpose

Summary

The Fred Hutchinson Cancer Center PSAPC microsimulation model is a joint model of longitudinal prostate-specific antigen (PSA) levels and prostate cancer natural history, screening, diagnosis, treatment, and disease-specific and other-cause death. The model has been used to study epidemiological trends, landmark randomized screening and treatment trials, racial disparities, and alternative implementations of screening and treatment interventions designed to improve long-term harm-benefit tradeoffs in the general United States population and in other settings.

Purpose

The Fred Hutchinson Cancer Center PSAPC microsimulation model was originally developed to study trends in prostate cancer incidence and mortality--and the roles played by PSA screening and changes in treatments. The widespread adoption of PSA screening in the late 1980s initially doubled the number of prostate cancers diagnosed each year, both by advancing the date of diagnosis for some cancers and by finding some cancers that never would have been diagnosed without screening--so-called "overdiagnosed" cancers. Analyses using the PSAPC and other models estimated that 28-42% of screen detections were overdiagnoses.[1] Beginning in the early 1990s, the number of prostate cancer deaths declined each year, reflecting a 50% drop in 2012 relative to its peak. However, the relative contributions of screening and changes in treatment to the observed declines have been intensely debated. Analyses using the PSAPC and other models estimated that screening explained 45-70% of the mortality decline in the year 2000,[2] changes in receipt and efficacy of initial curative treatments explained 22-33% of the decline in the year 2005,[3] and screening explained 48-52% of the decline in the year 2010.[4]

Results from large randomized trials of PSA screening appeared to conflict. The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial in the US found no difference in the rates of death from prostate cancer in men who underwent annual PSA screening compared with men who were assigned usual care.[5-7]The European Randomized Study of Screening for Prostate Cancer (ERSPC) found that PSA screening every 4 years (every 2 years in the Swedish study center) reduced the rate of death from prostate cancer by 20% compared with men randomized to no screening.[8-10]Analyses using the PSAPC and other models found that differences in the trial settings and implementations largely explained the apparently conflicting results, with both trials reflecting a mortality reduction that was commensurate with differences in the intensity of screening in the two arms.[11] Subsequently, the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) found that an invitation for a single PSA test did not reduce prostate cancer mortality.[12] The CAP results appear to be compatible with analyses of the PLCO and ERSPC when accounting for differences in the intensity of screening in the two arms.

Results from randomized trials of primary treatments also appeared to conflict. The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) randomized trial found that radical prostatectomy reduced the rate of death from prostate cancer by 45% compared to watchful waiting.[13-15]The Prostate Cancer Intervention Versus Observation Trial (PIVOT) in the US found that radical prostatectomy did not significantly reduce the rate of death from prostate cancer.[16,17]Analysis using the PSAPC showed that differences in the trial populations largely explained conflicting results, with artificial inflation of survival due to lead time and overdiagnosis in the PIVOT patients--many of whom were diagnosed by screening--sufficient to explain differences in outcomes compared to SPCG-4 patients--most of whom were not diagnosed by screening.[18] Subsequently, the Prostate Testing for Cancer and Treatment (ProtecT) trial found similarly low rates of death from prostate cancer among patients--all of whom were diagnosed by screening--randomized to radical prostatectomy, radiation therapy, or active monitoring.[19,20]The ProtecT results appear to be compatible with analyses of the SPCG-4 and PIVOT when accounting for artificially inflated survival among patients diagnosed by screening.

Prostate cancer has the largest racial disparities in incidence and mortality rates of any cancer in the US. The incidence rate for Black men is 1.7 times that for White men, and the mortality rate for Black men is 2.0 times

that for White men. Historical PSA screening rates do not differ substantially between races, and multiple studies have found that Black and White patients have similar oncologic outcomes when accounting for clinical and tumor features at diagnosis. Analysis using the PSAPC and other models estimated that the rate of preclinical onset for Black men is 1.3-1.6 times that for White men, and the rate of metastasis before diagnosis for Black men is 1.4-1.8 times that for White men.[21] A separate study using the PSAPC model estimated that these differences each explained approximately one-third of the observed disparity and mortality rates, with the remaining one-third attributable to unspecified differences in prostate cancer survival.[22] Still another study using the PSAPC and another model projected that annual screening starting at age 45 years in Black men is expected to reduce mortality more than that estimated under historical screening even when screening stops at age 70 years, which is expected to materially reduce overdiagnosis.[23]

The PSAPC model has been used to study comparative effectiveness and cost-effectiveness of alternative screening strategies, such as risk-based strategies with age-specific PSA thresholds for biopsy referral,[24] inter-screening intervals that depend on previous PSA levels,[25] stopping ages that depend on age-specific PSA levels,[25] and ages and inter-screening intervals tailored by germline genetic risk scores.[26] The model has also been used to study screening strategies with first-line PSA screening with reflex testing using MRI,[27] urinary biomarkers,[27,28]and hypothetical tests before prostate biopsy.[27,28]Outside the US, versions of the PSAPC model have been used to study screening strategies in British Columbia,[29] Sweden,[30] The Bahamas,[31] the United Kingdom,[32] and Australia.[33]

Developing effective strategies for prostate cancer control requires rigorous analysis of empirical evidence. Bridging the inevitable gaps in empirical evidence requires equally rigorous analysis using quantitative frameworks for evidence synthesis like the PSAPC model.

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Model Overview

Summary

This document reviews the motivation for developing a new model of prostate cancer natural history, prostate-specific antigen (PSA) screening, and treatment practices in the US population. A brief model description is also included.

Background

An earlier version of the Fred Hutchinson Cancer Center PSAPC model involved a direct link between prostate cancer progression and PSA growth. Although this implementation may seem intuitively reasonable, the link could not be tested empirically. In addition, the cross-model dependence of its components and the large number (over 30) of parameters made systematic estimation intractable. Additionally, while univariate estimation and informal experimentation provided important information about prostate cancer progression and helped us to understand ways to improve our modeling efforts, we recognized the imperative of a more coherent modeling approach.

The deficiencies of the PCSIM model motivated an overhaul and the adoption of a new, simpler, unified, statistically coherent model framework. At its core, the resulting Fred Hutchinson Cancer Center PSAPC model continues to exploit a link between prostate cancer progression and PSA growth. In contrast with the earlier formulation, however, this link is now formally parameterized and the parameters are estimated via statistical methods. In other words, the link between progression and PSA growth is now captured through model parameters instead of representing an inflexible assumption buried deep in the internal model structure.

Since the original overhaul, the PSAPC model has continued to be developed, often with the main changes documented in appendices to relevant publications. The following model description summarizes the original version of the model and updates over time.

Model Description

The PSAPC model involves two submodels. The first submodel simulates longitudinal PSA levels before and after onset of preclinical prostate cancer. PSA levels were originally estimated using linear mixed models fit to longitudinal PSA test results for prostate cancer cases and non-cases in the Prostate Cancer Prevention Trial placebo arm, which included annual PSA testing for up to 7 years.[1] Case status was determined by screen detection, interval detection, or end-of-study biopsies. Specifically, the estimated models provided means and variances of the intercept (PSA level at age 35 years), pre-onset growth rate, post-onset growth rate, and within-individual variance.[2] To overcome weak identifiability of pre-onset parameters, we simulated positive tests and detection rates in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial.[3,4]Subsequently, we refit the linear mixed models for cases after partitioning those with Gleason score ≤7 versus ≥8[5] and then further partitioning those with Gleason score ≤7 into Gleason score ≤6 versus 7.[6]

The second submodel governs prostate cancer onset, progression, and diagnosis. Parameters controlling hazards of these events were estimated by simulating prostate cancer incidence to match observed rates in the general US population before and after the introduction of PSA screening. The hazard of onset was modeled as proportional to a man's age, and hazards of progressing from localized to distant stage and from preclinical to clinical states were modeled as proportional to a man's PSA level.[2] Specifically, these hazard rate parameters were estimated using a simulated maximum likelihood procedure to identify the closest match to prostate cancer incidence in the Surveillance, Epidemiology, and End Results (SEER) program for cases diagnosed at ages 50-84 by 5-year age group, in the calendar period 1975-2000 by single year, and by stage (local-regional or distant) at diagnosis.[2] When the model was extended to allow different PSA levels by Gleason score, the probability of Gleason score ≥8 was modeled as a quadratic function of age at onset.[5] Subsequent model extensions generalized the hazard of onset from a 1-parameter to a 2-parameter Weibull distribution,[7] allowed for grade-specific proportionality constants in the hazard of clinical diagnosis,[7] and partitioned local-regional stage into clinical T-stage ≤T2a versus ≥T2b using a logistic regression model fit to cases in the Cancer of the

Prostate Strategic Urologic Research Endeavor program given a man's age, PSA level, and Gleason score at diagnosis.[6]

The second submodel was recalibrated to incidence data for Black men from SEER,[8] and selected natural history parameters were recalibrated to incidence data for participants in the PLCO and European Randomized Study of Screening for Prostate Cancer[8,9]and for residents of The Bahamas.[10] The second submodel was re-implemented and calibrated to incidence data from a Swedish cancer registry[11] and from the Cluster Randomised Trial of PSA Testing for Prostate Cancer.[12] Separately, the second submodel was also re-implemented and calibrated to incidence data from an Austrialian cancer registry.[13]

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Assumption Overview

Summary

This document describes the assumptions about PSA growth and prostate cancer natural and clinical history (initiation, progression, and diagnosis in the absence of screening) in the Fred Hutchinson Cancer Center PSAPC model.

Background

The main idea behind the PSAPC model is to link individual PSA levels with prostate cancer initiation and progression. The model is similar to models that link tumor volume with stage progression and clinical diagnosis, but the PSAPC model replaces tumor volume with the PSA level. The model consists of two submodels: (1) a submodel of longitudinal PSA levels before and after preclinical onset and (2) a natural history submodel of health states (i.e., healthy, preclinical localized, preclinical metastatic, clinical localized, clinical metastatic) and transitions from one state to the next that depend on individual age or PSA level.

Assumption Listing

PSA growth

The original model specification assumed[1]:

- PSA levels (on a logarithmic scale) are normally distributed across individuals at age 35 years
- Before onset, PSA levels (on a logarithmic scale) increase linearly with age
- After onset, PSA levels (on a logarithmic scale) still increase linearly with age but the PSA slope increases
- PSA slopes before and after onset follow truncated normal distributions across individuals
- PSA levels are measured with normally distributed noise across time points for the same individual

The post-onset PSA slopes were later re-estimated to account for tumor grade[2]:

- After onset, PSA levels (on a logarithmic scale) still increase linearly with age but the PSA slope is, on average, even higher after onset of a Gleason score ≥8 tumor than after onset of a Gleason score ≤7 tumor.

More formally, we assume that the PSA level (on a logarithmic scale) for individual i at age t is:

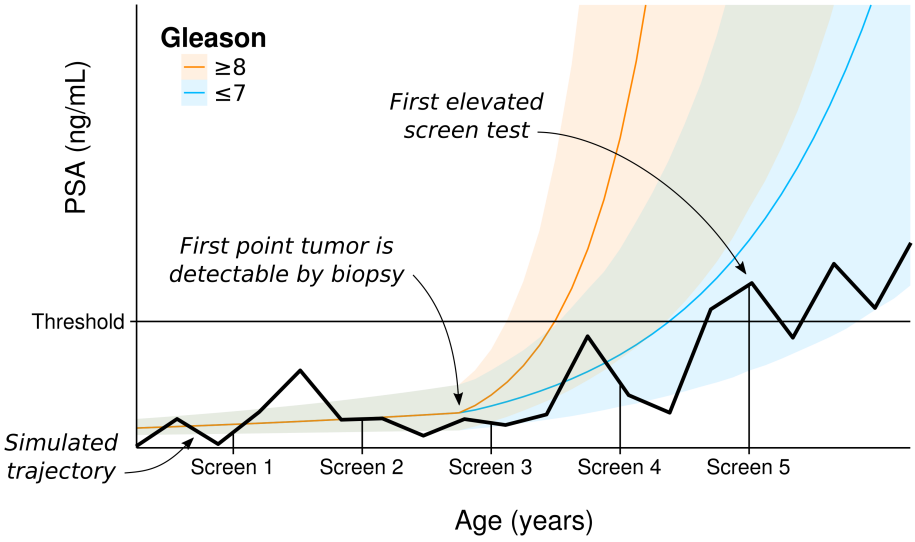
$$\log(y_i(t)) = \beta_{0i} + \beta_{1i}t + \beta_{gi}(t - t_{oi})I(t > t_{oi}) + \varepsilon$$

where

- $\beta_{0i} \sim \mathcal{N}(\mu_0, \sigma_0^2)$
- $\beta_{1i} \sim \mathcal{N}(\mu_1, \sigma_1^2)I(\beta_{1i} > 0)$
- $\beta_{gi} \sim \mathcal{N}(\mu_g, \sigma_g^2)I(\beta_{gi} > 0), g = \text{Gleason score } \leq 7, \text{Gleason score } \geq 8$
- $\varepsilon \sim \mathcal{N}(0, \tau^2)$
- $I(\cdot)$ is the usual indicator function (i.e., $I(A) = 1$ if A is true and $I(A) = 0$ otherwise)

Here $\mathcal{N}(\mu_k, \sigma_k^2)I(\beta_{ki} > 0)$ represents a truncated normal distribution to disallow negative mean PSA growth with age. Estimated mean PSA growth trajectories and interquartile ranges are illustrated in Figure 1. The figure also shows an example simulated PSA trajectory before and after onset of a Gleason score ≤7 tumor and a schematic of when the PSA level would exceed an example threshold under an example screening protocol.

Figure 1. Mean and interquartile range of PSA levels before and after onset of preclinical Gleason score ≤7 or Gleason score ≥8 prostate tumors. An example simulated PSA trajectory before and after onset of a Gleason score ≤7 tumor is superimposed, and the time at which the simulated PSA level exceeds a threshold for biopsy referral under a specific screening strategy is also indicated.

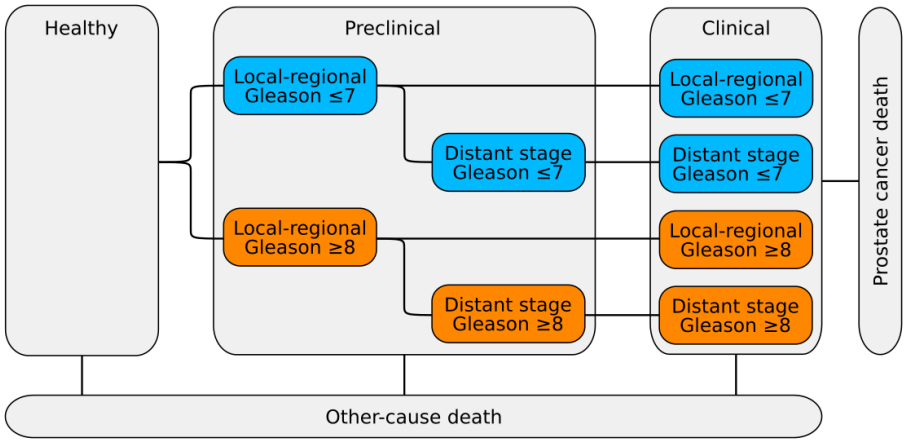


In a later extension, we further partitioned Gleason score ≤7 tumors into Gleason score ≤6 versus 7 using the PSA slope [3]. In applications of the model for Black men, we assume that PSA growth parameters do not differ by race.

Natural and clinical history

The original specification for prostate cancer natural history did not account for tumor grade.[1] When the model was extended to incorporate tumor grade, i.e., using grade-specific PSA growth after onset and calibrating to grade-specific incidence targets, the conceptualized natural and clinical history states and transitions between states became as shown in Figure 2.

Figure 2. Multi-state model of prostate cancer natural and clinical history states, including preclinical onset by grade (Gleason score ≤7 or ≥8), progression from localized to metastatic stage and from preclinical to clinical states.



The following subsections give details about the transitions between the natural and clinical history states.

Onset

The original specification for the hazard of onset was that it is proportional to age[1]:

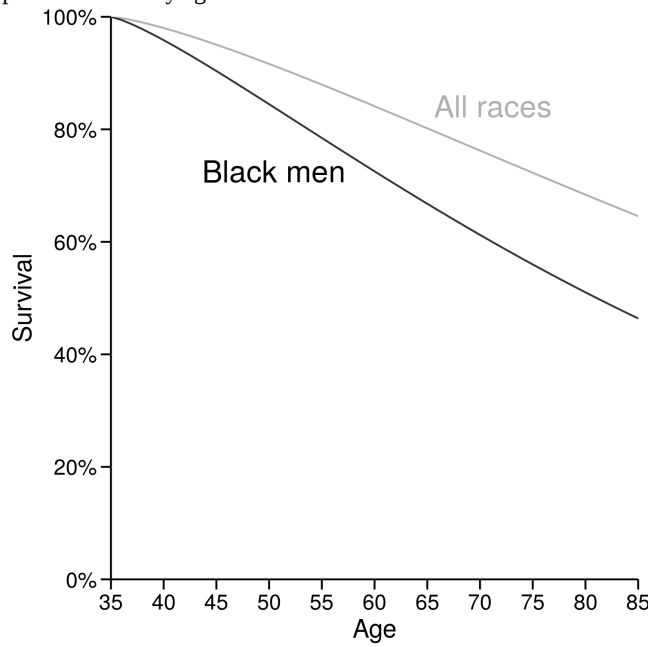
$$\lambda_o(t) = \gamma_o t.$$

This specification corresponded to a 1-parameter Weibull distribution. Subsequently this hazard was extended to a 2-parameter Weibull distribution[4]:

$$\lambda_o(t) = \frac{\phi}{\psi}\left(\frac{t}{\psi}\right)^{\phi-1}.$$

Using the extended specification, Figure 3 shows survival curves for the probability of remaining free of onset estimated for all races and for Black men.

Figure 3. Estimated survival curves showing the probability of not having onset of preclinical prostate cancer by age and race.



Grade

When the model was extended to use grade-specific PSA growth after onset, we originally specified that the probability of Gleason score ≥8 was modeled as a quadratic function of age at onset[2]:

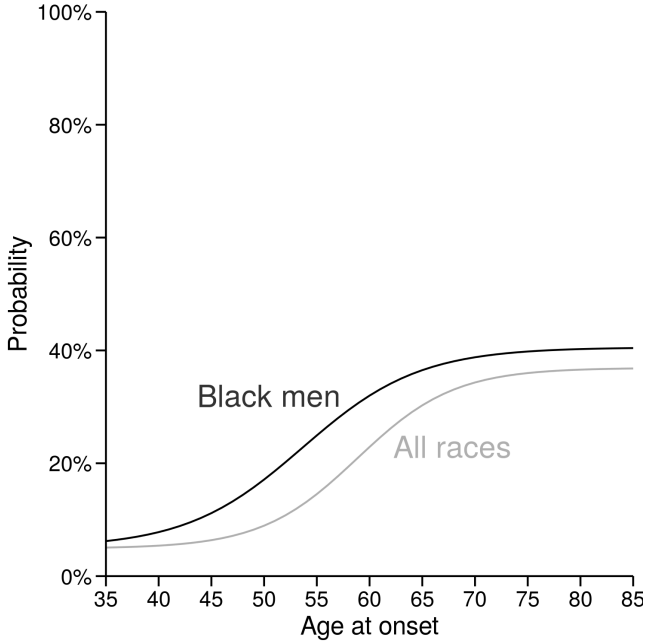
$$\Pr(\text{Gleason score} \geq 8 \mid t_o) = \theta_0 + \theta_1 t_o + \theta_2 t_o^2.$$

To more closely replicate incidence rates for Black men, we replaced this quadratic specification with a generalized logistic growth curve [5]:

$$\Pr(\text{Gleason score} \geq 8 \mid t_o) = L + (U - L)/(1 + e^{-\theta(t_o - M)}),$$

where L and U are lower and upper asymptotes, M is the offset for the age at onset for the inflection point of the logistic growth, and θ is the logistic growth rate. Figure 4 shows the probability of Gleason score ≥8 by age at onset estimated for all races and Black men.

Figure 4. Estimated probability of Gleason score ≥8 by age at onset and race.



Metastasis

The original specification for the hazard of transitioning from localized to metastatic cancer is proportional to an individual's (noise-free) PSA level[1]:

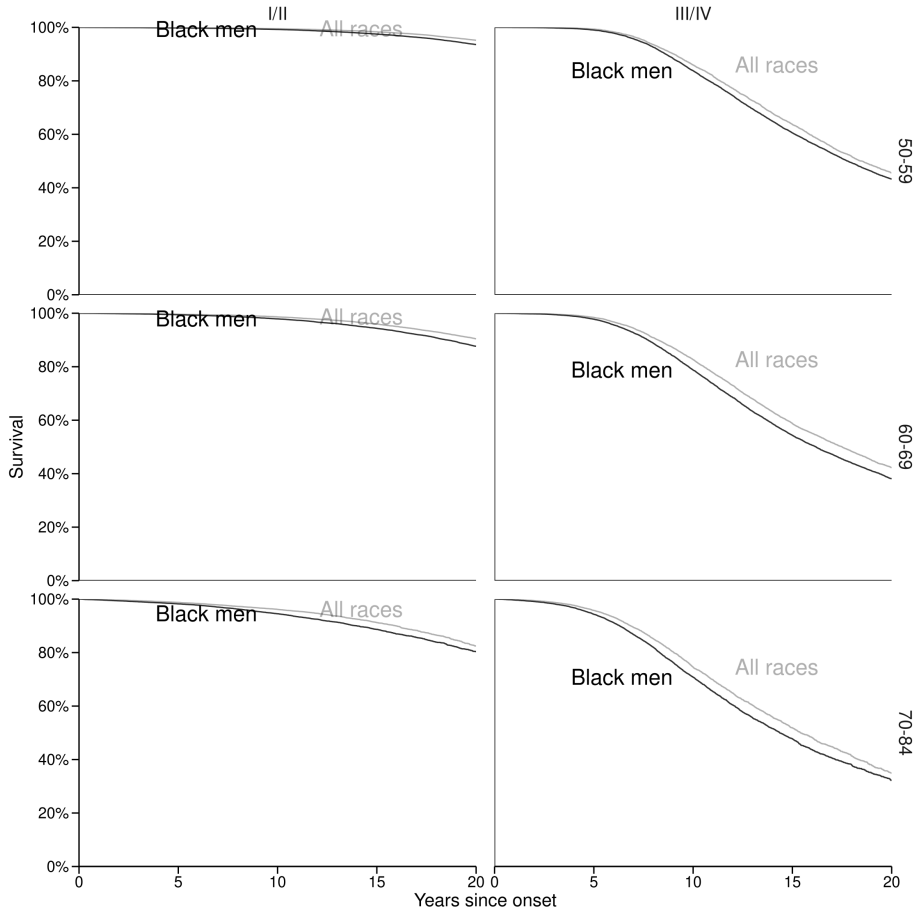
$$\lambda_m(t) = \gamma_m \tilde{y}_i(t),$$

where

$$\tilde{y}_i(t) = \exp\Big\{\beta_{0i} + \beta_{1i}t + \beta_{gi}(t - t_{oi})I(t > t_{oi})\Big\}$$

denotes the individual-specific mean PSA trajectory. Figure 5 shows survival curves for the probability of remaining free of metastasis after onset in the absence of screening estimated for all races and for Black men. Results are stratified by age decade and tumor grade.

Figure 5. Probability of not progressing to metastatic prostate cancer in the absence of PSA screening by age decade at onset, tumor grade, years since onset, and race.



In a later extension, we partitioned localized stage at diagnosis into clinical T-stage ≤T2a versus ≥T2b using a logistic regression model fit to cases in the Cancer of the Prostate Strategic Urologic Research Endeavor program given individual age, PSA level, and Gleason score at diagnosis.[3]

Clinical diagnosis

The original specification for the hazard of clinical diagnosis, i.e., transitioning from preclinical to clinical states, was that it is proportional to an individual's (noise-free) PSA level[1]:

$$\lambda_c(t) = \gamma_c \tilde{y}_i(t).$$

We also considered a variant specification with different proportionality constants for localized versus metastatic cancer:

$$\lambda_c(t) = \begin{cases} \gamma_c \tilde{y}_i(t) & (\text{localized}), \\ \theta_c \gamma_c \tilde{y}_i(t) & (\text{metastatic}). \end{cases}$$

For $\theta_c > 1$, this latter specification implies a greater chance that an individual with metastatic cancer will present symptoms and be diagnosed than one with localized disease. Extensions of the model specified different proportionality constants depending on stage and grade[4]:

$$\lambda_c(t) = \gamma_{sg} \tilde{y}_i(t).$$

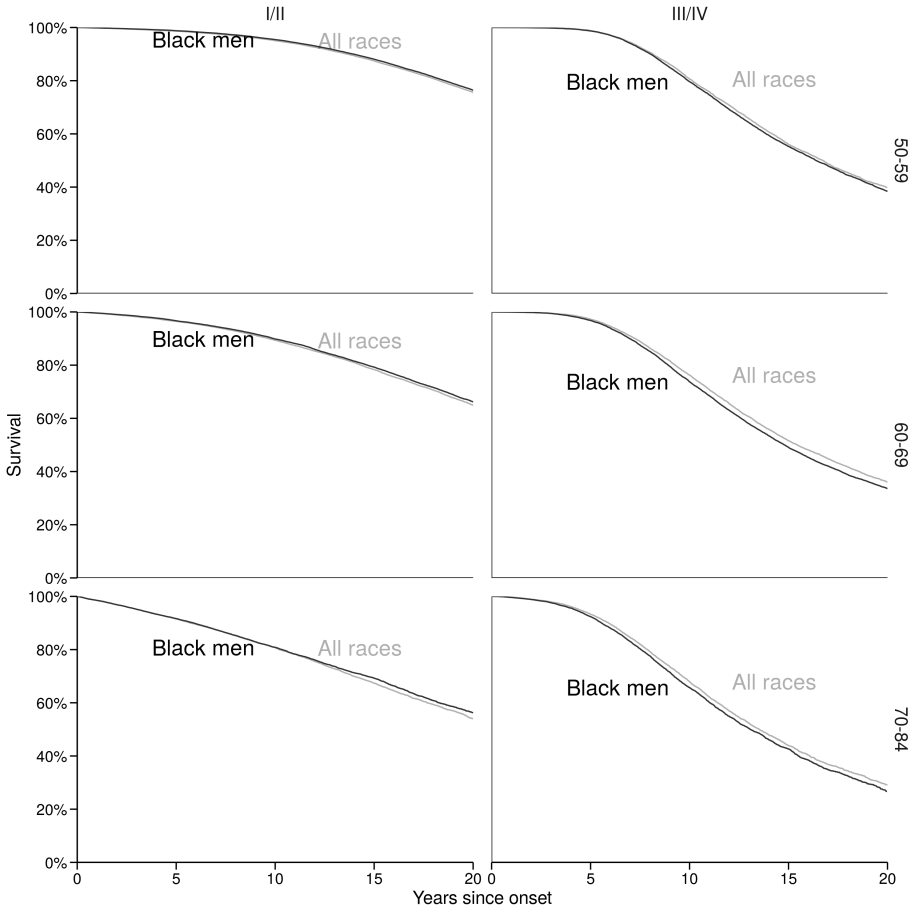
where $s =$ localized or metastatic, $g =$ Gleason score ≤ 7 or Gleason score ≥ 8, and

$$\tilde{y}_i(t) = \exp\Big\{\beta_{0i} + \beta_{1i} t + \beta_{gi}(t - t_{oi}) I(t > t_{oi})\Big\}.$$

Figure 6 shows survival curves for the probability of remaining free of diagnosis after onset in the absence of screening estimated for all races and for Black men. Results are stratified by age decade at onset and tumor

grade.

Figure 6. Probability of not being diagnosed with prostate cancer in the absence of PSA screening by age decade at onset, tumor grade, years since onset, and race.



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Parameter Overview

Summary

This document describes parameters in the Fred Hutchinson Cancer Center PSAPC model.

Background

In sourcing data to estimate model parameters for the US male population, our main goal was to obtain data that are representative and unbiased. For this reason, PSA level submodel parameters were estimated using data from the placebo arm of the Prostate Cancer Prevention Trial[1] and incidence rates in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial,[2] and natural and clinical history submodel parameters were estimated via calibration to incidence rates in the Surveillance, Epidemiology, and End Results (SEER) program based on PSA screening dissemination patterns reconstructed from the National Health Interview Survey (NHIS) and linked SEER-Medicare claims data.[3] Biopsy compliance frequency depends on age and PSA level as observed in the PLCO.[4] Primary treatment frequencies and prostate cancer survival for unscreened and untreated cases were estimated using SEER data. All of these data sources reflect large population-based registries, surveys, or trials. Since we do not have large trials in the US comparing initial treatments for prostate cancer, efficacy of curative treatment is based on data from the Scandinavian trial[5-7]of radical prostatectomy versus watchful waiting, which we have shown[8] is consistent with a limited US-based trial[9,10]and selected observational studies to set cause-specific hazard ratios associated with different initial treatment choices. Efficacy of screening is based on the European Randomized Study of Screening for Prostate Cancer (ERPSC), which we have shown is consistent with PLCO results after accounting for differences in settings and implementations.[11,12]Finally, we base our estimates of biopsy sensitivity on a review of relevant literature and a reconstruction of the dissemination of progressively more intensive biopsy schemes over calendar years.[13-16]

Parameter listing

Parameters in the PSAPC model are listed below. Each set of parameters is identified as either internal (i.e., estimated via calibration to observed prostate cancer incidence) or external (i.e., provided to the model based on external analyses or model assumptions).

PSA submodel parameters (external)

- PSA level intercept (level at age 35) mean and variance (μ_0, σ_0^2)
- Pre-onset PSA level slope mean and variance (μ_1, σ_1^2)
- Post-onset PSA level slope mean and variance for Gleason score ≤7 tumor ($\mu_{\text{Gleason score } \leq 7}$, $\sigma^2_{\text{Gleason score } \leq 7}$)
- Post-onset PSA level slope mean and variance for Gleason score ≥8 tumor ($\mu_{\text{Gleason score } \geq 8}$, $\sigma^2_{\text{Gleason score } \geq 8}$)
- PSA noise or within-individual error (τ^2)

Probability tumor is Gleason score $\geq$8 given age at onset (internal)

- Lower asymptote (L)
- Upper asymptote (U)
- Offset for age at onset for the inflection point of the logistic growth (M)
- Logistic growth rate (θ)

Natural and clinical history submodel parameters (internal)

- Onset hazard rate and shape (ϕ, ψ)
- Metastasis hazard (γ_m)
- Pre-metastasis clinical diagnosis hazard for Gleason score ≤7 tumor ($\gamma_{\text{localized,Gleason score } \leq 7}$)

- Pre-metastasis clinical diagnosis hazard for Gleason score ≥8 tumor ($\gamma_{\text{localized,Gleason score } \geq 8}$)
- Post-metastasis clinical diagnosis hazard for Gleason score ≤7 tumor ($\gamma_{\text{metastatic,Gleason score } \leq 7}$)
- Post-metastasis clinical diagnosis hazard for Gleason score ≥8 tumor ($\gamma_{\text{metastatic,Gleason score } \geq 8}$)

Biopsy parameters (external)

- Biopsy frequency, i.e., probability a biopsy is performed if referred; increases with PSA level and decreases with age
- Biopsy sensitivity, i.e., probability that a biopsy will detect a preclinical tumor if present; increases across calendar years

Experimental early detection parameters (external)

- Transurethral resection of the prostate (TURP) frequency; increases in pre-PSA years and decreases in PSA years
- Digital rectal exam (DRE) sensitivity when PSA < 4.0 ng/mL; decreases with PSA level
- Biopsy frequency and sensitivity increase to 100% for individuals within δ years of transitioning to metastatic disease

Prostate cancer survival parameters (external)

- Baseline prostate cancer survival; depends on age, race, tumor grade, and stage
- Improvement in baseline prostate cancer survival over time; constant or depends on age at diagnosis

Primary treatment for localized prostate cancers (external)

- Initial treatment frequencies; depends on age, year, race, and tumor grade
- Hazard ratios associated with initial treatments; constant or depends on age, year, and tumor grade

Early detection benefit (external)

- Stage-shift mechanism: cases diagnosed with localized disease by screening who would have been diagnosed with metastatic disease without screening receive a corresponding improvement in baseline prostate cancer survival
- Cure rate (constant) mechanism: non-overdiagnosed screen-detected cases who would have died due to prostate cancer are randomly reassigned to die at their independently generated age at other-cause death
- Cure rate (lead-time dependent) mechanism: Same as constant cure rate mechanism but the cure rate increases exponentially with lead time

Competing mortality (external)

- US life tables; depends on birth year and age at entry into population
- Comorbidity-adjusted life tables; depends on birth year and age at entry into population

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Component Overview

Summary

This document describes the main components of the Fred Hutchinson Cancer Center PSAPC model.

Overview

The primary components of the PSAPC model are as follows:

- PSA growth before and after onset of a prostate tumor
- Prostate cancer natural history and clinical diagnosis
- Early detection testing receipt and efficacy
- Primary treatment receipt and efficacy
- Prostate cancer survival
- All-cause mortality

PSA growth before and after onset of a prostate tumor

The PSA growth submodel is described in the Assumption Overview.

Prostate cancer natural history and clinical diagnosis

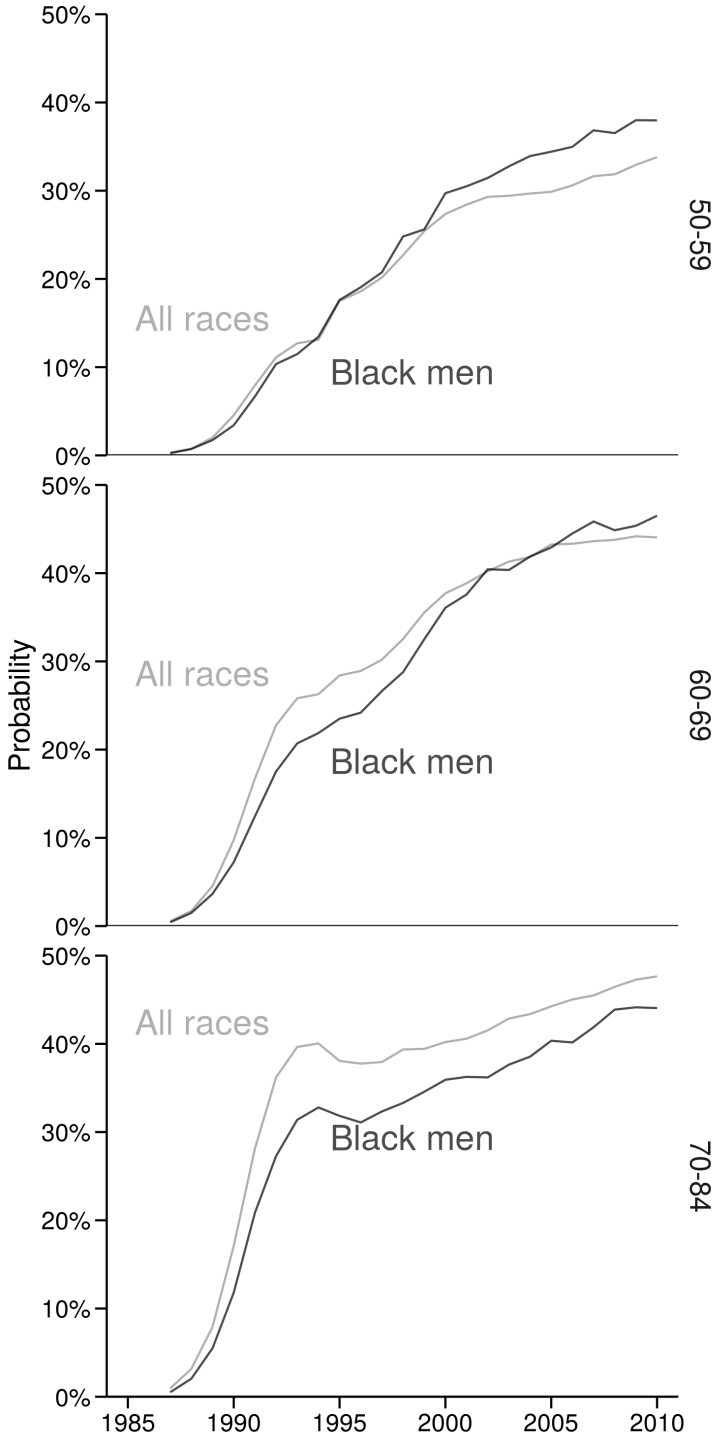
The prostate cancer natural history and clinical diagnosis submodel is described in the Assumption Overview.

Early detection testing

Receipt

First-line screening for prostate cancer has primarily involved the prostate-specific antigen (PSA) test. PSA screening dissemination in the general US population was previously reconstructed using self-reported age at first PSA test from the National Health Interview Survey and distributions of intervals between PSA tests estimated using claims data from Surveillance, Epidemiology, and End Results (SEER)-Medicare database.[1] To calibrate the natural and clinical history model for the general population, we assumed that men with PSA >4 ng/mL were referred to biopsy, with receipt increasing with PSA level and decreasing with age as observed in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial [2]. We assumed that biopsy sensitivity to detect preclinical disease increased during the 1990s with the dissemination of biopsy schemes with more cores.[3-8]
Figure 1 shows reconstructed probabilities of having received at least one PSA test by calendar year for all races and for Black men. Results are stratified by age decade.

Figure 1. Probability of at least one PSA test reconstructed using a model fit to data from the National Health Interview Survey for age at first test and the linked Surveillance, Epidemiology, and End Results and Medicare 5% random sample of the cancer-free population for intervals between tests by age decade, calendar year, and race.



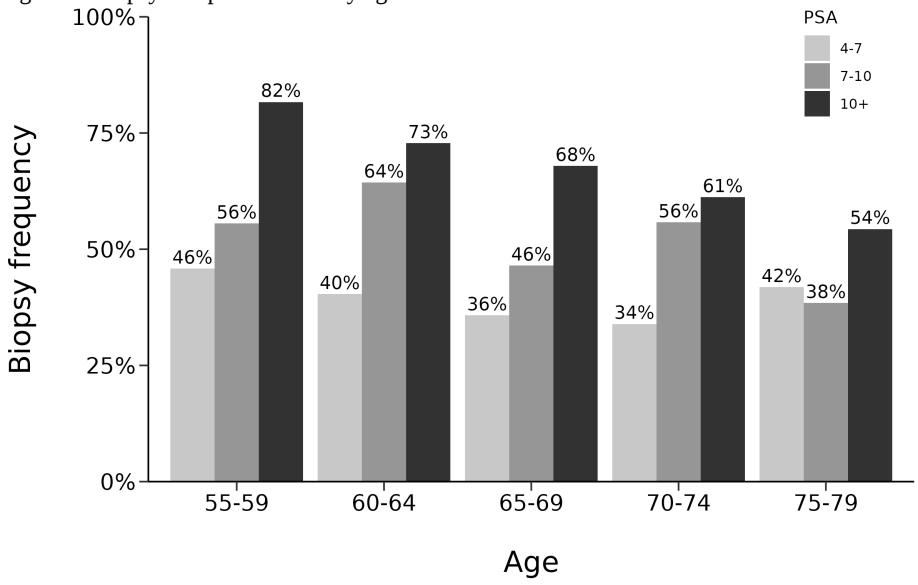
PSA screening patterns in the general US population were updated to account for effects of US Preventive Services Task Force recommendations against screening for ages ≥75 in 2008 and for all ages in 2012. Experimental parameters that filtered the reconstructed screening rates for these age groups starting in these years were identified so that the model approximately matched observed incidence rates.[9]

Applications of the model to trial settings, e.g., the PLCO and European Randomized Study of Screening for Prostate Cancer (ERSPC), assumed that screening followed trial protocols subject to reported adherence

patterns. These studies also explicitly modeled receipt of digital rectal exam (DRE) tests when applicable.[10-12] Specifically, DRE sensitivity to detect latent disease in men with negative PSA test results was based on a ERSPC study[13] that found DRE sensitivity is approximately 20% for PSA below 3.0 ng/ml and 40% for PSA from 3.0 to 3.9 ng/mL. One study of pre-PSA incidence rates examined possible contributions due to assumed trends due to sporadic transurethral resection of the prostate.[14] More recent studies explored second-line "reflex" tests in men with elevated PSA levels before prostate biopsy.[15,16]

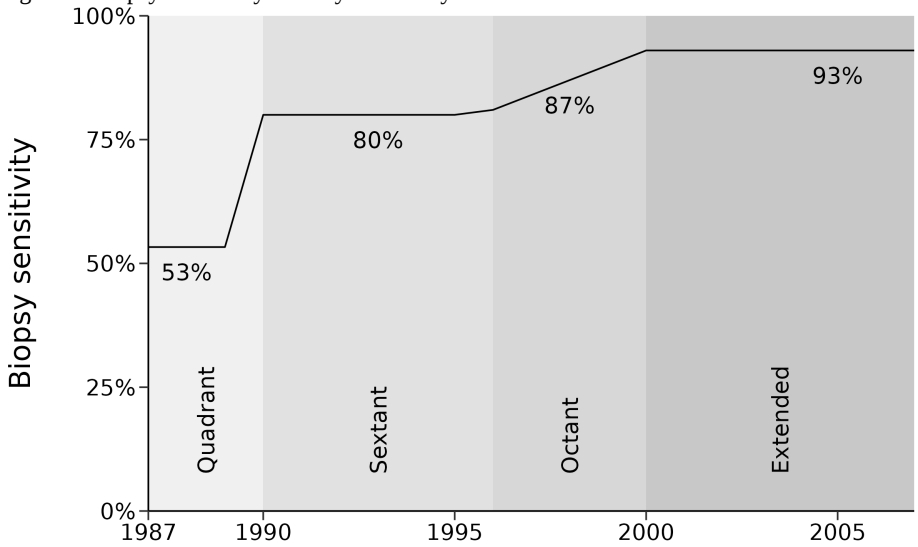
Receipt of prostate biopsy was assumed to decrease with age and increase with PSA level as observed in the PLCO.[2] Figure 2 illustrates biopsy frequency by age and PSA level.

Figure 2. Biopsy compliance rates by age and PSA level.



Biopsy sensitivity is based on a literature review of how biopsy schemes changed over time.[2,3,4,5,6,7,17,18,19] Figure 3 shows assumed sensitivity of prostate biopsy under if the index scheme (sextant) sensitivity is 80%.

Figure 3. Biopsy sensitivity rates by calendar year.



Efficacy

Multiple mechanisms of early detection benefit have been investigated. Under a fixed stage shift, patients who would have been diagnosed with metastatic prostate cancer in the absence of screening and who are detected with localized prostate cancer by screening receive a corresponding survival improvement. Under a flexible stage shift, the full stage shift improvement is tempered by the patient's lead time, i.e., the time by which

diagnosis is advanced by screening. Under a hazard ratio, patients whose prostate cancer is detected by screening have a modified hazard of prostate cancer death. Under a fixed cure rate, a fraction of patients whose prostate cancer is detected by screening and who would have died of disease in the absence of screening are re-assigned to die at their independently generated age at death from other causes. Under a flexible cure rate, the cure fraction is mediated by the patient's lead time. Figure 4 shows 13-year prostate cancer mortality observed in the ERSPC and corresponding projections under selected mechanisms of screening benefit.

Figure 4. Cumulative hazard of prostate cancer death in the European Randomized Study of Screening for Prostate Cancer with 13 years of follow-up and projected mortality under selected mechanisms of early detection benefit calibrated to the trial with 20 years of follow-up.

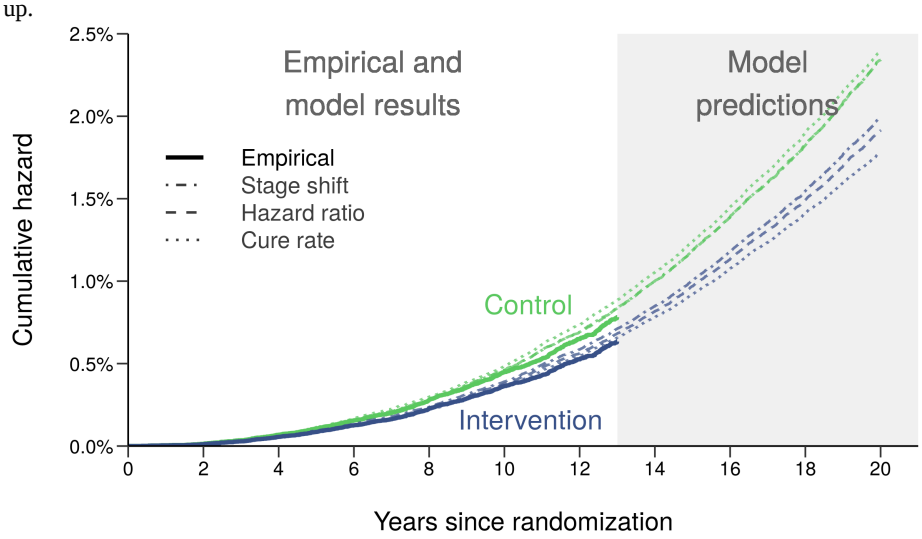
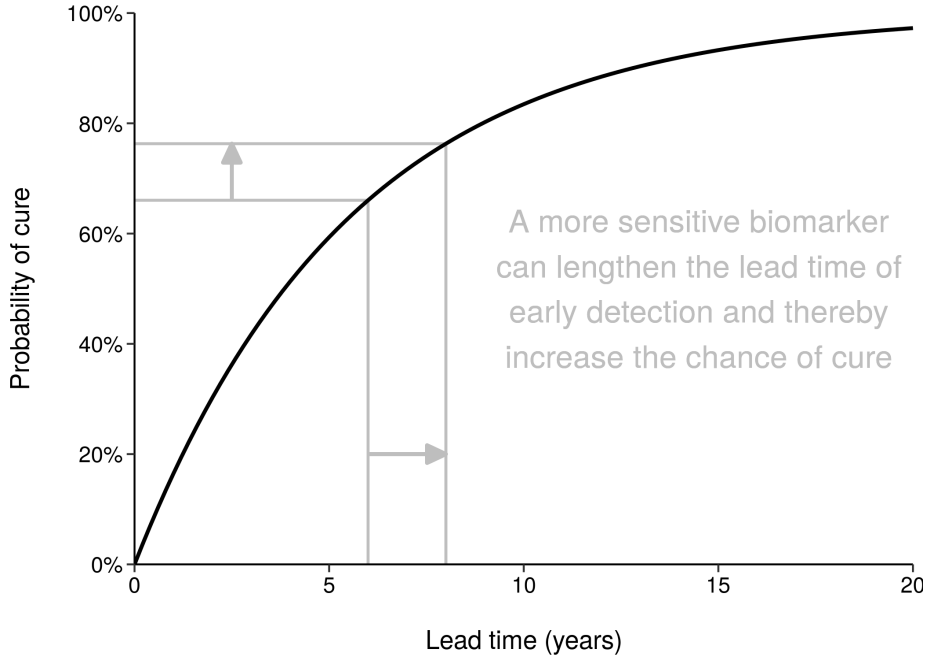


Figure 5 shows schematically how a flexible cure fraction depends on an individual's lead time.[15]

Figure 5. Schematic of a lead-time-dependent cure fraction used to represent continuous benefit of early detection.



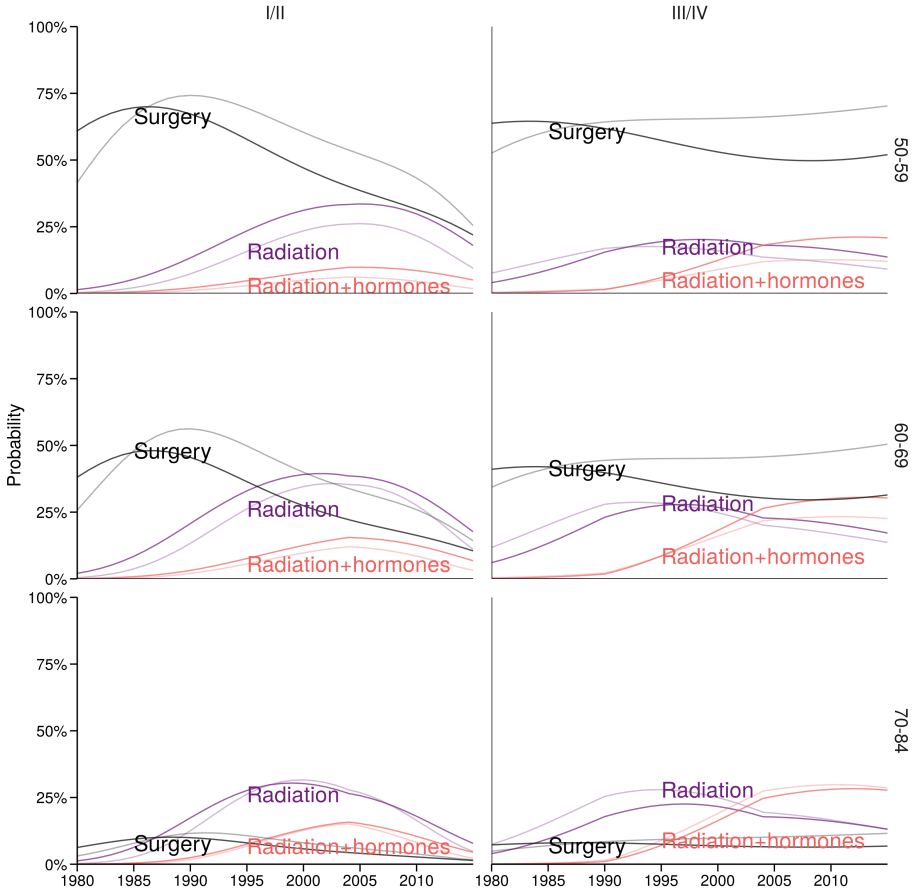
Primary treatment

Receipt

Receipt of primary treatments (surgery or radiation) within 12 months of diagnosis of localized prostate cancer was previously estimated for the general US population using frequencies in SEER catchment areas by age and tumor grade.[20,21]A recent extension of this regression model estimated receipt of curative treatment for Black men.[22] Receipt of concurrent androgen deprivation therapy (ADT) was previously estimated using data from the Cancer of the Prostate Strategic Urologic Research Endeavor registry.[21] In applications of the model for Black men, we assumed receipt of adjuvant ADT in Black men was similar to that for all races combined.

Figure 6 shows probabilities of receiving surgery, radiation, or radiation plus ADT by calendar year for all races and for Black men. Results are stratified by age decade at diagnosis and tumor grade.

Figure 6. Probability of receipt of curative treatment for localized prostate cancer estimated from a multinomial regression model fit to data from the Surveillance, Epidemiology, and End Results program for surgery or radiation and the Cancer of the Prostate Strategic Urologic Research Endeavor registry for adjuvant hormonal therapy by age at diagnosis, tumor grade, calendar year, type of treatment, and race. Heavy lines are for Black men and light lines are for all races.



Applications of the model to trial settings, e.g., the PLCO or ERSPC, assumed that primary treatments followed empirical distributions reported in those trials.

Efficacy

Efficacy of primary treatment has been based on results of the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) randomized trial of radical prostatectomy versus watchful waiting, operationalized using an overall or age-dependent hazard ratio.[21,23,24,25]We previously found that the Prostate Cancer Intervention

Versus Observation Trial (PIVOT) in the US[26,27]was consistent with SPCG-4 results after accounting for artifacts of screening, i.e., lead time and overdiagnosis, in the PIVOT patients.[28] More recently, the Prostate Testing for Cancer and Treatment (ProtecT) trial also found low rates of death due to prostate cancer in patients whose disease was found by screening irrespective of whether they were followed initially with radical prostatectomy, radiation therapy, or active monitoring.[29,30]The ProtecT results appear to be compatible with analyses of the SPCG-4 and PIVOT after controlling for the inflated survival among patients diagnosed by screening.

Prostate cancer survival

Prostate cancer survival was estimated using Cox regressions fit to SEER data in 1980--1986, just before widespread uptake of PSA screening in the US population. Separate models were fit to men diagnosed with localized and metastatic prostate cancer in the absence of primary treatment. The model for localized prostate cancer depended on age at diagnosis, tumor grade, and race. The model for metastatic prostate cancer depended on tumor grade and race. Figures 7 and 8 visualize the fitted Cox regressions superimposed over Kaplan-Meier estimates.

Figure 7. Probability of not dying from prostate cancer estimated using Cox regression (“Cox”; blue lines) and stratified Kaplan-Meier (“K-M”; black lines) for untreated cases diagnosed in the Surveillance, Epidemiology, and End Results program in 1980--1986 with local-regional stage prostate cancer by age at diagnosis, disease grade, years since diagnosis, and race. Cox regression curves use the midpoint of each age group.

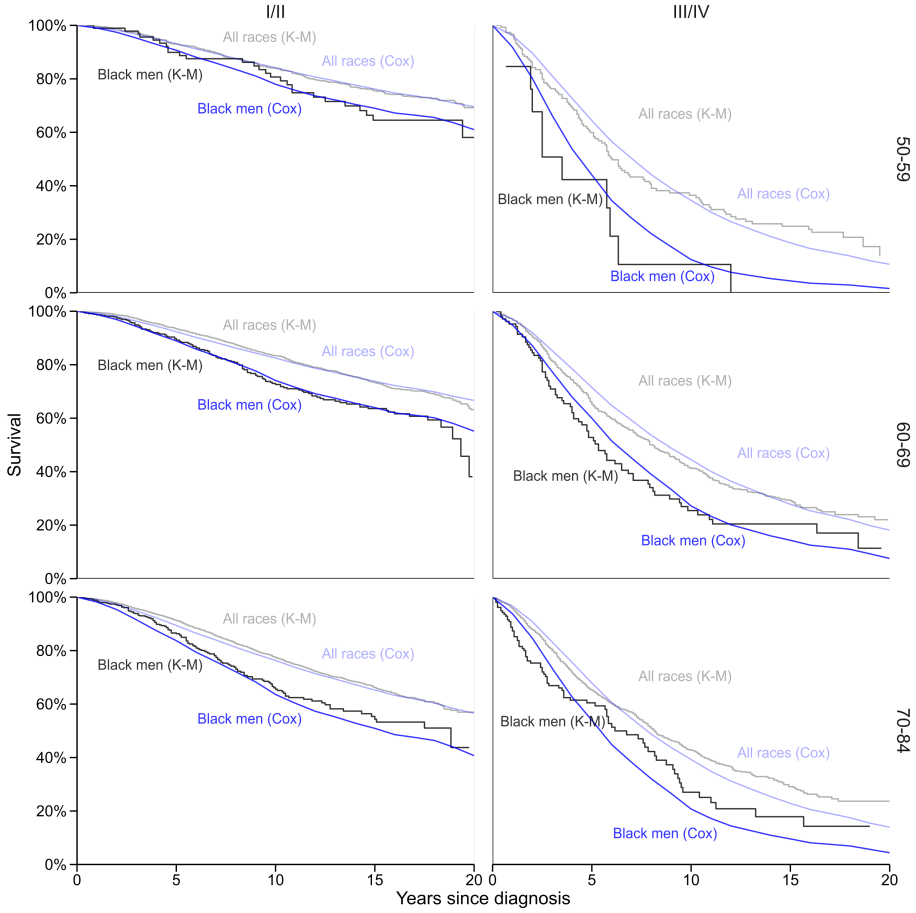
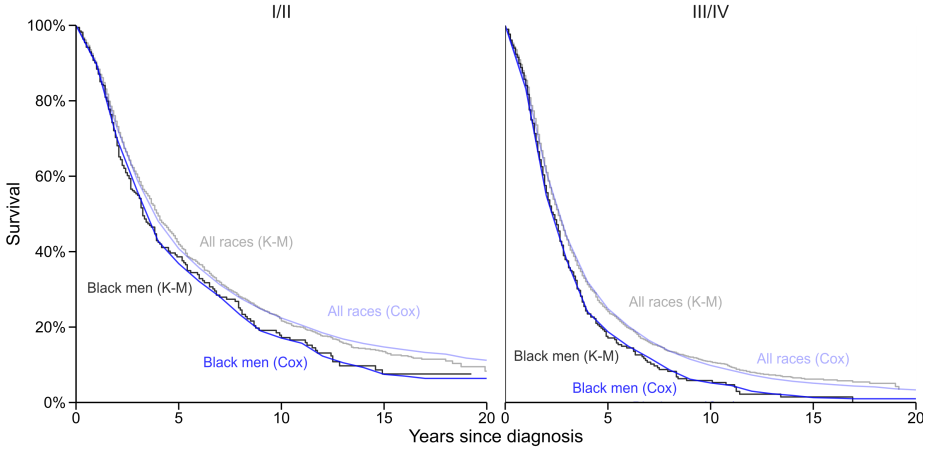


Figure 8. Probability of not dying from prostate cancer estimated using Cox regression (“Cox”; blue lines) and stratified Kaplan-Meier (“K-M”; black lines) for untreated cases diagnosed in the Surveillance, Epidemiology, and End Results program in 1980--1986 with distant stage prostate cancer by disease grade, years since diagnosis, and race.

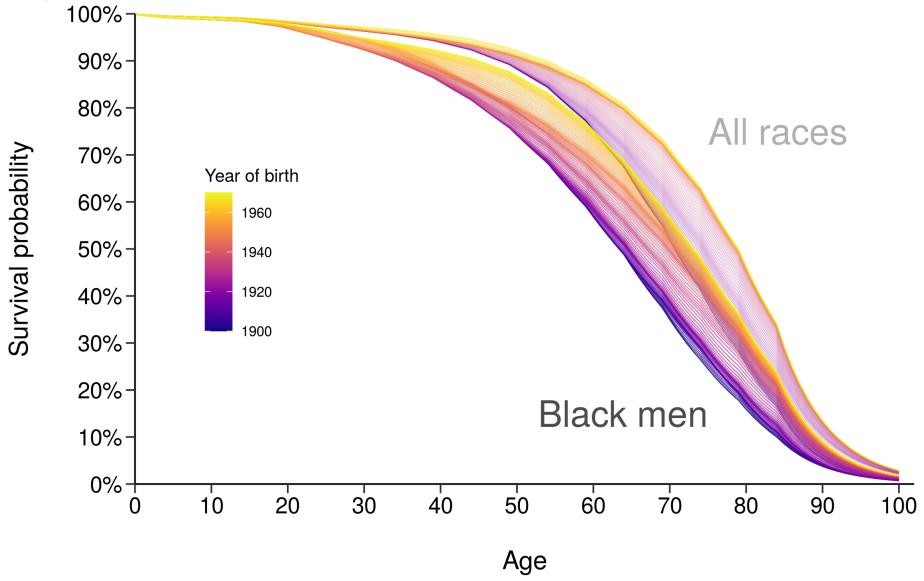


These models extend earlier Poisson regressions fit to pre-PSA SEER data for untreated cases. Those fitted models agreed closely with long-term empirical estimates.[31] The extended models used Cox instead of Poisson regressions and incorporated race.

All-cause mortality

Age at death from all causes is generated for all simulated individuals and competes with prostate cancer-specific outcomes such as incidence and mortality. Figure 9 shows all-cause mortality from life tables for US males by birth cohort and race.

Figure 9. Probability of not dying from any cause according to US life tables by age, year of birth, and race.



For simplicity, men born before 1903 are assumed to follow the all-cause survival for men born in 1903, and men born after 1959 are assumed to follow the all-cause survival for men born in 1959.

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Output Overview

Summary

This document describes the main outputs of the Fred Hutchinson Cancer Center PSAPC model.

Overview

The main outputs of the PSAPC model are:

- Life histories
- Aggregate outcomes
- Incidence data
- Mortality data

Life histories

Simulated individual life histories reflect preclinical and clinical events and their characteristics over time. A typical model run tracks events with and without assumed screening interventions and includes:

- Age at entry in the study
- Age at preclinical onset of prostate cancer
- Age at progression from localized to metastatic prostate cancer
- Age at prostate cancer diagnosis without screening
- PSA submodel parameters (intercept, pre-onset slope, post-onset slope)
- PSA level at prostate cancer diagnosis without screening
- Grade at prostate cancer diagnosis without screening (Gleason score ≤6, 7, ≥8)
- Stage at prostate cancer diagnosis without screening (early localized, advanced localized, or metastatic)
- Primary treatment without screening (radical prostatectomy, radiotherapy, conservative management)
- Hormone treatment without screening (yes or no)
- Age at prostate cancer-specific death without screening
- Age at prostate cancer diagnosis with screening
- PSA level at prostate cancer diagnosis with screening
- Stage at prostate cancer diagnosis with screening (early localized, advanced localized, or metastatic)
- Primary treatment with screening (radical prostatectomy, radiotherapy, conservative management)
- Hormone treatment with screening (yes or no)
- Age at prostate cancer-specific death with screening
- Age at other-cause death

These simulated life histories are written to output files for each screening and treatment intervention considered. Various summary statistics are then calculated using these data. For example:

Overdiagnosis: the proportion of individuals with prostate cancer diagnosed by screening who would not have been diagnosed without screening before other-cause death.

Lead time: the time from diagnosis with screening to diagnosis without screening. More precisely, three definitions of lead times have been used:

- **Relevant lead times**: calculated only for non-overdiagnosed individuals, i.e., individuals for whom age at diagnosis without screening precedes age at other-cause death.
- **Censored lead times**: calculated for both non-overdiagnosed individuals and for overdiagnosed individuals, with lead times for overdiagnosed individuals censored at death from other causes.
- **Uncensored lead times**: calculated for both non-overdiagnosed individuals and for overdiagnosed individuals, with lead times for overdiagnosed individuals not censored at death from other causes.

Sojourn time: the time from preclinical onset to diagnosis without screening. In principle, the three definitions for lead time could also be used for sojourn time.

Prostate cancer survival: the probability of surviving prostate cancer estimated over time since diagnosis or evaluated at a specific point in time (e.g., 20-year survival).

Aggregate outcomes

Specific event counters are tracked for comparative effectiveness and cost-effectiveness analyses. These include:

- Total first-line screening (e.g., PSA) tests
- True positive first-line screening tests
- True negative first-line screening tests
- False positive first-line screening tests
- False negative first-line screening tests
- Total second-line screening (e.g., MRI) tests
- Total biopsies
- Total prostate cancer diagnoses
- Localized prostate cancer diagnoses
- Low-grade prostate cancer diagnoses
- Screen diagnoses
- Overdiagnoses
- Total radical treatments
- Radical prostatectomies
- Radiotherapy courses
- Hormone therapy courses
- Overtreatments
- Total deaths
- Prostate cancer deaths
- Other-cause deaths
- Time spent in asymptomatic state
- Time spent in conservative management state
- Time spent in short-term treatment state
- Time spent in long-term treatment state
- Time spent in metastatic state
- Time spent in end-of-life state

Event counters are output by age and year to facilitate age-based analyses and discounting of future health outcomes (in addition to discounting future costs).

Incidence data

Simulated prostate cancer diagnosis counts and corresponding population counts from which rates can be calculated are tabulated and output by age and year of diagnosis, tumor stage and grade, and mode of detection (i.e., diagnosis with or without screening).

Mortality data

Simulated prostate cancer and other-cause deaths and corresponding population counts from which rates can be calculated are tabulated and output by age and year of death, tumor stage and grade at diagnosis, and mode of detection (i.e., diagnosis with or without screening).

Fred Hutchinson
Cancer Center
Results Overview

Results Overview

Summary

This document summarizes selected results of the Fred Hutchinson Cancer Center PSAPC model.

Prostate cancer incidence and mortality in the US

The calibrated PSAPC model approximately reproduces prostate cancer incidence rates in the general US population by age, year, stage, and grade. Figure 1 shows observed and projected incidence rates for the general US population.[1]

Figure 1. Observed prostate cancer incidence rates from the Surveillance, Epidemiology, and End Results program and corresponding model projections with (solid line) and without (dashed line) screening by age, year, and stage at diagnosis.

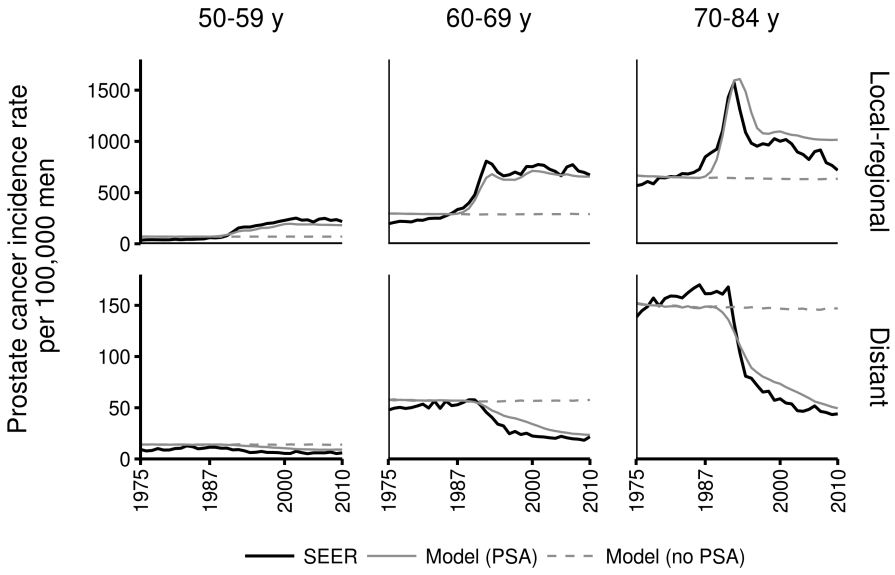


Figure 2 shows observed and projected incidence rates by age at diagnosis, for all races combined and for Black men, with projections partitioned into overdiagnosed and non-overdiagnosed cases.[2]

Figure 2. Observed prostate cancer incidence rates from the Surveillance, Epidemiology, and End Results program and corresponding model projections by age, year, and race paritioned into overdiagnosed (light gray) and non-overdiagnosed (dark gray) cases.

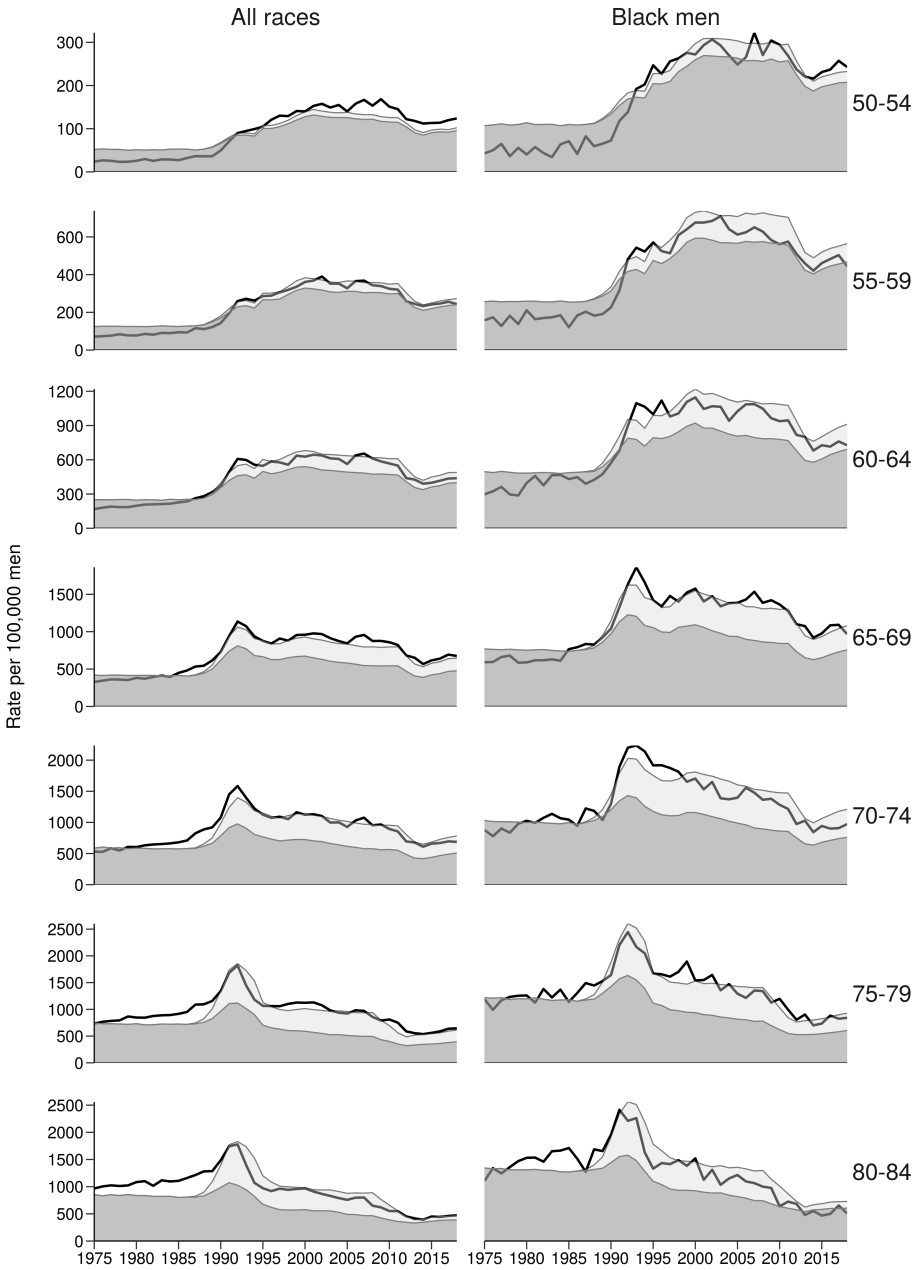


Figure 3 shows observed prostate cancer mortality rates from the National Center for Health Statistics (NCHS) and projections from the PSAPC model with and without screening or changes in care. Because the model does not attempt to replicate the transitory increase in mortality in the early 1990s, modeled mortality estimates are initially lower than the observed mortality. Under modeled effects of screening and changes in care, the model reasonably approximates observed mortality rates in later years.

Figure 3. Prostate cancer mortality rates for ages 50-84 years from the National Center for Health Statistics (NCHS) and projections from the PSAPC with and without screening or changes in care.

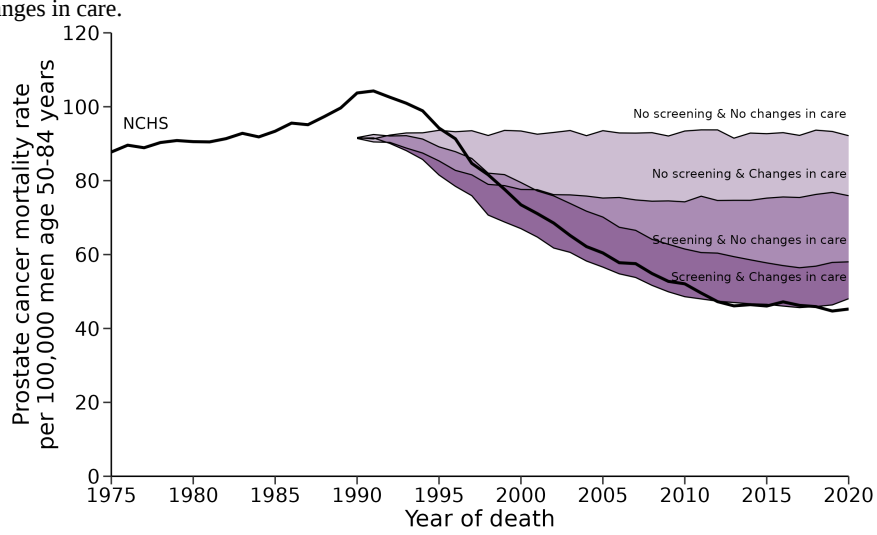
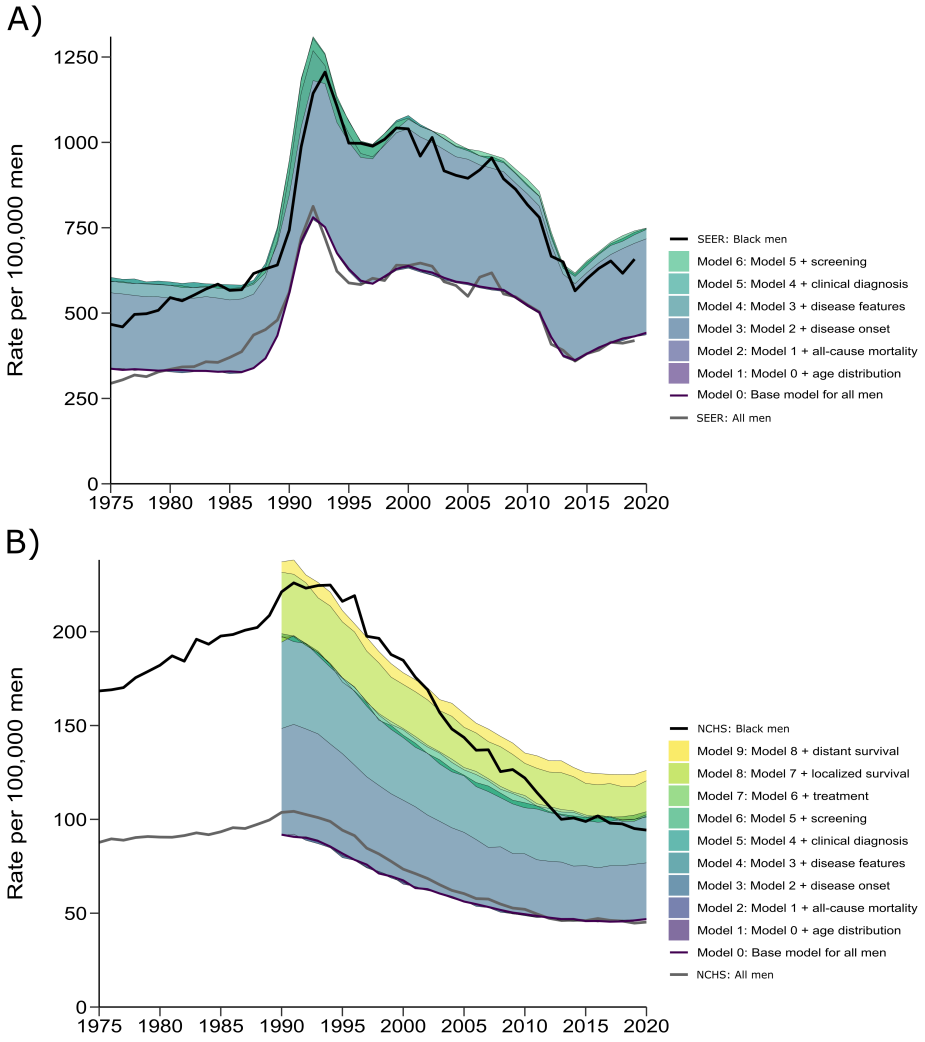


Figure 4 shows observed prostate cancer incidence rates from Surveillance, Epidemiology, and End Results (SEER) and prostate cancer mortality rates from the NCHS and projections from the PSAPC model by race. Model projections for all races were systematically replaced with inputs for Black men to quantify the relative contributions to observed disparities.[3] In 2019, the increased frequency of developing disease, more aggressive tumor features, and worse cancer-specific survival in Black men each explained approximately one-third of the modeled disparity in mortality. These results point to intensified screening and improved care in Black men as priority areas to achieve greater equity.

Figure 4. Prostate cancer A) incidence and B) mortality rates for all races and for Black men aged 40-84 years at diagnosis from the Surveillance, Epidemiology, and End Results program and corresponding model projections after sequentially replacing model components for all men with components for Black men.



Prostate cancer incidence and mortality in the PLCO

The calibrated PSAPC model approximately reproduces prostate cancer diagnoses and death in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial by age, year, stage, grade, and arm.[4] Figure 5 shows observed and projected prostate cancer diagnoses by arm and age at randomization.

Figure 5. Observed cumulative prostate cancer diagnoses from the PLCO cancer screening trial and corresponding model projections by arm and age at randomization.

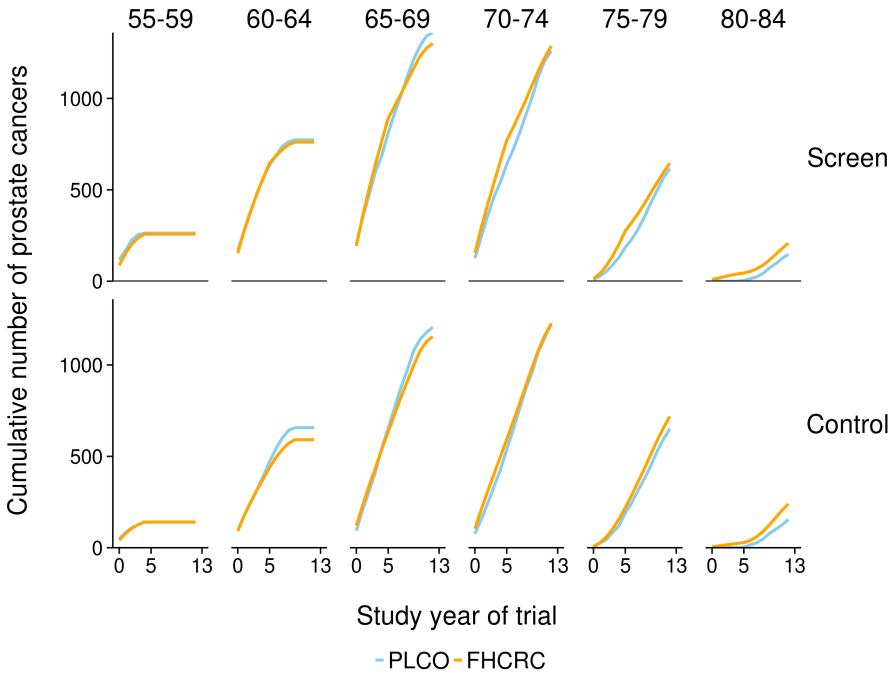
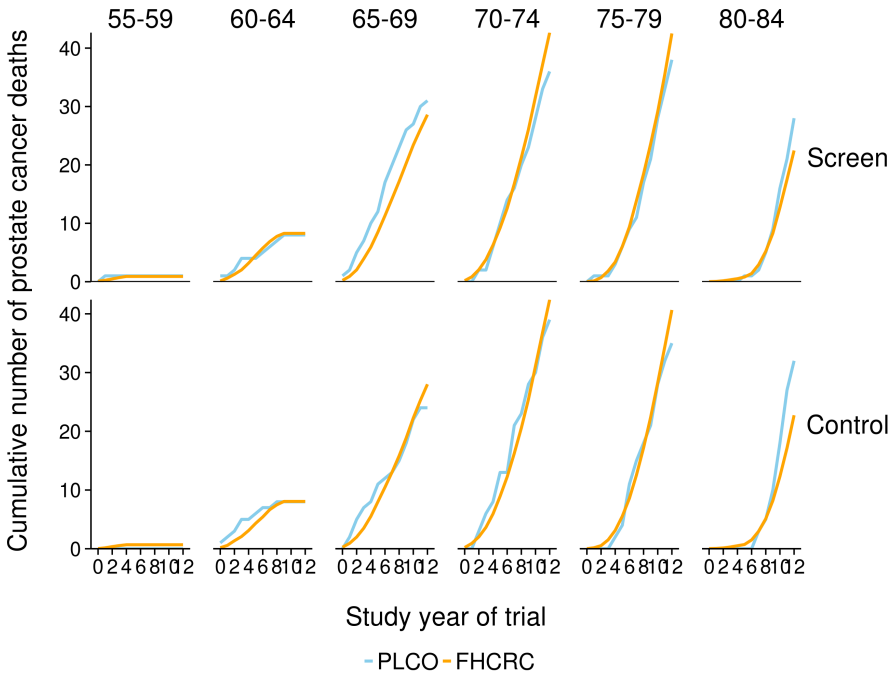


Figure 6 shows observed and projected prostate cancer deaths by arm and age at randomization.

Figure 6. Observed cumulative prostate cancer deaths from the PLCO cancer screening trial and corresponding model projections by arm and age at randomization.



Prostate cancer incidence and mortality in the ERSPC

The calibrated PSAPC model approximately reproduces prostate cancer diagnoses and death in the European Randomized Study of Screening for Prostate Cancer (ERSPC) by age, year, stage, grade, and arm.[4] Figure 7 shows observed and projected prostate cancer diagnoses by arm and age at randomization.

Figure 7. Observed cumulative prostate cancer diagnoses from the ERSPC and corresponding model projections by arm and age at randomization.

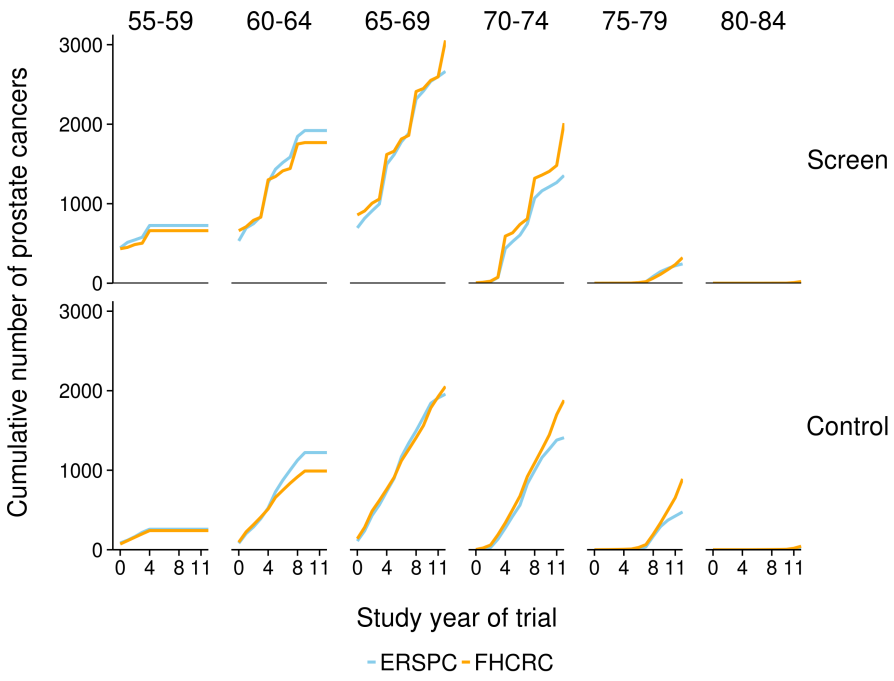
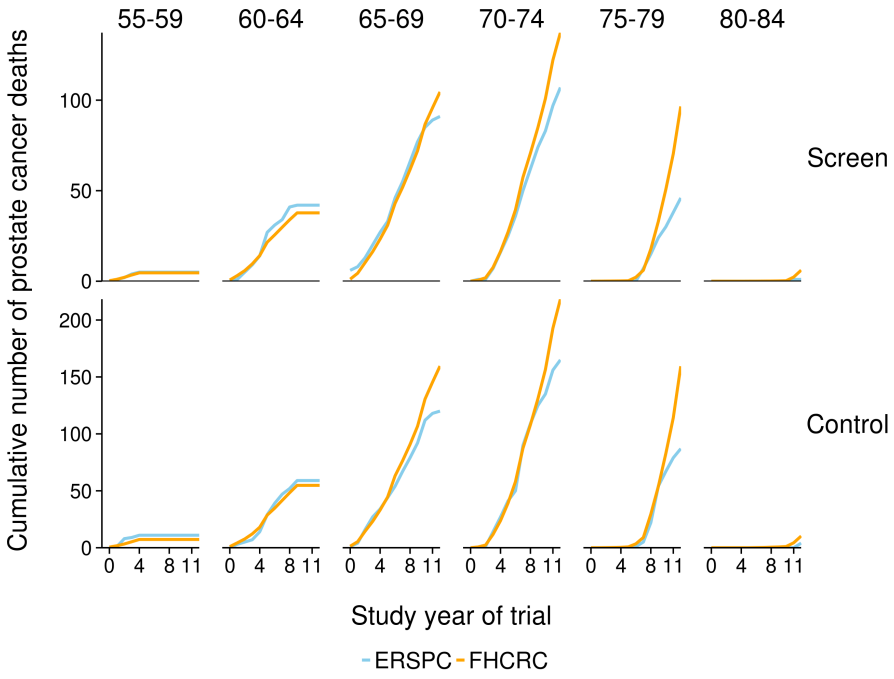


Figure 8 shows observed and projected prostate cancer deaths by arm and age at randomization.

Figure 8. Observed cumulative prostate cancer deaths from the ERSPC and corresponding model projections by arm and age at randomization.

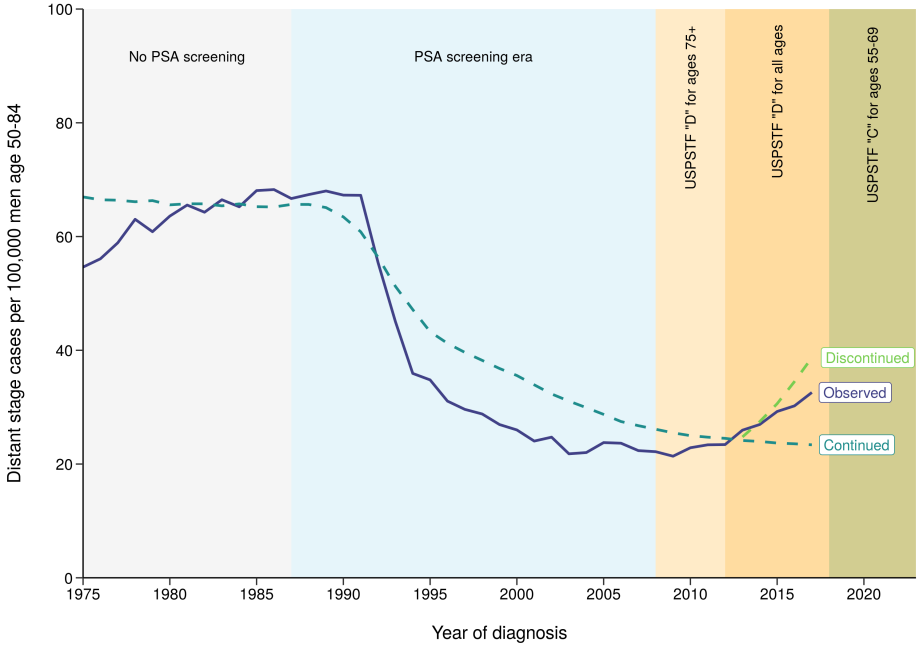


Role of decreased screening on rising incidence of de novo metastasis

After the US Preventive Services Task Force recommended against PSA screening for all ages in 2012, the PSAPC model projected incidence of de novo metastatic disease under a continuation of historical screening

and under completely discontinued screening.[5] A later study examined the plausible role of decreased screening in the subsequent increasing trend in de novo metastatic disease.[6] Figure 9 shows that observed incidence of de novo metastatic disease fell midway between the previously projected extremes.

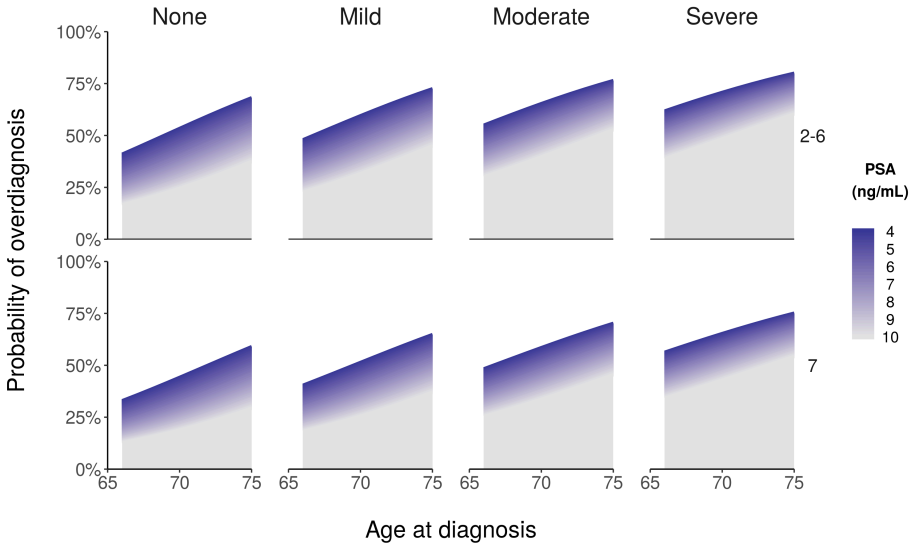
Figure 9. Metastatic prostate cancer incidence rates for men aged 50-84 years from the Surveillance, Epidemiology and End Result program and projections from the PSAPC model under a continuation of historical screening and discontinued screening beginning January 1, 2013.



Personalized risk of overdiagnosis

A study exploring how modeled overdiagnosis depends on patient age, PSA level, and biopsy grade[7] was extended to also stratify estimates by comorbid conditions at diagnosis.[8] Figure 10 visualizes estimated risks of overdiagnosis within comorbidity strata.

Figure 10. Estimated probability of overdiagnosis in patients based on comorbidity-dependent logistic regression models fit to life histories simulated using the PSAPC model.

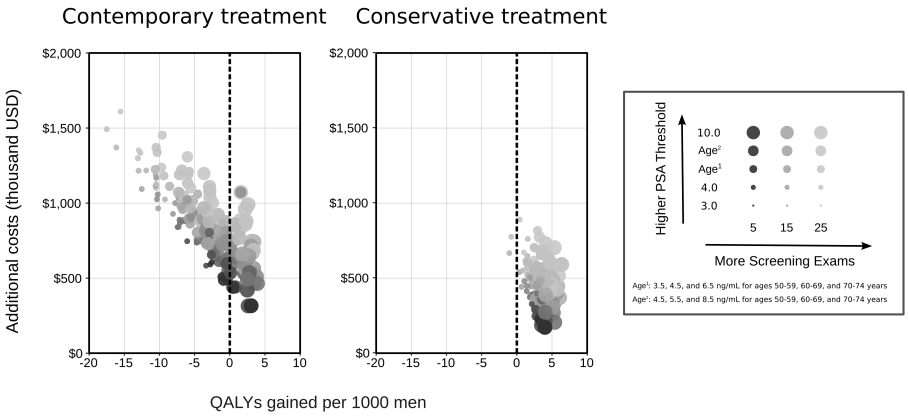


An online calculator that provides personalized estimates of risks of overdiagnosis is available here.

Cost-effectiveness of screening and treatment strategies

Additional costs and quality-adjusted life years (QALYs) gained associated with 150 PSA screening strategies of varying screening parameters (ages, intervals, and PSA thresholds for biopsy) were projected under historical versus increased adoption of active surveillance for low-risk prostate cancers.[1] Figure 11 visualizes cost-effectiveness planes for these two settings.

Figure 11. Additional costs and additional QALYs projected for 150 screening strategies relative to no screening.



Comparative effectiveness of stratified screening using PSA levels

Multiple studies have shown that a man's PSA levels are prognostic for future prostate cancer morbidity and mortality, prompting proposals to extend the interval to the next screening test or stop screening entirely in men with sufficiently low PSA levels at certain ages. Figure 12 shows projected outcomes for selected screening strategies that examine these PSA-based risk stratifications.[9]

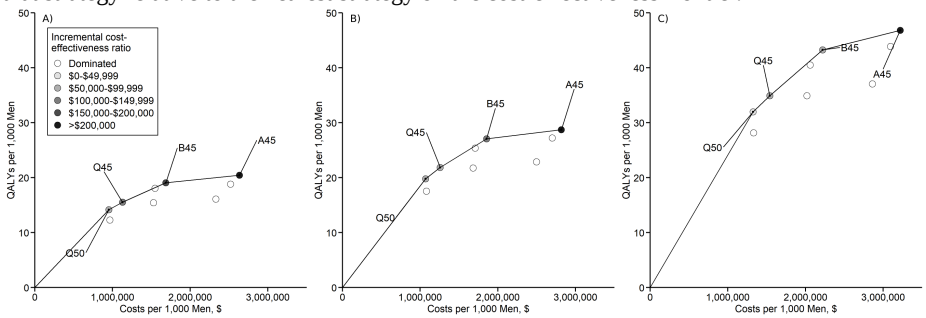
Figure 12. Projected lifetime outcomes under no screening and selected screening strategies that extend the inter-screening interval in men with low PSA levels, stop early early in men with low PSA levels at age 60 years, or both.

Model outcome	No screening	Screening ages 45-69 every 2 years				Screening ages 45-59 every 2 years
		(a) No stratification	(b) 8 years if PSA < 1.0 ng/mL, change to 2 years if PSA > 1.0 ng/mL	(c) Stop if PSA < 1.0 ng/mL at age ≥ 60	(b) and (c)	
Tests	0	**112,849**	59,846 (-47%)	98,379 (-13%)	55,233 (-51%)	74,986 (-34%)
Cancers detected	1,130	**1,479**	1,476 (0%)	1,460 (-1%)	1,459 (-1%)	1,203 (-19%)
Screen detected	0	**1,115**	1,108 (-1%)	1,065 (-5%)	1,060 (-5%)	424 (-62%)
Overdiagnosed	0	**348**	345 (-1%)	329 (-5%)	328 (-6%)	72 (-79%)
Lives saved	0	**160**	155 (-3%)	152 (-5%)	148 (-7%)	84 (-48%)
Life-years gained	0	**1,312**	1,251 (-5%)	1,270 (-3%)	1,217 (-7%)	882 (-33%)
Overdiagnosis/lives saved		**2.2**	2.2	2.2	2.2	0.9

Cost-effectiveness of stratified screening using polygenic risk scores

Another approach to improving harm-benefit tradeoffs of screening involves risk-stratification using polygenic risk scores. The PSAPC model was used to estimate the risk of developing prostate cancer within pre-specified risk strata to match incidence in the placebo arm of the Prostate Cancer Prevention Trial. Then it was used to project lifetime health outcomes and cost-effectiveness for a range of risk-stratified strategies.[10] As illustrated in Figure 13, cost-effectiveness of risk-stratified screening depends on the comparator strategy, the sizes of the strata, and how screening is done within each stratum. Across the strategies considered, only certain settings seem promising.

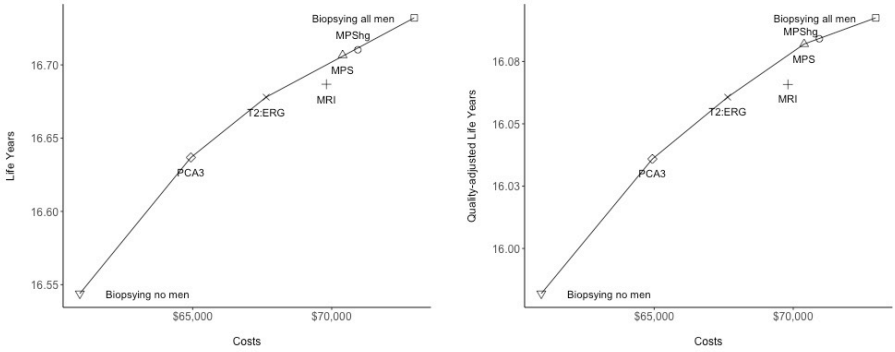
Figure 13. Costs and quality-adjusted life years (QALYs) gained for screening strategies for A) low-, B) intermediate-, and C) high-risk men relative to no screening. Strategy labels indicate frequency (Q=quadrennial, B=biennial, A=annual) and starting age. Only nondominated strategies are labeled; the fill of each point indicates the incremental cost-effectiveness ratio for that strategy relative to the nearest strategy on the cost-effectiveness frontier.



Cost-effectiveness of reflex testing in men with intermediate PSA levels

Other efforts to reduce prostate cancer overdiagnosis have considered triage or "reflex" tests before prostate biopsy in men with intermediate PSA levels. The PSAPC was used to evaluate comparative effectiveness and cost-effectiveness of selected reflex tests.[11] Figure 14 shows cost-effectiveness frontiers for selected reflex tests in men with PSA between 4 and 10 ng/mL at age 55 years.

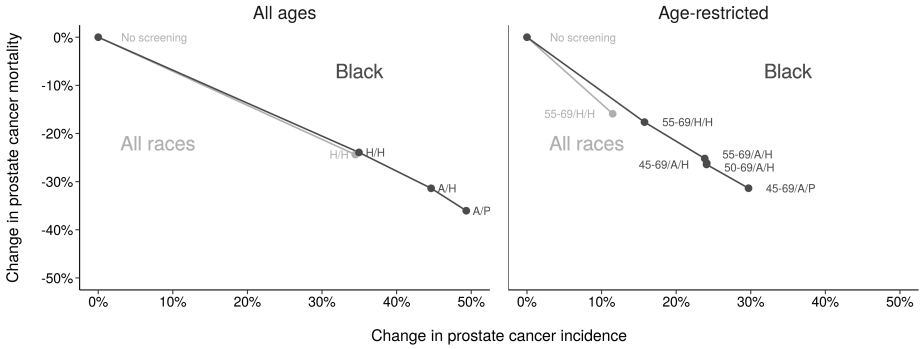
Figure 14. Life years and quality-adjusted life years projected following reflex testing using urinary biomarkers or multiparametric MRI before prostate biopsy in men with PSA levels between 4 and 10 ng/mL.



Projected impact of intensified screening in Black men

Comparative modeling work previously estimated that men who self-identified as Black race in SEER registries have increased risk of preclinical onset of prostate cancer and, after onset, increased risk of metastasis before diagnosis.[12] A follow-up study projected the expected impact of intensified screening in Black men (i.e., starting screening at a younger age, annual testing, and idealized adherence to biopsy when PSA > 4 ng/mL).[13] As shown in Figure 15, intensified screening in Black men is expected to reduce mortality more than that estimated under historical screening, and limiting screening to men younger than 70 years is expected to help control overdiagnosis.

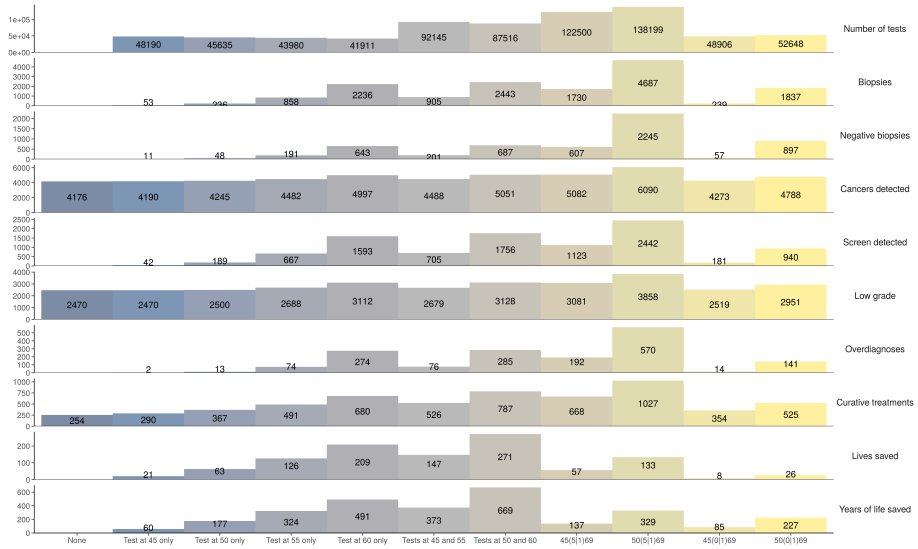
Figure 15. Changes in prostate cancer incidence (overdiagnosis) and mortality under no screening and historical early detection strategies for all races (light gray) and under no screening, historical, and intensified early detection strategies for Black men (dark gray) projected by the PSAPC model. Lines connect results for each race group. A/H = annual frequency/historical biopsy; A/P = annual frequency/perfect biopsy; H/H = historical frequency/historical biopsy.



Prostate cancer screening in low-resource high-risk men in The Bahamas

Following validation of the PSAPC model adapted to The Bahamas population, resource utilization and mortality impact of one- or two-time screening strategies was projected.[14] Figure 16 shows these results, which provided data to help inform local cancer control policy and priorities.

Figure 16. Projected absolute numbers of medical resources and corresponding mortality benefits for specified screening strategies.



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Validations Overview

Summary

This document describes calibration of the Fred Hutchinson Cancer Center PSAPC model and selected validations.

Calibration

The PSAPC natural history and clinical diagnosis model parameters were calibrated to the US population as follows.

- A single set of candidate values for natural and clinical history parameters was randomly generated from pre-specified ranges.
- A population of simulated individuals was generated to match male population counts in the core 9 catchment areas of the Surveillance, Epidemiology, and End Results (SEER) program in the year 1975. Each simulated individual had a date of birth and a date of all-cause death. Simulated individuals were then randomly assigned prostate-specific antigen (PSA) growth parameters and ages at natural history events and clinical diagnosis. (The assignment of natural and clinical history events depended on the candidate model parameters.) The resulting simulated life history represents the course of events that were simulated to occur in the absence of screening.
- Historical screening and biopsy patterns were superimposed on the simulated life histories described above. Specifically, each simulated individual was randomly assigned a schedule of ages at which PSA screening events could occur. (Screening could not occur after clinical diagnosis.) At any scheduled PSA screening event, if the individual PSA level exceeded the historical threshold of 4 ng/mL, a random indicator was generated that determined receipt of biopsy, in which case another random indicator was generated that determined whether preclinical cancer (if present) would be detected. Proceeding in this fashion, outcomes of PSA screening could lead to early detection--or overdiagnosis--of prostate cancer. The resulting modified simulated life history represents the sequence of events that were simulated in the presence of screening.
- Prostate cancer diagnoses simulated in the presence of historical screening and biopsy patterns were tabulated by age using 5-year age groups (50-54, ..., 80-84), calendar year (1975-2000), stage (local-regional vs distant), and grade (I-II vs III-IV) at diagnosis. These counts were compared to corresponding observed counts in SEER data after missing stage and/or grade were imputed. Specifically, the comparison took modeled counts as the mean in a Poisson likelihood.
- The set of candidate values for the natural and clinical history event parameters were then modified, the simulated life histories were regenerated, and the likelihood was recalculated. The calibration process iterated in this fashion based on a Nelder-Mead algorithm to maximize the Poisson likelihood.[1]

  Calibrations of the PSAPC model to settings other than the US male population began with this version of the model and re-estimated only selected parameters, e.g., allowing the dependence of the risk of clinical diagnosis on stage to depend on grade via an interaction term[2] or re-estimating the risk of preclinical onset within strata defined by genetic risk scores.[3] A version of the PSAPC model in which the probability of high-grade disease was modeled using a logistic instead of a quadratic growth curve was calibrated for Black men and, separately, for all races combined.[4] In these calibrations, all natural and clinical history parameters were re-estimated.

Validations

Prostate Cancer Prevention Trial

A key validation of the PSAPC model evaluated PSA test performance in a simulation of the Prostate Cancer Prevention Trial (PCPT).[5] Because longitudinal PSA trajectories in the model were estimated using longitudinal PSA measurements and outcomes observed in the placebo arm of the PCPT, this trial represents an important setting to evaluate modeled PSA performance and disease natural history. For simplicity, we assumed all participants were enrolled on January 1, 1993. The validation exercise involved the following steps.

- Life histories of PCPT participants were simulated to match the observed age distribution at enrollment.
- PSA screening before enrollment was simulated according to reconstructed dissemination patterns in the general US population,[6] biopsy frequency as observed in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial,[7] and an assumed sensitivity of quadrant biopsy (60%). Individuals who were simulated to have a prostate cancer diagnosis before enrollment were replaced.
- Immediately before enrollment, simulated participants received baseline digital rectal exam (DRE) and PSA tests. Participants with PSA >3 ng/mL or abnormal DRE culminating in diagnosis at baseline tests were replaced for consistency with PCPT eligibility criteria. We used estimates of DRE sensitivity and specificity for PSA strata 0-1, 1-2, and 2-3 ng/mL obtained by investigators of the European Randomized Study of Screening for Prostate Cancer.[8]
  * During the trial, simulated participants received annual DRE and PSA tests for up to 7 years. We assumed random attendance at visits consistent with the empirically estimated adherence rate (74%). If PSA >4 ng/mL or DRE was abnormal, participants received biopsy with a probability that depended on their age and PSA level as observed in the PLCO, with an assumed sensitivity of sextant biopsy (80%).

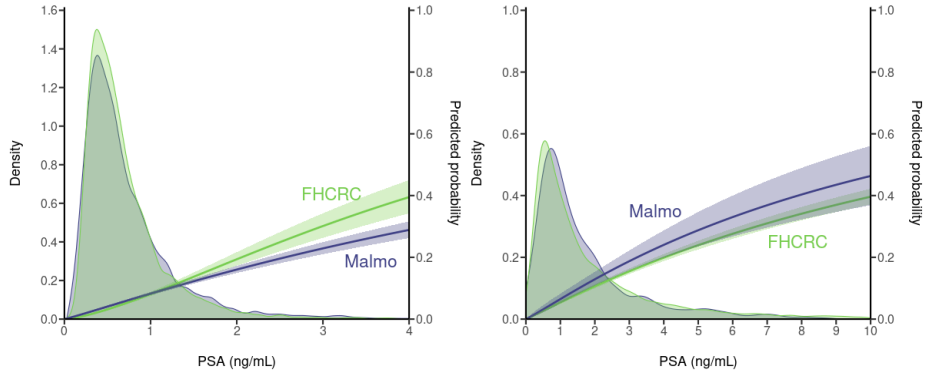
The following table shows estimated sensitivity and specificity of screening as implemented in the PCPT to detect any prostate cancer and to detect Gleason score ≥7 prostate cancer based on 100 simulated trials and corresponding empirical results. Both model-estimated and empirical results were restricted to participants age <70 years. The model underpredicts sensitivity of annual PSA and DRE testing to detect Gleason score ≥7 prostate cancers.

Target condition	Sensitivity, %		Specificity, %	
	PSAPC	Empirical	PSAPC	Empirical
Any prostate cancer	29.1	27.7	90.0	91.7
Gleason score ≥7	34.0	42.7	90.0	89.0

Malmo Preventive Project

An external validation of the PSAPC model examined the concordance between model projections and (1) empirical summaries of PSA levels and (2) predicted 25-year risk of prostate cancer diagnosis based on the Malmo Preventive Project stored serum study.[9] Figure 1 shows densities of individual PSA levels observed in the study at ages 44-50 and at age 60 years at venipuncture and corresponding measurements simulated by the PSAPC model. The figure also shows predicted risk of prostate cancer diagnosis from logistic regressions fit to 25-year case status conditional on the (log-transformed) PSA levels.

Figure 1. Observed PSA distributions for men ages 44–50 (left) and 60 (right) years at venipuncture and predicted 25-year risk of prostate cancer diagnosis based on empirical analysis of Malmo Preventive Project and corresponding projections from the PSAPC model in the absence of screening.



The following table summarizes median PSA levels and corresponding 25-year predicted probabilities of prostate cancer diagnosis using empirical records from the Malmo Preventive Project and simulated records from the PSAPC model.

Age, y	Median PSA (IQR), ng/mL		Predicted risk (95% CI), %	
	PSAPC	Malmo	PSAPC	Malmo
44-50	0.57 (0.39-0.86)	0.58 (0.37-0.91)	4 (2-7)	5 (4-5)
60	1.25 (0.63-2.65)	1.08 (0.66-1.98)	6 (3-10)	9 (8-10)

Overall, the model broadly replicates age-specific PSA distributions and empirically estimated risks of diagnosis in the absence of screening in the Malmo Preventive Project.

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