Combined Model Profile
Version: 1.0.00
Released: 2025-09-30

Prostate Cancer Combined Model Profile

Individual Model Profiles

MIcrosimulation SCreening ANalysis Prostate Cancer Model (MISCAN-Prostate): Model Profile
Erasmus University Medical Center
Version: 1.0.00
Released: 2025-09-30

MSM-CanProg: Model Profile
University of Cambridge & University College London
Version: 1.0.00
Released: 2025-09-30

A joint model of PSA growth and prostate cancer natural history and outcomes (PSAPC): Model Profile
Fred Hutchinson Cancer Center
Version: 1.0.00
Released: 2025-09-30

Suggested citation

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Combined Model Profile Version Table

Version	Date	Notes
1.0.00	2025-09-30	Initial release

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Erasmus MC
Version: 1.0.00
Released: 2025-09-30

MIcrosimulation SCreening ANalysis Prostate Cancer Model (MISCAN-Prostate): Model Profile

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Version Table

Version	Date	Notes
1.0.00	2025-09-30	Major update
HI.001.12152009.69754	2009-02-15	Historical release

Other Publications

De Koning HJ, Gulati R, Moss SM, Hugosson J, Andriole GL, Auvinen A, Crawford, Roobol M, Berg C, Nelen V, Kwiatkowski M, Zappa M, Lujan M, Villers A, de Carvalho TM, Feuer EJ, Tsodikov A, Mariotto AB, Heijnsdijk EAM, Etzioni R. The efficacy of PSA screening: impact of key components in the ERSPC and PLCO trials. Cancer. 2018 Mar 15;124(6):1197-1206

Erasmus MC
Readers Guide

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.

KeyReferences
A list of references used in the development of the model.

Erasmus MC
Model Purpose

Model Purpose

Summary

The MISCAN (MIcroSimulation of CANcer) prostate micro-simulation model is a model based on progression in disease stages and includes prostate cancer natural history, screening, diagnosis, treatment and disease-specific and other-cause death. The model has been used to study epidemiological trends, randomized screening and treatment trials, racial disparities, and alternative implementations of screening and treatment interventions designed to improve long-term harm-benefit tradeoffs in various populations.

Purpose

The MISCAN model was originally developed to quantify the role of PSA screening in prostate cancer incidence and mortality. For this purpose, the model first had been calibrated to the Rotterdam section of the ERSPC trial [1] and later to the entire ERSPC trial [2]. Using the MISCAN model, based on the results of ERSPC Rotterdam, we tried to understand the trends in the US and how they differ from European or Dutch conditions [3]. Also, the models are used to estimate unobservable processes and variables (natural history of the disease, the amount of overdiagnosis and lead time) in the ERSPC trial as well as the US population [1,4,5,6,7,8].

In the first years after the publications of the results of the trials, we have studied the contributions of screening and treatment to a decline in mortality [9-11]. Also, the models have been used to explain the results of the PLCO and ERSPC trials [1,12,13,14].

The impact of active surveillance and different biopsy schedules during active surveillance on overtreatment and mortality have been studied using an extension of the model allowing for following disease progression after diagnosis [15-19].

Finally, the models are used to determine optimal screening ages and test intervals and to calculate QALYs and cost-effectiveness of various screening policies, compared with a situation without screening to optimise strategies to different settings [20-26]. The effects of screening and/or optimal strategies have been determined for populations varying by race [27,28], comorbidity [29], biomarkers [30] and MRI [31,32].

We have demonstrated that MISCAN can be helpful in analyzing and explaining results of cancer screening trials, predicting the (cost-) effectiveness of different screening policies and predicting the potential of present and new interventions on future national trends.

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Model Overview

Summary

This document provides an overview of the MISCAN-prostate model, by describing the model in general terms.

Background

The MISCAN prostate model is one of the MISCAN models developed for evaluating cancer screening. Other models are the colorectal, breast, lung, cervix and esophageal models, also used in CISNET. The models share the MISCAN core code, which is a common set of processes to generate a population, natural history of disease and screening. The MISCAN prostate cancer model has been used to model trends of prostate cancer incidence and mortality in the ERSPC-trial Rotterdam, and in the ERSPC-trial Sweden, the Dutch population and in the US population. With these models it is possible to compare trends of prostate cancer with and without treatment and screening. The base model of MISCAN prostate has been extended to allow modelling active surveillance and to allow for screening protocols based on previous PSA results.

Model Description

MISCAN model is a micro-simulation model. Using the model inputs, independent life histories are generated including a possible cancer history, the effects of treatment and the effects of early detection by screening. The MISCAN-prostate model contains four primary components:

1. Demography component
2. Natural History component
3. Treatment component
4. Screening component.

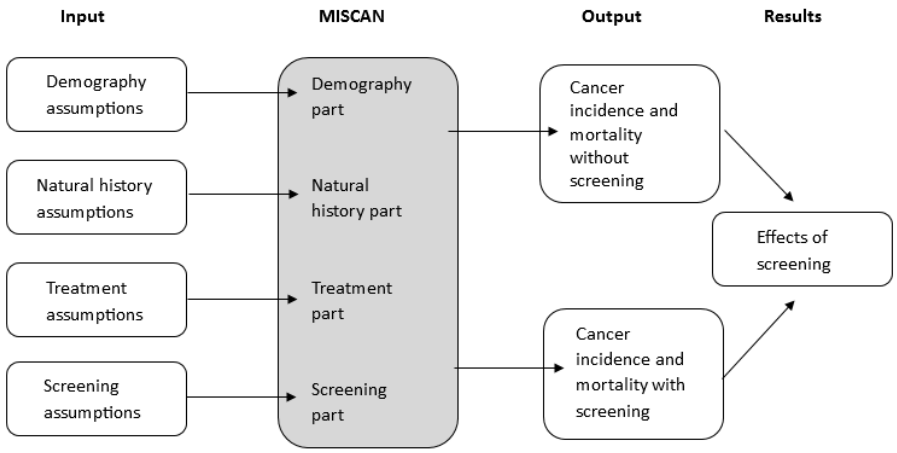

Figure 1. The components in the MISCAN prostate model.

First the demography component simulates a population of individual life histories, according to the demography parameters. Each individual in the population consists of a date of birth and age of death. The parameters of this part (birth tables and life tables) can be adjusted to the population that is being modeled, for example the Netherlands [1], the US [2], The Bahamas [3], or a trial population [4].

Subsequently the natural history component simulates prostate cancer histories for each individual life history separately. Some individuals will have no prostate cancer in their lifetime and others will have prostate cancer

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in their lifetime. Once the individual has prostate cancer the cancer can progress to different preclinical states. In the preclinical phase the tumor is asymptomatic, but can be detected by screening. In this definition, the preclinical phase does not only depend on biological processes, but also on the state of medical technology. Eighteen preclinical detectable states are defined by combinations of clinical T-stage (T1, T2 and T3), Gleason grade (6 or smaller, 7, and 8 or larger) and metastatic stage (local-regional and distant). From each preclinical detectable state the cancer can progress to the clinical disease state, which implies that cancer is diagnosed because of symptoms. The parameters (hazard of onset by age, transition probabilities and dwell times) are calibrated to various studies, for example the ERSPC [4].

In the third part the treatment component simulates the life history after clinical diagnosis. Detection with cancer is followed by treatment and possibly prostate cancer death. Different treatments have their treatment-specific survival of prostate cancer death. The distribution of treatment can be adjusted to treatment by age and grade in the modelled population, for example the ERSPC trial [4].

The screening component super-imposes screening on the life histories in the absence of screening. Screening tests applied to a person in a preclinical disease state may result in detection and alter the life history of this individual. Screen detection may alter the cause of events since part of the screen-detected men is cured from cancer and for the other part the life history course will be the same as without screening. The frequency of screening, screening ages, compliance with biopsy and combined sensitivity for PSA and biopsy can be adjusted and/or calibrated for different populations, for example the ERSPC trial [4].

To explicitly model active surveillance (AS), we have developed an extension of the MISCAN model. In the original model, disease progression stops at the moment of clinical or screen-detection and based on age, stage and treatment a men gets a survival time. In the AS model, the progression of disease still continues after diagnosis. Therefore, it is possible to determine the moment of progression of disease from for example Gleason 6 to Gleason7. By modelling biopsies during the AS period, the detection of progression can be modeled and therefore the effect of AS or immediate treatment on overtreatment and prostate cancer mortality [5-9].

Another version of the MISCAN model includes a sub-model for PSA growth. In this model the natural history is still modelled by progression between disease stages, and a PSA growth function is added. A man's PSA level is dependent on age and age of onset. Men having PSA level above a given threshold receive a biopsy and depending on the sensitivity of the biopsy the cancer can be detected. This model has been used in several studies and is currently being updated [3,10,11].

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Assumption Overview

Summary

This documents describes the assumptions in the demography, natural history, screening and treatment part of the MISCAN-prostate model.

Background

The MISCAN prostate cancer model can be used to simulate prostate cancer screening and treatment policies in a dynamic population, based on assumptions on demography, natural history of prostate cancer, treatment and screening. Most of the assumptions relate to the unobservable part in the screening and treatment of prostate cancer: the natural history of the disease and the effect of screening on survival.

Assumption Listing

Demography

- The (country specific) life table is the same for all men in the same birth cohort
- Death from prostate cancer and death from other causes are independent
- The life time prostate cancer risk is the same for all men in a the same birth cohort

Natural history

- Tumor onset:
    - Tumors are assumed to initiate with the same age specific initiation rate for all men.
- Progression of disease:
    - There are eighteen preclinical detectable states which are derived from combinations of clinical T-stage (T1, T2 and T3), Gleason grade (Gleason 6 or less, 7 and 8 or more) and metastatic state (M0 and M1). At onset, the tumour starts in the preclinical stage Gleason 6, T1 and M0.
    - Progression is defined by a matrix of transition probabilities between states, and dwelling time distributions for the time spent in each state. The dwelling times are determined by Weibull distributions.
    - A correlation between duration in subsequent states is assumed, to model fast and slow growing tumors.
    - In each preclinical state there is a probability to transit to the next state (in Gleason or T stage), or to clinical detection.
    - During the period in a state, there is a hazard to progression from a localized/regional state to a metastatic state. This hazard is higher for more progressed states.
    - In any state in the preclinical phase the cancer can be detected by screening.
- Clinical detection:
    - From each preclinical detectable state the cancer can progress to the clinical disease state, which implies that cancer is diagnosed because of symptoms. The progression to the clinical state is defined by the matrix of transition probabilities between states, and dwelling time distributions determined by Weibull distributions, with higher probabilities for more progressed cancers.
    - To account for a higher incidence and a more favorable stage distribution in the control arm of the trials compared to incidence in the US and Dutch population before the trials, it is assumed that in the trial population prostate cancer was clinically diagnosed earlier than in the baseline situation in 1991. Specifically, it is assumed that the hazard of being clinically diagnosed is larger. This difference can for instance be attributed to changes in clinical practice leading to

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earlier diagnosis, for example the use of PSA testing for symptomatic disease in a clinical setting.

Treatment

After prostate cancer diagnosis the treatments radical prostatectomy, radiation therapy and active surveillance can be assigned.

Treatment dissemination:

ERSPC model: treatment is modeled as a multinomial logit model with covariates age, T-stage and Gleason score at diagnosis. The categories of the multinomial model are radical prostatectomy, radiation therapy and active surveillance. The parameter estimates are based on data of the Rotterdam section of the ERSPC trial from the year 2000.
US model: treatment is modeled as a multinomial logit model with covariates age, year and grade at diagnosis. The categories of the multinomial model are radical prostatectomy, radiation therapy and active surveillance. The parameter estimates are based on SEER data.

Survival after treatment:

Baseline survival:
The baseline survival has been estimated from SEER (Surveillance, Epidemiology and End Results) data in the pre-PSA era, specifically of cases diagnosed between 1983 and 1986. The survival curves are modeled using Poisson regression with grade, stage, age and treatment type as explanatory variables. To not over-project observed prostate cancer mortality we included a baseline survival hazard ratio to improve the baseline survival, reasoning there have been improvements in disease management since the period 1983-1986 beyond screening or primary treatment.

Treatment effect:
This baseline survival is improved for localized cases who received radical prostatectomy, or radiation therapy using a hazard ratio, obtained from treatment trials. For distant prostate cancer it is assumed that treatment has no effect on the survival, implying that irrespective of the treatment type all men diagnosed with prostate cancer in the distant stage have a survival generated from the corresponding baseline survival curve.

Effect of screening on mortality:
The mortality benefit of PSA screening is modeled as a cure probability that depends on the lead time (years by which detection of the cancer is advanced by screening compared to the clinical situation) and is implemented only for screen-detected, non-metastatic, and non-overdiagnosed cases as cure probability = 1 – exp (-cure parameter x lead time), Figure 1 [1]. Thus the probability of cure increases with lead time, with diminishing incremental benefit for longer lead times. Cured men are assigned to die at their independently generated date of other-cause death. Men who are not cured die at the same time they would have died if they had not been screened.

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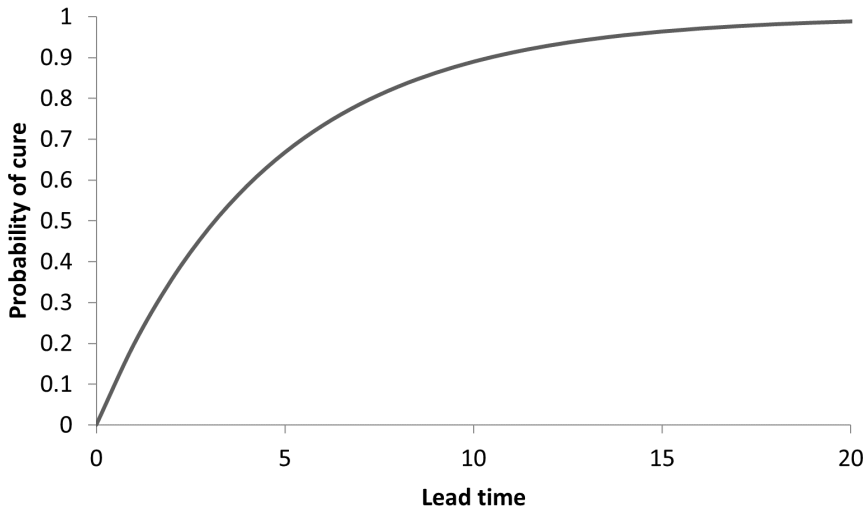

Figure 1. The lead time-dependent cure rate calibrated to the ERSPC trial.

Screening

- Attendance to screening:
    - In the model, men can only be screened when they are still alive at the moment of the screen and when they have not already been diagnosed with prostate cancer.
    - Per cohort, a probability to attend a test at a certain age is assigned.
    - Also per cohort, a probability to attend a test if the previous test has been attended, and if not attended is assigned.
- Sensitivity of the test:
  In the base model, PSA screening and subsequent biopsy are modeled as one single test. The test has a T-stage-dependent sensitivity, calibrated to for example the ERSPC trial. We do not model digital rectal exam (DRE) explicitly.

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Parameter Overview

Summary

Provides a complete overview of the parameters used in the MISCAN-prostate model.

Background

The MISCAN-Prostate model consists of four basic components: The demography component, the natural history component, the treatment component and the screening component. Each component has its own set of parameters.

Parameter Listing Overview

Demography Parameters

- Number of birth cohorts
- Proportion of the population in each birth cohort
- For each birth cohort probability to be born by year
- For each birth cohort probability to die by age

Natural history Parameters

- Hazards for the age specific distribution of onset of the first screen detectable state
- For each birth cohort the life time prostate cancer risk
- The distribution of the duration in each preclinical state
- The transition probability in each preclinical state
- Hazard of metastatic state in each preclinical state
- Correlation between duration in subsequent states
- Baseline prostate cancer survival for survival after clinical diagnosis by age, year, grade and stage of disease at diagnosis and race
- Improvement in baseline prostate cancer survival over time

Screening Test Parameters

- Dissemination of PSA screening by age and year
- Test-sensitivities, including biopsy compliance and biopsy sensitivity, depending on stage, age and period
- Cure rate defining the benefit because of early detection, depending on lead time

Treatment parameters

- Dissemination of treatment by age at diagnosis, year of diagnosis, grade and stage of disease at diagnosis
- Hazard ratios associated with radical prostatectomy, radiation therapy (constant for all individuals)

Parameter estimation

Model parameters for the natural history component and the test-sensitivity are estimated as follows: A model is constructed for a specific situation, such as prostate cancer incidence in the US or both arms of the ERSPC trial Rotterdam. Parameters are then estimated by numerical minimization of the deviance between observed numbers of cases and the corresponding numbers predicted by the model. Deviances are calculated assuming Poisson likelihood for incidence data or a multinomial likelihood for stage distribution data. For the minimization an adapted version of the simplex optimization method of Nelder and Mead is used. Optimization is initiated with small sample sizes and repeated with larger sample sizes (up to 2 million men) when optimization progress is no longer statistically significant.

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Component Overview

Overview

As described in the Model overview document, the MISCAN-prostate model contains four primary components: Demography, Natural History, Treatment and Screening.

Demography Component

The demography component simulates a population of individual life histories, according to the demography parameters. Each individual in the population is assigned a date of birth and a date of death. It is possible to define a dynamic population of all ages, which can be adjusted for different countries. Also it is possible to define a cohort of people with the same age or age range.

Natural History Component

The cancer related event history is defined by a sequence of disease states and the ages at which these states are entered. The life histories are generated by a semi-Markov process, defined by a matrix of transition probabilities between states, and dwelling time distributions for the time spent in each state. The disease history is divided in a preclinical phase and a clinical phase. The preclinical phase corresponds to the asymptomatic states. Its parameters have to be estimated from indirect evidence. In the MISCAN prostate cancers model there are eighteen preclinical detectable states which are derived from combinations of clinical T-stage (T1, T2 and T3), Gleason grade (Gleason 6 or less, 7 and 8 or more) and metastatic stage (M0 and M1). The progression through these states is illustrated in Figure 1. From each preclinical detectable state the cancer can progress to the clinical disease state, which implies that cancer is diagnosed because of symptoms.

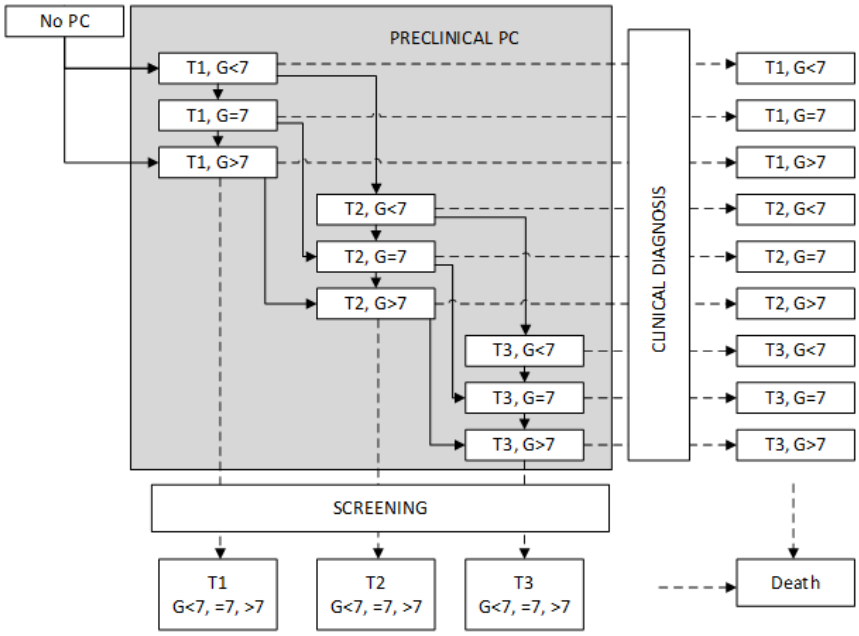

Figure 1. Transitions in the preclinical phase in the MISCAN model. Prostate cancer develops from no prostate cancer via 1 or more screen-detectable preclinical stages to a clinically diagnosed cancer. There is also a distinction between local and metastatic stage, but for simplicity this is not illustrated. Screening is superimposed on the life histories in the absence of screening. Screening may detect cancers earlier in one of the preclinical screen-detectable states.

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Screening Component

Screening is super-imposed on the life histories in the absence of screening. Screening tests applied to a person in a preclinical disease state may result in detection and alter his life history. A screening test is defined by its stage-specific sensitivity. A screening policy, is defined by the tests used, attendance rate and screening ages. Screening ages may be selected at regular intervals, or stochastically, allowing the modeling of both regular screening as in trials or screening programs and opportunistic screening. Screen detection may alter the course of events. We assume that the consequence of early detection by screening is that a part of the screen-detected men is cured from cancer and that for the other part detection does not alter the life history.

Treatment Component

The life history after clinical diagnosis is defined by stage-specific survival functions.
Detection with cancer is followed by treatment and a survival of prostate cancer death. Different treatments can be assigned and are followed by a treatment-specific survival of prostate cancer death.

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Output Overview

Summary

This document describes the main outputs of the Miscan-prostate model.

Overview

The main outputs of the 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 preclinical onset of prostate cancer
- Age at progression to a next preclinical stage
- Age at prostate cancer diagnosis without screening
- Grade at prostate cancer diagnosis (Gleason score ≤6, 7, ≥8)
- Stage at prostate cancer diagnosis (T1, T2, T3)
- Metastatic stage at prostate cancer diagnosis (M0, M1)
- Primary treatment (radical prostatectomy, radiotherapy, conservative management/active surveillance)
- Age at prostate cancer-specific death
- 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.
- Sojourn time: the time from preclinical onset to diagnosis without screening.
- 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 PSA tests
- Total biopsies
- Total prostate cancer diagnoses by stage, grade and metastatic state
- Screen diagnoses
- Overdiagnoses
- Total treatments, split by type
- Overtreatments
- Prostate cancer deaths
- Other-cause deaths
- Time spent in asymptomatic state
- Time spent in treatment state
- Time spent in end-of-life state

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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).

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Results Overview

Summary

This document describes selected results of the MISCAN-prostate model.

Prostate cancer incidence in the US

Figure 1 shows the model generally reproduces the incidence in the US in the period 1975-2009 [1].

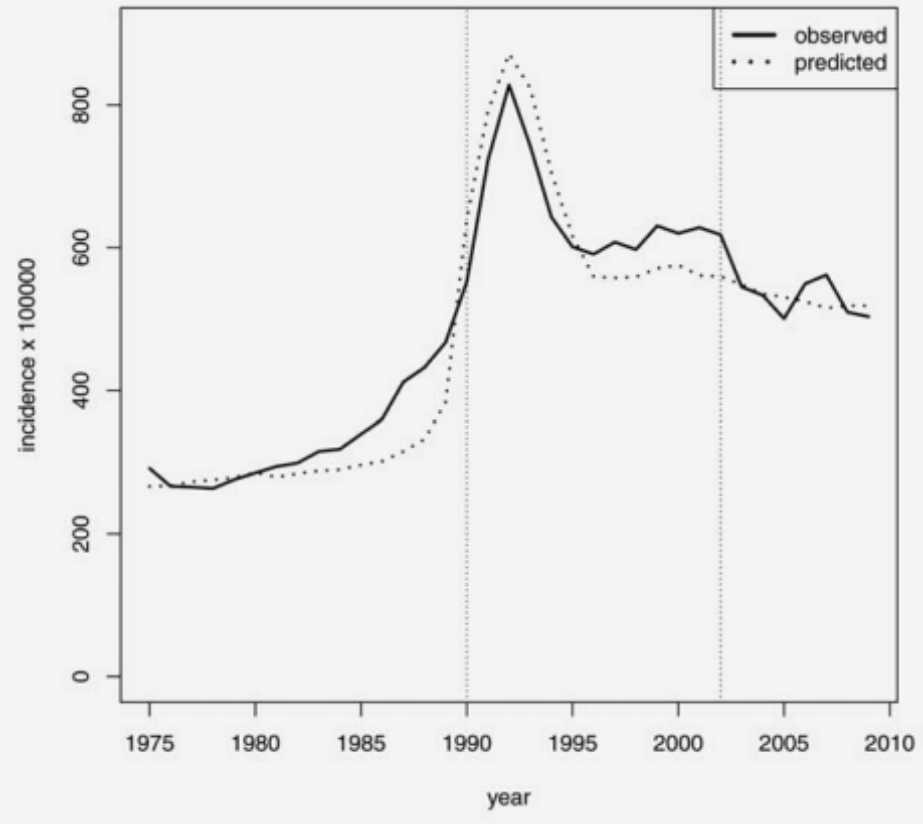

Figure 1. Incidence of prostate cancer in the US population for age-groups 50-85. The data used for calibration is the period between the vertical dots.

Prostate cancer incidence and mortality in the PLCO trial

The calibrated MISCAN 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 [2]. Figure 2 shows observed and projected prostate cancer diagnoses by arm and year after randomization and Figure 3 shows the grade distribution. Figure 4 and 5 show the grade distributions by arm.

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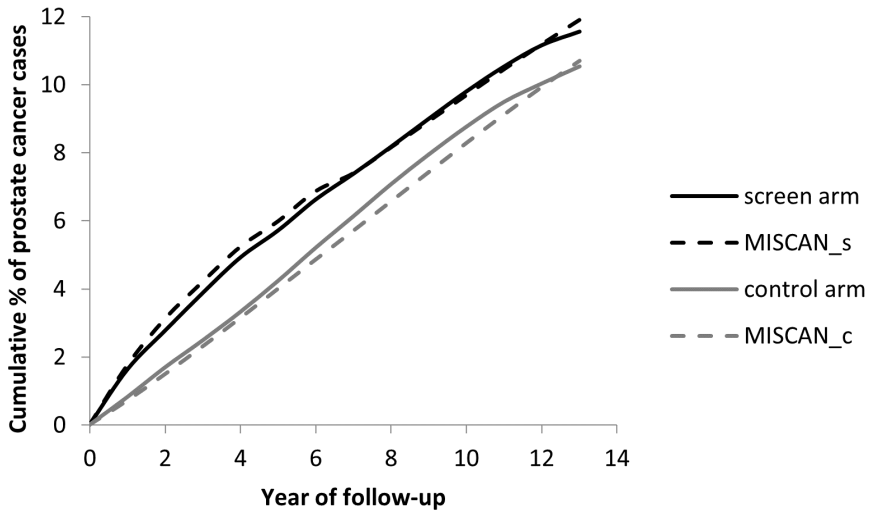

Figure 2. Incidence in the PLCO trial. The solid lines are the observed values in the screen (black) and control (grey) arm. The dashed lines are the MISCAN predictions.

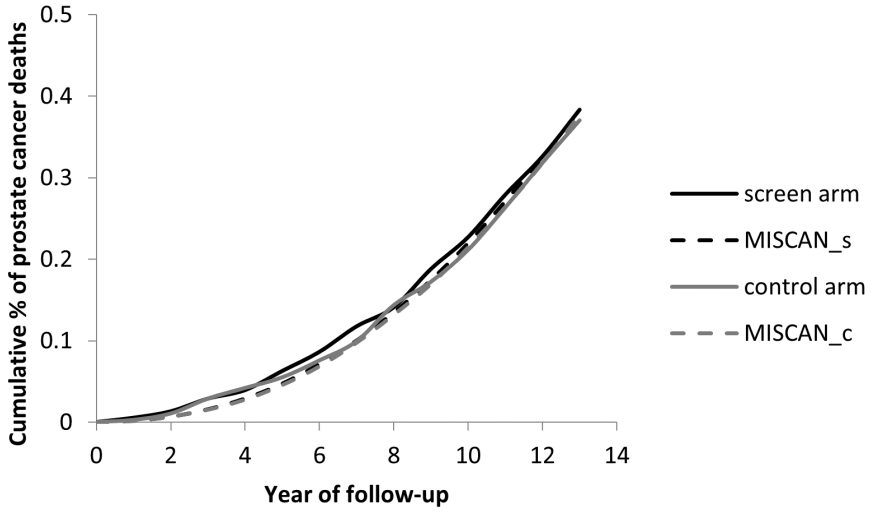

Figure 3. Prostate cancer mortality in the PLCO trial. The solid lines are the observed values in the screen (black) and control (grey) arm. The dashed lines are the MISCAN predictions.

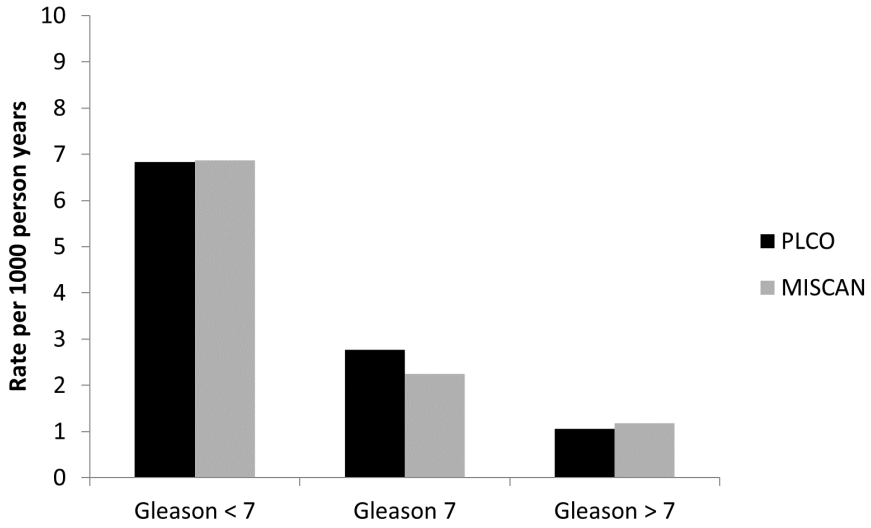

Figure 4. Grade distribution in the screen arm of the PLCO trial.

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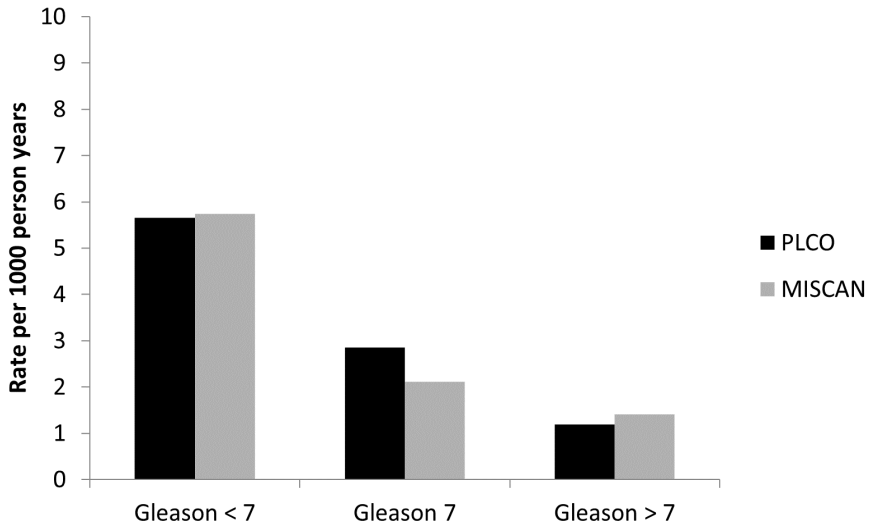

Figure 5. Grade distribution in the control arm of the PLCO trial.

Prostate cancer incidence and mortality in the ERSPC trial

The calibrated MISCAN 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 [2]. Figure 6 shows observed and projected prostate cancer diagnoses by arm and year after randomization and Figure 7 shows the grade distribution. Figure 8 and 9 show the grade distributions by arm.

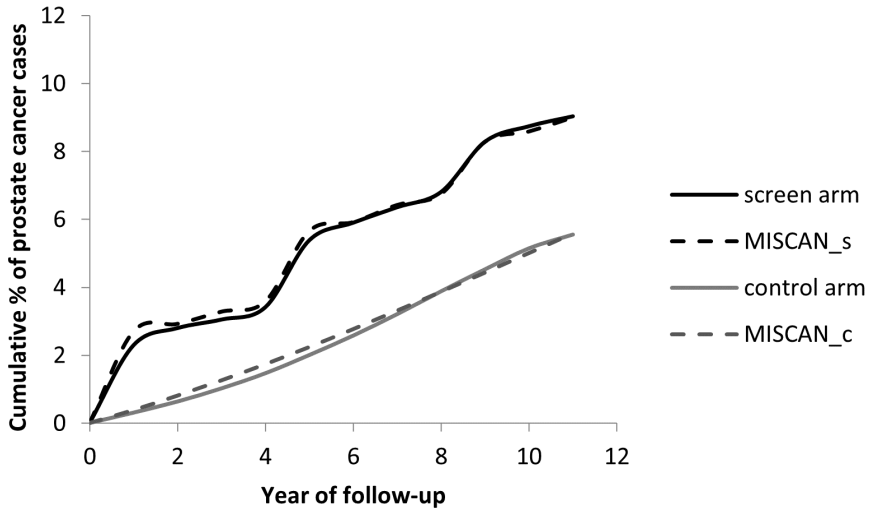

Figure 6. Incidence in the ERSPC trial. The solid lines are the observed values in the screen (black) and control (grey) arm. The dashed lines are the MISCAN predictions.

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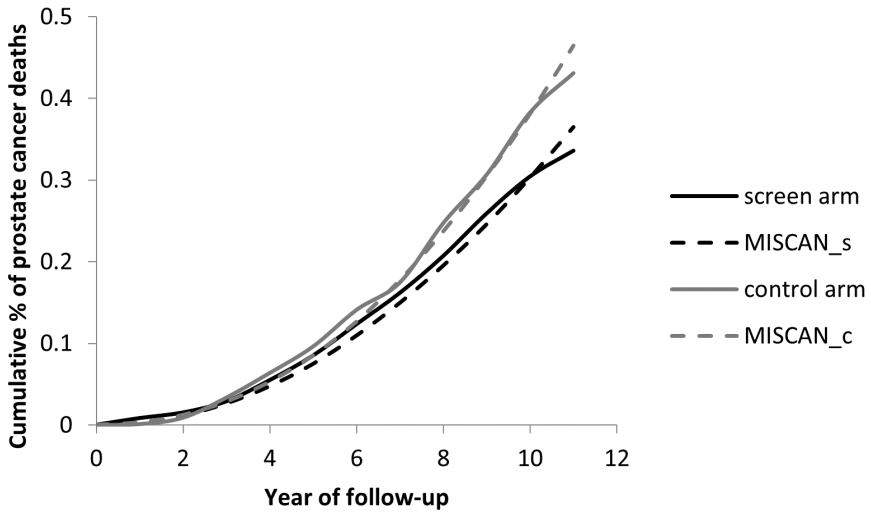

Figure 7. Prostate cancer mortality in the ERSPC trial. The solid lines are the observed values in the screen (black) and control (grey) arm. The dashed lines are the MISCAN predictions.

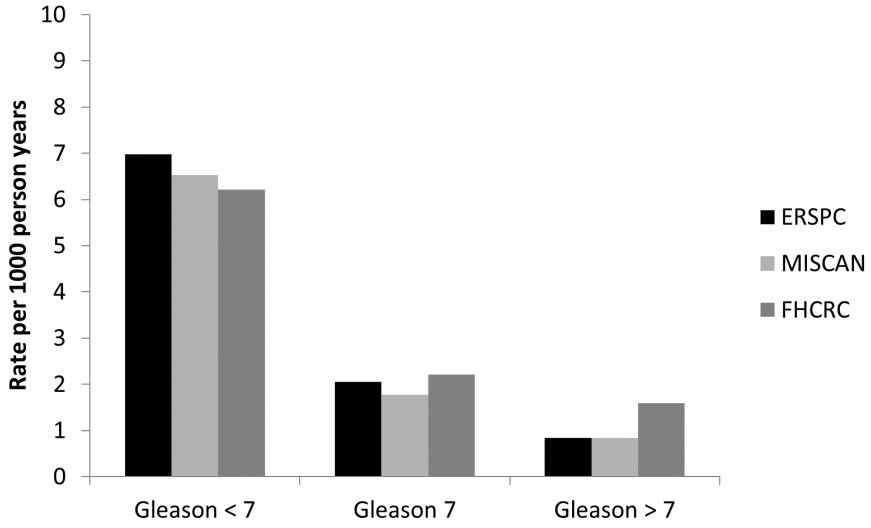

Figure 8. Grade distribution in the screen arm of the ERSPC trial.

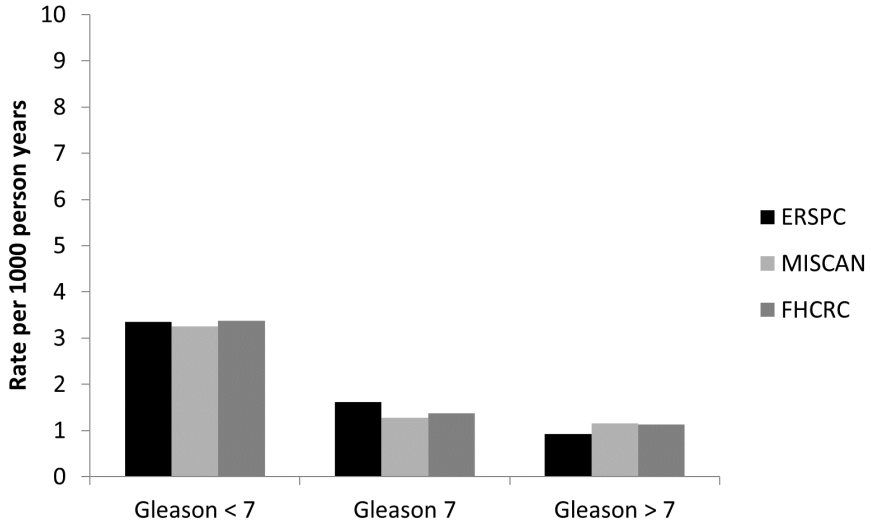

Figure 9. Grade distribution in the control arm of the ERSPC trial.

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Cost-effectiveness

Figure 10 shows the cost-effectiveness of different screening protocols, varying by start and end age and screening interval [3].

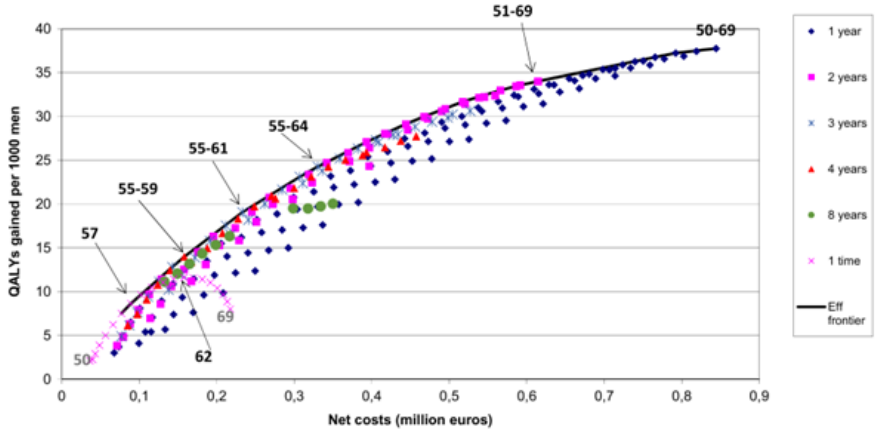

Figure 10. Net costs and QALYs gained per 1000 men. The start and end age of most optimal strategies given 1, 2, 3, 4 and 8 years interval are depicted in the figure. Numbers in the legend indicate the screening intervals used in the mode. Eff frontier = efficient frontier; the strategies leading to the highest QALYs at the lowest costs.

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Validations

Summary

This document describes calibration of the MISCAN-prostate model and selected validations.

Calibration

Over the years, the model has been calibrated to different data sources. In most calibrations, parameters of onset (age-specific hazards), disease progression (transition probabilities and duration in the states), test and/or biopsy sensitivities and PSA growth parameters or subsets of these parameters have been calibrated.
Data sources that are used are:

- SEER prostate cancer incidence by age and year
- Incidence and stage distribution and PSA distributions in the PLCO trial
- Incidence and stage distribution and PSA distributions in the ERSPC trial and in the Rotterdam section of the ERSPC trial
- PSA around age 45 of the Malmo study

Model parameters are estimated by numerical minimization of the deviance between observed numbers of cases and the corresponding numbers predicted by the model. Deviances are calculated assuming Poisson likelihood for incidence data or a multinomial likelihood for stage distribution data. For the minimization an adapted version of the simplex optimization method of Nelder and Mead is used. Optimization is initiated with small sample sizes and repeated with larger sample sizes (up to 2 million men) when optimization progress is no longer statistically significant.
Some results of the calibration are presented in the Results section.

Validation

One of the analyses that demonstrating the validity of the model is the analysis of the ERSPC and PLCO [1]. In this analysis we calibrated the model to the ERSPC data. Starting with reproducing the ERSPC trial, we changed the input one-by-one, ending with a simulation of the PLCO trial. Without changes to the cure parameter, we could reproduce the result of the PLCO trial well within the confidence limits.

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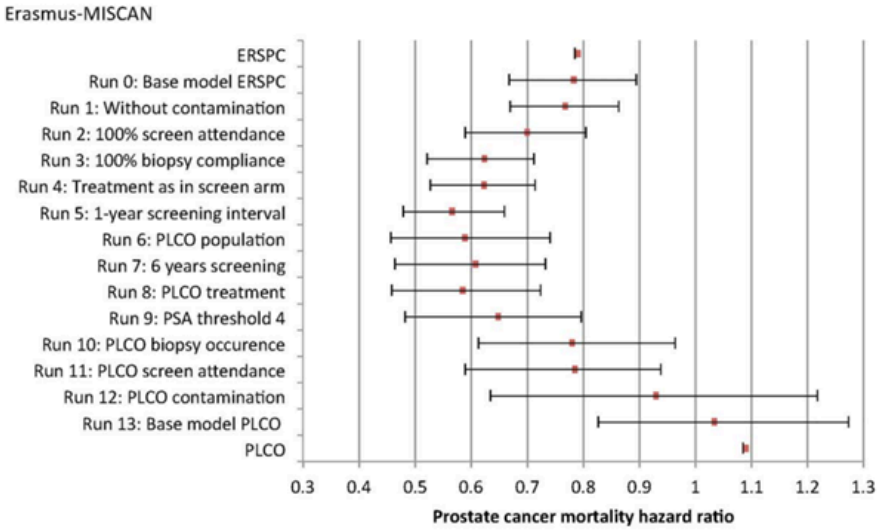

Figure 1. Step-by-step prostate cancer mortality rate ratios and simulation-based uncertainty ranges for the MISCAN model. The changes in the models are cumulative. In run 13, a cure parameter of 0 was used; in all other runs, the European Randomized Study of Screening for Prostate Cancer (ERSPC)-based cure parameter was used. For each run of 0 to 13, 100 simulations of a single ERSPC or Prostate, Lung, Colorectal, and Ovarian (PLCO) trial population were performed to generate sample mortality rate ratios; the line (uncertainty range) and dot represent, respectively, the range and mean of the sample mortality rate ratios observed over the 100 simulations. In runs 0 to 5 a follow-up of 11 years was used, whereas in runs 6 to 13 the follow-up was 13 years. In each step, the listed implementation change was added to the previous step.

Malmo Preventive Project

An external validation of the MISCAN 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 [2]. Figure 2 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 MISCAN 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.

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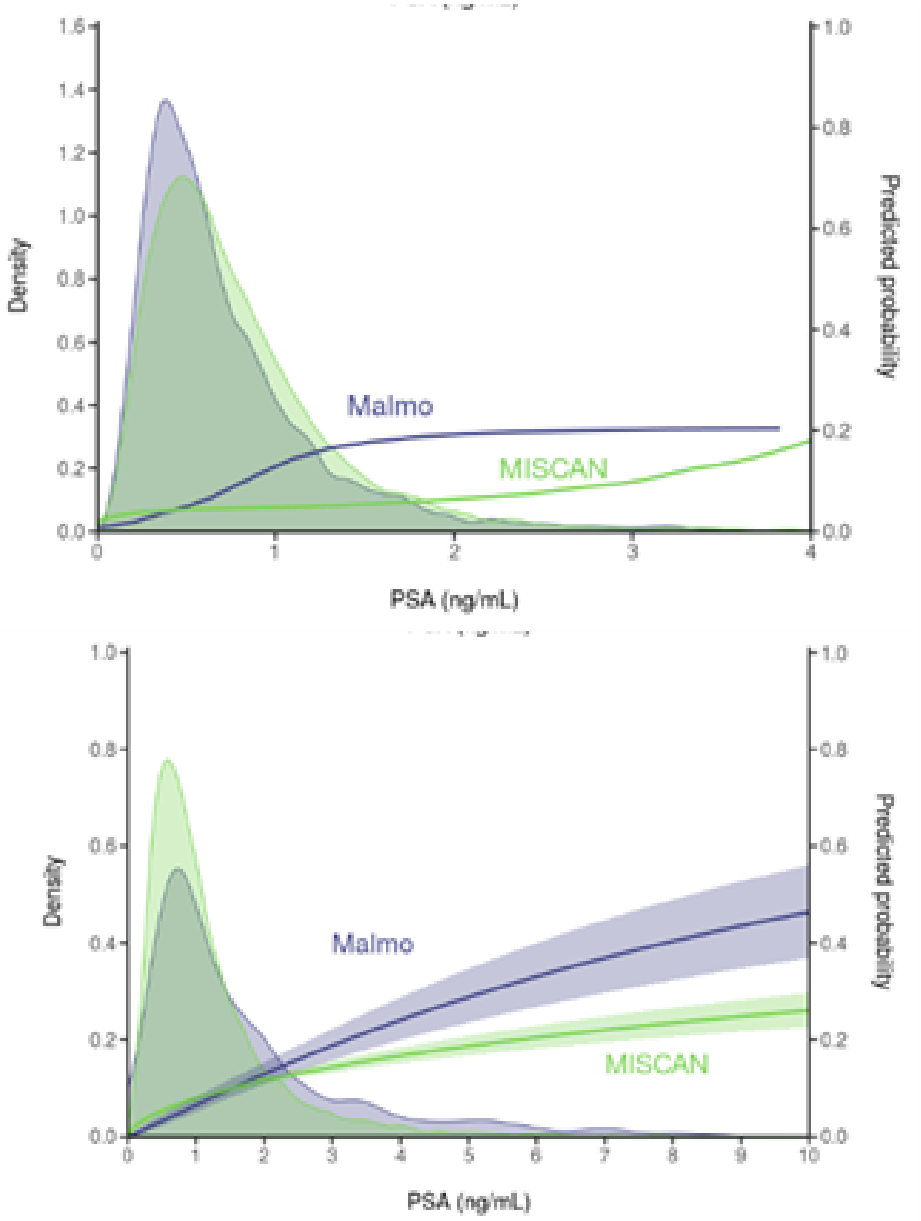

Figure 2. Observed PSA distributions for men ages 44–50 (top) and 60 (bottom) years at venipuncture and predicted 25-year risk of prostate cancer diagnosis based on empirical analysis of Malmo Preventive Project and corresponding projections from the PSAPC model in the absence of screening.

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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MSM-CanProg: Model Profile

University of Cambridge & University College London

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Version Table

Version	Date	Notes
1.0.00	2025-09-30	Initial release

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Readers Guide

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.

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

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Model Purpose

The MSM-CanProg (UK) encompasses continuous-time multistate survival models (MSM) and a microsimulation based on the MSM framework. The main aims of our models are:

1. To estimate natural history parameters such as sojourn time, sensitivity, age of entry into screen-detectable state, and the effect of covariates, including time-varying covariates, on transition parameters.[1,2]
2. To simulate life trajectories and evaluate outcomes of screening strategies, including screen-detected cancers, interval cancers, clinically diagnosed cancers, overdiagnoses, and cancer deaths, across varying screening frequencies and age ranges.[1-4]
   Further work is in progress to incorporate time varying PSA into MSM to inform PSA-tailored screening frequency and time to next investigation in active surveillance[5].

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1. Rikesh Bhatt, Ardo Van Den Hout, Nora Pashayan. A multistate survival model of the natural history of cancer using data from screened and unscreened population. Statistics in Medicine. 2021;40(16):3791–3807.
2. Mai Ngoc Bui, Ardo van den Hout, Rikesh Bhatt, Nora Pashayan. Non-homogeneous multistate partial Markov models: A simulation scheme for evaluating cancer screening strategies. Under review.
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Model Overview

We use a non-homogeneous multistate model with time varying transition probabilities to estimate natural history parameters, and a microsimulation based on multistate framework to investigate how often and when to offer screening to optimise the benefit-harm trade-off of a screening programme.

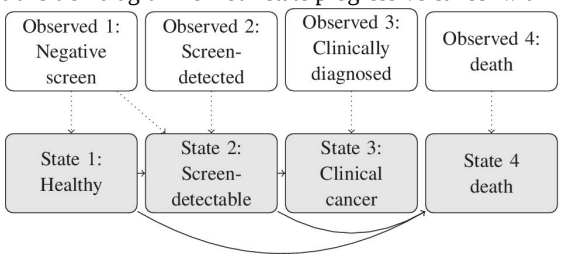
The MSM-CanProg (UK) is a multistate model with six states: 'healthy'/no-detectable cancer (S1), screen-detectable (S2-a), screen-detected (S2-b), clinically diagnosed (S3), death from other causes (S4), and cancer-specific death (S5) (see Figure 1 in Component Overview).

The transition to S2-a is interval censored, while the transitions to S3, S4 and S5 occur at exact times, with death acting as a competing risk on the transition between S1 and S2-a, and between S2-a and S3. The first observation in non-screened individuals is considered left censored. All individuals are assumed to be truly in state S1 at some initial age. An individual with negative screening test may truly be in S1 or could be in S2-a but misclassified as being in S1 (see Figure 2). Sojourn time is the length of time spent in S2-a given that an individual transitions to S3.

Key features of the multistate survival model are:

- It allows using interval censored, left censored, right censored, and left truncated panel data.
- Data can be used from both screened and unscreened populations to derive transition parameters to clinical states.
- Each transition can be specified by a variety of parametric models including exponential, Weibull, and Gompertz hazard models.
- With a parametric approach, the model can be used for prediction and out-of-sample extrapolation.
- Age varying transition hazards and age-varying misclassification are estimated simultaneously.
- The transition parameters are estimated by optimisation process to maximise the likelihood function built from the transition intensity function (see Transition Intensity and Likelihood).

Figure 2: State transition diagram for four-state progressive cancer with misclassification



Source: Bhatt et al, 2021

The microsimulation is built on the multistate framework, projecting individuals' life trajectories from birth to death while embedding the natural history of cancer (see Figure 1 in Component Overview). The screening process and follow-up period are integrated into the simulation scheme.

Key features of our microsimulation are:

- A flexible simulation scheme that allows for the superimposition of different screening strategies by varying calendar years, age range, frequency, and uptake of screening. This enables projection and comparison of screening outcomes between no screening and various screening strategies, including screen-detected cancers, interval cancers, overdiagnoses, and cancer-specific deaths.
- Estimates of transition parameters and misclassification, derived from the multistate survival model, are used as input parameters for the microsimulation model.
- When panel data are not available, the microsimulation model could be used as a tool to derive estimates of transition parameters. We can use cross-sectional data with screening outcomes to estimate natural history parameters. Here, the outputs of the microsimulation model are calibrated against observed data (see Calibration), and the multistate model is fitted to the simulated data to estimate the transition parameters and misclassification (see Microsimulation).

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Assumption Overview

Assumption Overview

We have used the following assumptions:

- Progressive disease – all individuals with screen-detectable cancer if they live long enough will eventually present with clinical cancer. The disease progression is not reversible, that means there is no regression back to an earlier state.
- Screen-detectable state is a latent state that precedes progression to clinical diagnosis.
- The transition rates from S1 (healthy) and S2-a (screen-detectable states) to S4 (death from other causes) are the same.
- Misclassification is independent of misclassification in previous screening rounds.
- We set the age (age 40) at which we assumed all men will be in S1 (healthy / no prostate cancer) state.

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Parameter Overview

This document outlines the list of parameters used in our MSM-CanProg (UK) multistate model and microsimulation.

List of parameters

A. For the multistate model

- Age (t) : age at each observation
- States (S_t) : the true state of subject at age (t)
    - State 1 (Healthy), State 2-a (Screen-detectable cancer), State 2-b (Screen-detected cancer), State 3 (Clinically diagnosed), State 4 (Death from other-causes), and State 5 (Cancer-specific death)
- Observed States (O_t) : the observed state at age (t)
    - State 1 (Negative Screen – which could be true negative or false negative), State 2-b (Screen-detected cancer), State 3 (Clinically diagnosed cancer), State 4 (Death from other-causes), and State 5 (Cancer-specific death)
- Censored state : Here an individual could be in S1 or S2-a. This occurs when an individual has not attended screening or was not offered screening (such as in the control arm, and after the screening period ends)
- Q: Intensity matrix
    - $q_{ij}(t)$: the transition intensity from State i to j, where $i \neq j$
    - $q_{ii}(t) = -\sum_{j \neq i} q_{ij}(t)$
- Gompertz distribution: $q_{ij}(t) = exp(\lambda_{ij} + \beta_{ij}t + \alpha_{ij}Z)$ for $i \neq j$, when $\beta_{ij} > 0$
- Exponential distribution: $q_{ij}(t) = exp(\lambda_{ij} + \alpha_{ij}Z)$ for $i \neq j$
    - λ_{ij}: the intercept term of transition hazards from State i to State j
    - β_{ij}: the coefficient of age-varying hazard from State i to State j when the transition hazard has Gompertz distribution
    - Z: the vector of time-constant variables
    - α_{ij}: the coefficient of Z from State i to State j in the hazard function
- Misclassification probability: $e_{ij}(t) = P(O_t = j | S_t = i)$
- v_m: the intercept term in the misclassification model
- r_m: the coefficients of t (age) in the age-varying misclassification model
- $P(t_0, t_1)$: the transition probability matrix between age, t_0 and t_1
- $L(\theta | t_1, \ldots, t_n)$: the likelihood contribution across n observations for an individual

B. For the microsimulation

- t_0: the left truncated age (40)
- Y_0: the calendar year at the initial age
- S_0: the initial state at the preset initial age. We assumed that all individuals are truly in the State 1 at t_0.

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- Y_i: the calendar year at the $i\text{th}$ observation
- S_i: the true state at the $i\text{th}$ observation
- O_i: the observed state at the $i\text{th}$ observation
- t_{ij}: the time to stay at State i before transitioning to State j
- λ_{ij}: the intercept term of transition hazards from State i to State j
- β_{ij}: the coefficient of age-varying hazard from State i to State j when the transition hazard has Gompertz distribution
- α_{ij}: the coefficient of Z from State i to State j in the hazard function
- $e_{ij}(t) = P(O_t = j|S_t = i)$: the misclassification probability
- The frequency of screening
- The total number of screening episodes
- The age-range of screening
- The range of years during which screening is offered
- Uptake of screening (compliance rate)

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Component Overview

The estimation component

Our multistate model consists of three subcomponents (see Figure 1):

1. Natural history component (see Figure 1a – blue arrows)
2. Progression of disease from clinical diagnosis to death (see Figure 1a – red arrows)[1],
3. Progression of disease from screen-detection to death (see Figure 1b)

Figure 1: State transition diagram for the natural history model including the progression of disease from clinical diagnosis to death (Figure 1a) and the transition model from the screen detected prostate cancer to death (Figure 1b).

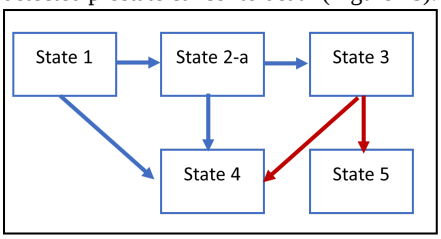

Figure 1a

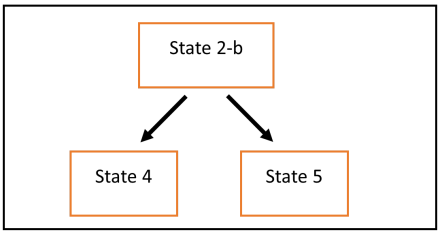

Figure 1b

State 1 (healthy), State 2-a (screen detectable cancer), State 2-b (screen detected cancer), State 3 (clinically diagnosed cancer), State 4 (death from other causes) and State 5 (cancer-specific death).

The simulation component

Our microsimulation consists of three subcomponents:

1. Projection of individual life histories from birth to death
2. An embedded natural history subcomponent
3. Overlaid screening processes

The details are described in the Model Overview (see Microsimulation)

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1. Rikesh Bhatt, Ardo Van Den Hout, Nora Pashayan. A multistate survival model of the natural history of cancer using data from screened and unscreened population. Statistics in Medicine. 2021;40(16):3791–3807.

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Output Overview

This document describes the output of our multistate models and microsimulation scheme.

Table1: Outputs from each subcomponent of our multistate model and microsimulation

Multistate model			**Microsimulation**		
Natural History	**Progression after screen-detection**	**Progression after clinical diagnosis**	**Life trajectory**	**Natural History**	**Screen Scenarios**
Age-varying state transition parameters: S1 to S2-a, S2-a to S3, S1 to S4, S2-a to S4	Age-varying state transition parameters from screen-detection to death: S2-b to S4 and S2-b to S5	Age-varying state transition parameters from clinical diagnosis to death:S3 to S4 and S3 to S5	Time span from birth to death	Screen- detectable cancer	Screen-detected Cancer
Misclassification (1-sensitivity)			Age at death from non-cancer causes	Age of entry to the screen-detectable state	Age at screen detection
Age of entry to the screen-detectable state			Deaths from non-cancer causes	Sojourn time	Misclassified state
Sojourn time				Symptomatic / clinically diagnosed cancers	Interval cancer
				Age at the diagnosis of clinical/symptomatic cancer	Overdiagnosed cancer
				Age at death from cancer cause	Sensitivity of the test / screening episode
S1: Healthy, S2-a: Screen-detectable prostate cancer, S2-b: Screen-detected prostate cancer, S3: Clinically diagnosed prostate cancer, S4: Other-cause Death, S5: Cancer-specific death					

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Results Overview

As an example, we present here the results of applying our microsimulation and the calibration approach to the Cluster Randomized Trial of PSA Testing for Prostate (CAP). The results are detailed in the published paper (see Martin et al, 2024).[1]

Overview

We aimed to estimate the sojourn time, PSA screening episode sensitivity, and probability of overdiagnosis by age in the CAP trial.

CAP is a cluster-randomized trial to evaluate the effect of single invitation for PSA screening for men 50 to 69 years, from 2002 to 2009 and followed up until March 2021, on cancer specific mortality as compared to no invitation for screening.

We applied the multistate survival model with parametric hazards and the following states: healthy, screen-detectable, screen-detected, clinically diagnosed, cancer-specific death, and death from other causes, to estimate the natural history parameters and time to death after cancer diagnosis [see Figure 1 in Component Overview]. We assumed Weibull distribution for the transition between the healthy and screen-detectable states, and Gompertz distribution for all other transitions. We estimated the transition parameters and the misclassification of states (i.e. 1- sensitivity) by maximising the likelihood functions (see Transition intensity).

We simulated a cohort of three million men aged 50-69 years and followed to death using the multistate model framework with the estimates of transition parameters, and calibrated them against CAP data – prostate cancer incidence rate, cancer-specific and all-other cause mortality rates (Figure A) and age at death (Figure B). We assumed that there was no screening in the control arm.

We derived the mean sojourn time and overdiagnosis from microsimulation using the estimated transition parameters and one-off screening between ages 50 to 69 and assuming 85% of men with elevated PSA level undertake biopsy. We calculated the sojourn time as the length of time in screen-detectable state given a transition to clinically diagnosed state.

We estimated the extent of overdiagnosis as the difference in the cumulative prostate cancer incidence between screened and unscreened groups over lifetime. The probability of overdiagnosis is the fraction overdiagnosed among screen-detected cases.

Results

Figures A and B are the outputs of the microsimulation model calibrated against the CAP data.

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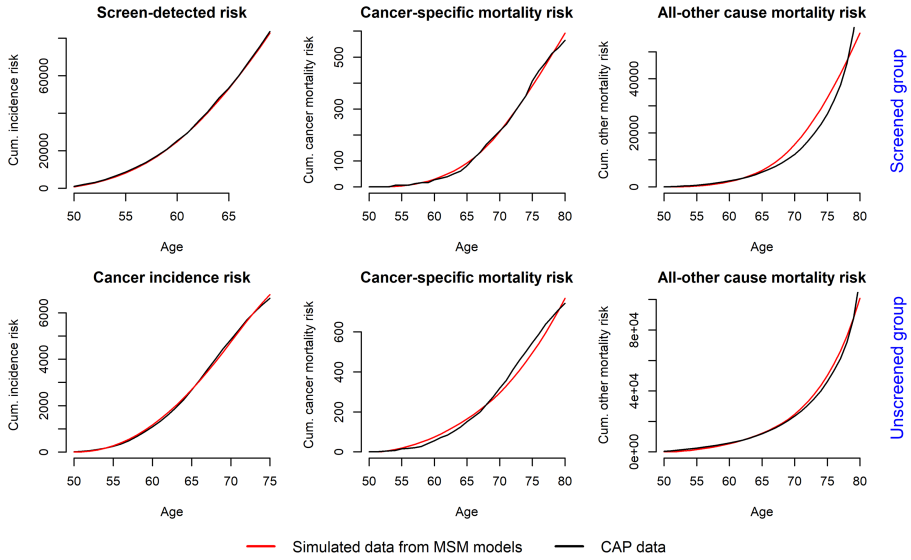
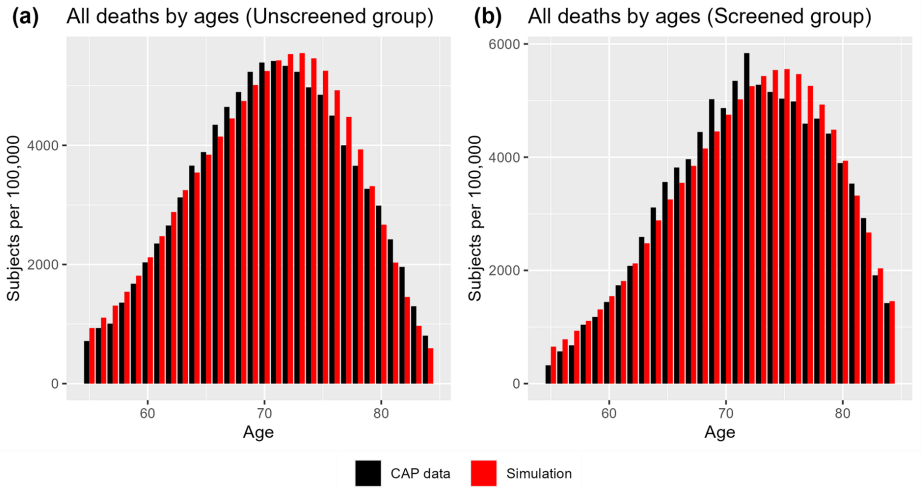
Figure A: Comparing simulated data to empirical data from CAP for the cumulative prostate cancer incidence and cancer-specific and all-other cause mortality risk among the screened men and the unscreened group.



The estimated curves for the simulation were derived by averaging the estimates across 200 simulations of 3 million subjects aged 50-69 years, with one screening in the screening group.

Source: Martin et al, 2024

Figure B: Comparing the number of all-cause deaths per 100,000 subjects by age between the simulated data and empirical data in the screened and unscreened groups.



The estimated curves for the simulation were derived by averaging the estimates across 200 simulations of 3 million subjects aged 50-69 years, with one screening in the screening group.

Source: Martin et al, 2024

The estimated curves for the simulation were derived by averaging the estimates across 200 simulations of 3 million subjects aged 50-69 years, with one screening in the screening group.

For the age group 50 to 69 years, the mean sojourn time was 13.4 years, increasing from 12.1 years in the 50-54 age group to 15.3 years in the 65-69 age group. For the age group 50 to 69 years, the probability of overdiagnosis was 15%, increasing from 9% in the 50-54 age group to 21% in the 65-69 age group. (See Table A.) The episode sensitivity (the ability of the full diagnostic process – testing and biopsy – to find cancer in the detectable preclinical phase) increased from 50.0% to 85.3% for ages 50 to 69.

Table A: Estimated mean sojourn time and probability of overdiagnosis.

Age group	Mean Sojourn time (years)	95% Confidence Interval (years)

50-54	12.1	12.1-12.2
55-59	13.2	13.1-13.2
60-64	14.2	14.2-14.3
65-69	15.3	15.2-15.3
50-69	13.4	13.4-13.4
Age group	**Mean Overdiagnosis (%)**	**95% Confidence Interval (%)**
50-54	9.2	8.9-9.4
55-59	13.3	13.1-13.5
60-64	17.1	17.0-17.3
65-69	20.8	20.6-21.0
50-69	15.0	14.4-15.5

Overdiagnosis estimates are based on simulation of 200 cohorts of 3 million men aged 50-69 years followed to death.

Source: Martin et al, 2024

References

1. Richard M. Martin, Emma L. Turner, Grace J. Young, Chris Metcalfe, Eleanor I. Walsh, J. Athene Lane, et al. Prostate-Specific Antigen Screening and 15-Year Prostate Cancer Mortality: A Secondary Analysis of the CAP Randomized Clinical Trial. JAMA. 2024;331(17):1460.

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Transition Intensity

Transition Intensity Matrix and Likelihood

Transition intensity and probability matrix

The transition intensity matrix at the age t, Q_t, is defined as

$$Q = \begin{bmatrix} -(q_{12}(t) + q_{14}(t)) & q_{12}(t) & 0 & q_{14}(t) & 0 \\ 0 & -(q_{23}(t) + q_{24}(t)) & q_{23}(t) & q_{24}(t) & 0 \\ 0 & 0 & -(q_{34}(t) + q_{35}(t)) & q_{34}(t) & q_{35}(t) \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

where $q_{ij}(t)$ is the transition rate from State i to State j at age, t. Each transition hazard is parametric with exponential or Gompertz distribution. The hazard function is built in a log hazard framework with age-varying elements and potentially other variables. The Gompertz hazard function for the transition between State i and j is

$$q_{ij}(t) = exp(\lambda_{ij} + \beta_{ij}t + \alpha_{ij}Z) \text{ for } i \neq j,$$

where $\beta_{ij} > 0$ is the coefficient of age, Z is the time-constant variable and α_{ij} is the coefficient of Z. The exponential hazard has only an intercept and time-constant terms when $\beta_{ij} = 0$.

Additionally, misclassification is considered only at the screening phase for un-detected cancers (false negatives) in the model. The misclassification rate, $e_{ij} = P(O_t = i \mid S_t = j)$, is defined

$$\begin{aligned} e_{12}(t) &= \frac{exp(v + rt)}{(1 + exp(v + rt))} \\ e_{22}(t) &= 1 - e_{21} \\ e_{ii}(t) &= 1 \text{ and } e_{ij} = 0, \text{ otherwise.} \end{aligned}$$

In a similar spirit, we constructed another multi-state model to explore the transition process after screen detection (see Figure 1-b). The transition intensity matrix is defined as

$$Q^* = \begin{bmatrix} (-(q^*_{24}(t) + q^*_{25}(t)) & q^*_{24}(t) & q^*_{25}(t) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

where each transition rate is derived equivalently to the previous five-state model.

The transition probability matrix in the time interval between t_0 and t_1 for $t_0 < t_1$ is defined as

$$P(t_0, t_1) = exp(Q_{t0}(t_1 - t_0))$$

where Q_{t0} is the transition matrix derived at t_0.

We applied a piecewise constant approximation using a grid with the regular length, l, and the approximate likelihood can be written as

$$P(t_0, t_1) = P(t_0, t_0 + l)P(t_0 + l, t_0 + 2l) \cdots P(t_0 + nl, t_1)$$

where $0 \leq n < \frac{(t_1 - t_0)}{l}$.

Likelihood function

The data for our model include left truncated, censored, interval-censored, right censored, and misclassified observations.

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The likelihood contribution for an individual, who has N observations, at ages t_1 to t_N, is given by Bhatt et al, 2021[1]:

$$L(\theta \mid t_1, \ldots, t_n) = \epsilon^T (\prod_{\pi=1}^{n} L_i(\theta | t_{i-1}, t_i))\ 1,$$

where θ is the set of parameters of the model and t_0 is the left truncated age (40) at which we assumed all mean are in the healthy state (S1). Additionally, $\epsilon^T = (1, 0, 0, 0)$, which implies that all men are healthy at the initial age, t_0, and $1^T = (1, 1, 1, 1)$ to sum up the likelihood contribution of possible states at the last observation, including censored states.

Misclassification can be incorporated into the model, when State 2 (Screen detectable state) can be misclassified as State 1 (Healthy). The probability of transition from State 1 or 2 to observing state o_n is

$$P(O_n = o_n | S_{n-1} = 1 \text{ or } 2) = \sum_{s_n=1,2} P(S_n = s_n | S_{n-1} = 1 \text{ or } 2) P(O_n = o_n | S_n = s_n).$$

The likelihood matrix, L_n, when the observed state is 1 or 2, can be written as

$$L_n = P(t_n, t_{n-1}) E_(t_n)$$

where $P(t_{n-1}, t_n)$ is the transition probability matrix in the interval, (t_{n-1}, t_n). Additionally, the misclassification matrix is

$$E_{t_n} = \begin{bmatrix} e_{1o_n}(t) & 0 & 0 & 0 & 0 \\ 0 & e_{2o_n}(t) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

where $e_{ij}(t) = P(O_j = o_j | S_i = s_i)$.

In our model, we assumed that all men are healthy at t_0 and individuals who had already clinical cancer or had died before entry to the study are censored from the analysis. Therefore, the probability of the first observation with left truncation is

$$\begin{aligned} P(O_1 = o_1 | S_0 = 1, S_1 \notin \{3, 4, 5\}) &= \frac{P(O_1 = o_1 \cap S_1 \notin \{3, 4, 5\} | S_0 = 1)}{P(S_1 \notin 3, 4, 5 | S_0 = 1)} \\ &= \sum_{i=1,2} \frac{P(S_1 = s_1 | S_0 = 1) P(O_1 = o_1 | S_1 = s_1)}{P(S_1 \notin 3, 4, 5 | S_0 = 1)}. \end{aligned}$$

Therefore, the contribution of the first observations, L_1, is

$$L_1 = \begin{bmatrix} \frac{1}{P_{11}(t_0, t_1) + P_{12}(t_0, t_1)} & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{P_{22}(t_0, t_1)} & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} P_0 E_1,$$

where P_0 is the transition probability matrix at t_0 and E_1 is the misclassification matrix at the first observation, t_1.

Clinical cancers and deaths are events whose times are observed exactly, and the likelihood contribution of state d is

$$L_n = P(t_n, t_{n-1}) Q(t_{n-1}) \delta_d$$

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where

$$\delta_3 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\delta_4 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

and

$$\delta_5 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}.$$

The likelihood function, L_K, of K individuals is a product of individual likelihood contributions:

$$L_K(\theta; t_1, \ldots, t_N) = \prod_{i=1}^{K} L^i(\theta; t_1, \ldots, t_{n_i})$$

where $L^i(t_1, \ldots, t_{n_i})$ is the likelihood contribution from the ith individual.

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Microsimulation

Model Overview – Microsimulation

We simulated the life trajectory of individuals from bith to death while embedding the natural history of cancer, following the steps given by Bui et al. (Under Review):

1. Set the initial calendar year (Y_0) at the pre-set initial age (t_0=40) when we assume that all men are in State 1 (healthy).

2. Men in State 1 can transition to either State 2 or 4. The transition time to event can be simulated from the transition distributions respectively, $t_{12} \sim Gomp(t_0; \lambda_{12}, \beta_{12})$ and $t_{14} \sim Gomp(t_0; \lambda_{14}, \beta_{14})$. If $t_{12} < t_{14}$, $t_1 = t_0 + t_{12}$ and proceed to Step 3. If $t_{12} > t_{14}$, $t_1 = t_0 + t_{14}$ and proceed to Step 5

3. The next state from State 2 can be either 3 or 4. Equivalently, the time to event is calculated as $t_{23} \sim Exp(t_1; \lambda_{12})$ and $t_{24} \sim Gomp(t_1; \lambda_{14}, \beta_{14})$. If $t_{23} < t_{24}$, $t_2 = t_1 + t_{23}$ and go to Step 4. If $t_{23} > t_{24}$, $t_2 = t_1 + t_{24}$ and proceed to Step 5.

4. The next state from State 3 can be either 4 or 5. The time to event is calculated as $t_{34} \sim Gomp(t_2; \lambda_{34}, \beta_{34})$ and $t_{35} \sim Gomp(t_2; \lambda_{35}, \beta_{35})$. If $t_{34} < t_{35}, t_3 = t_2 + t_{34}$. Otherwise, $t_3 = t_2 + t_{35}$. In either case, process to Step 5.

5. End the simulation and record the transition times along with the corresponding states.

The transition time to event is simulated from the assumed hazard distribution conditioned at time t. For example, when the transition has the Gompertz distribution with the parameters α and β at t_n : $Gomp(t; \alpha, \beta)$, the simulated survival time to event can be written

$$t_{n+1} = (\log(exp(\alpha + \beta t_n) - \beta \log U) - \alpha)/\beta$$

where $U \sim Unif(0, 1)$.

We superimposed a screening strategy onto the simulated life-trajectory and natural history of prostate cancer. This included defining age range of screening, frequency of screening, and calendar year of starting screening. We then compared the outcomes of different screening strategies with each other and with no screening.

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Calibration

Calibration

Model Overview – Calibration

For calibration of the simulated data against empirical data, we have used calibration, by comparing the simulated estimates of cumulative incidence of clinically diagnosed cancers, all-other cause mortality, cancer-specific mortality rate and distribution of age at death (see Box 1). Using the calibration approach we aimed to estimate the set of parameters related to the natural history of prostate cancer, transitions following screen detection and clinical diagnosis, as well as misclassification, that align with empirical data.

Box 1: Steps of the calibration process (This box will be released online following the publication of Bui et al. (Under review))

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Key References

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Fred Hutchinson Cancer Center
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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

Fred Hutchinson Cancer Center
Readers Guide

Fred Hutch Cancer Center

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.

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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

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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

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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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Fred Hutchinson Cancer Center

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.

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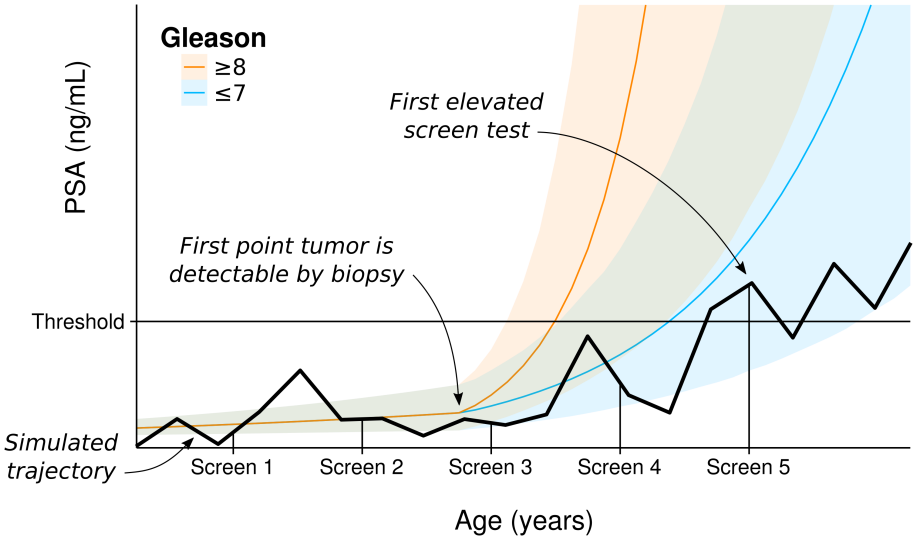
Figure 1. Mean and interquartile range of PSA levels before and after onset of preclinical Gleason score ≤7 or Gleason score ≥8 prostate tumors. An example simulated PSA trajectory before and after onset of a Gleason score ≤7 tumor is superimposed, and the time at which the simulated PSA level exceeds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

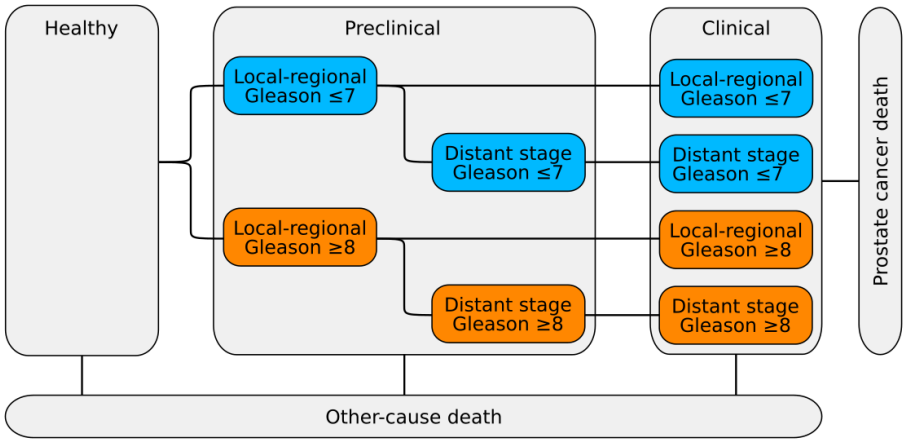


In a later extension, we further partitioned Gleason score ≤7 tumors into Gleason score ≤6 versus 7 using the PSA slope [3]. In applications of the model for Black men, we assume that PSA growth parameters do not differ by race.

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]:

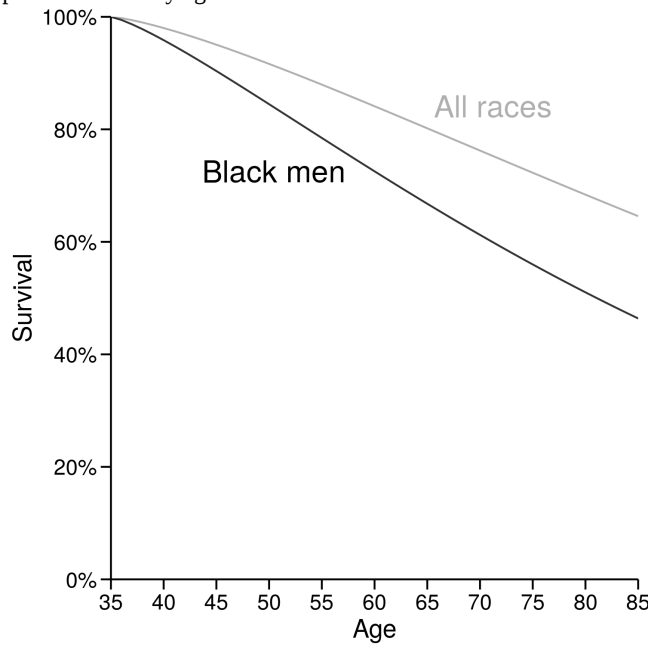
$$\lambda_o(t) = \gamma_o t.$$

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.

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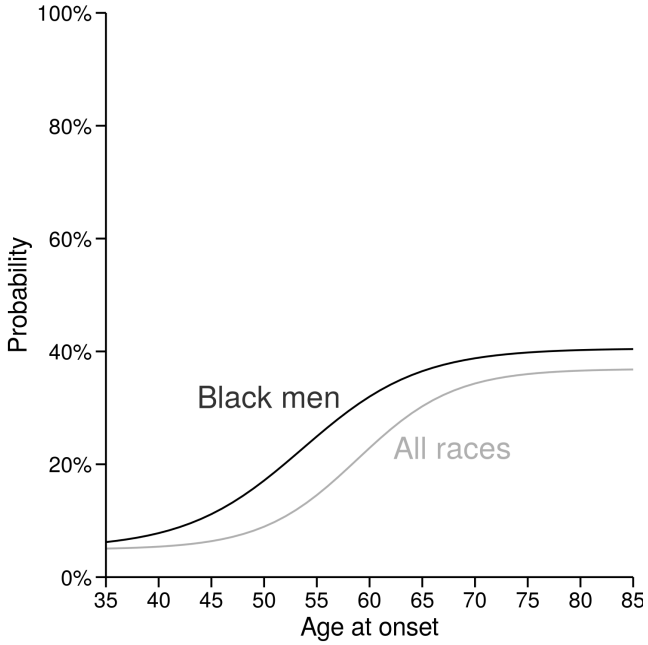
Figure 4. Estimated probability of Gleason score ≥8 by age at onset and race.



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.

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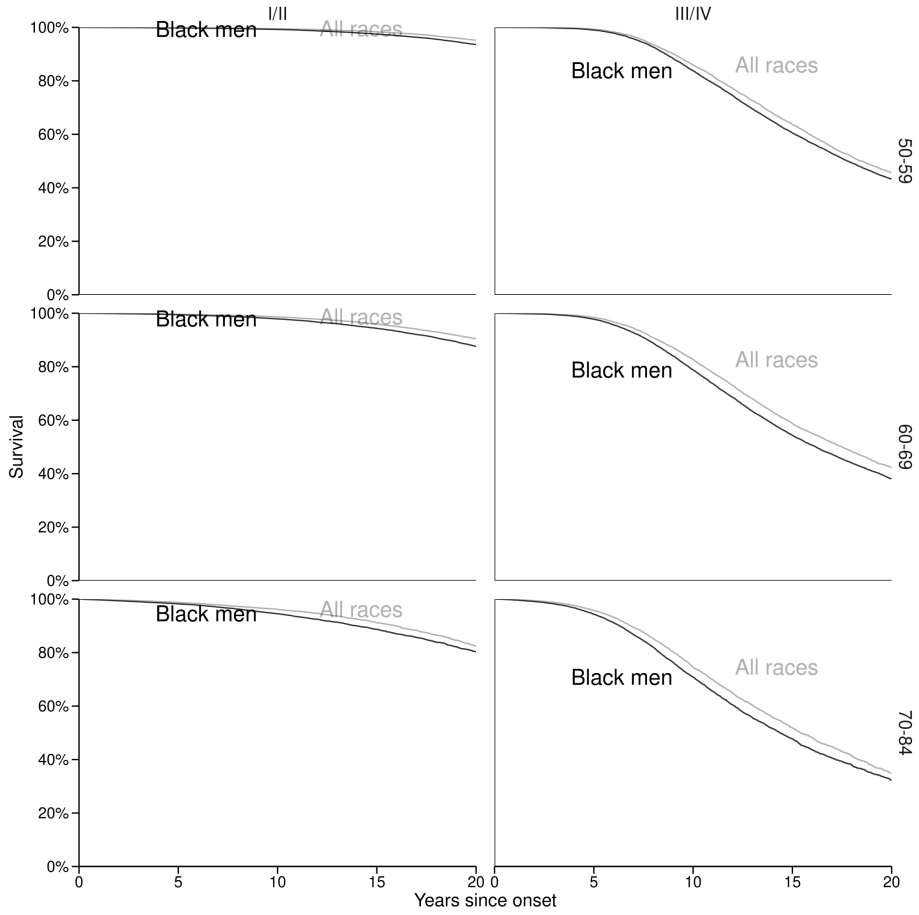
Figure 5. Probability of not progressing to metastatic prostate cancer in the absence of PSA screening by age decade at onset, tumor grade, years since onset, and race.



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

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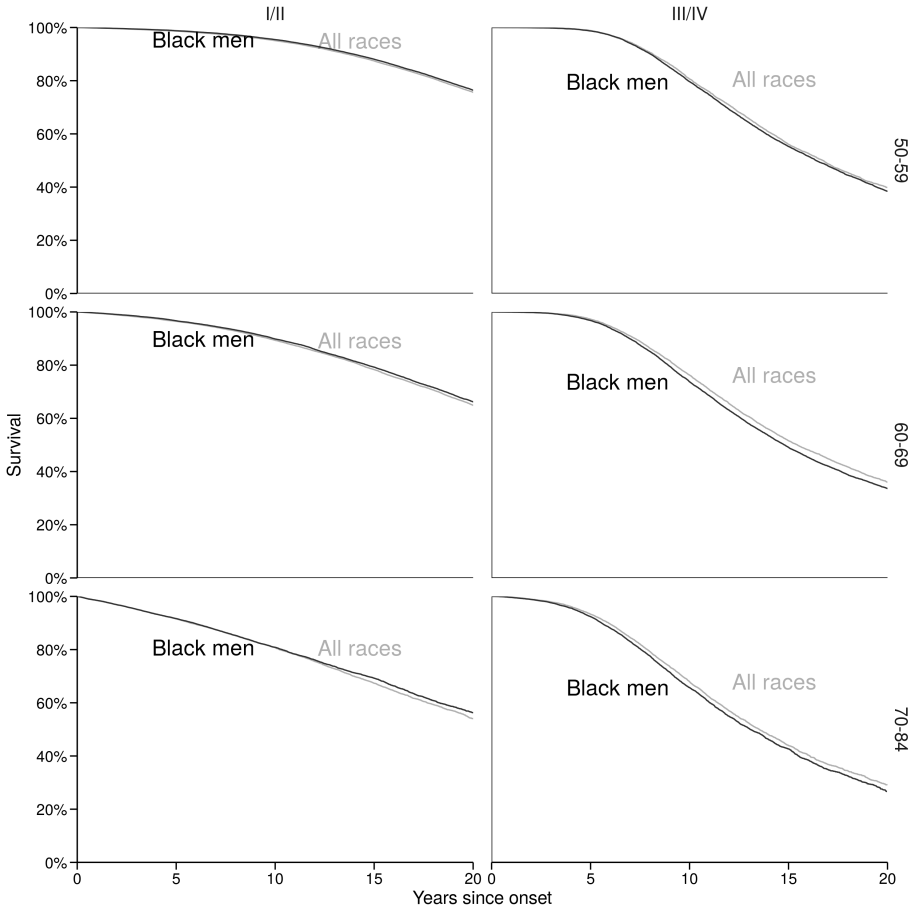
grade.

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 ($\gamma_{\text{localized,Gleason score } \leq 7}$)

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- 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.

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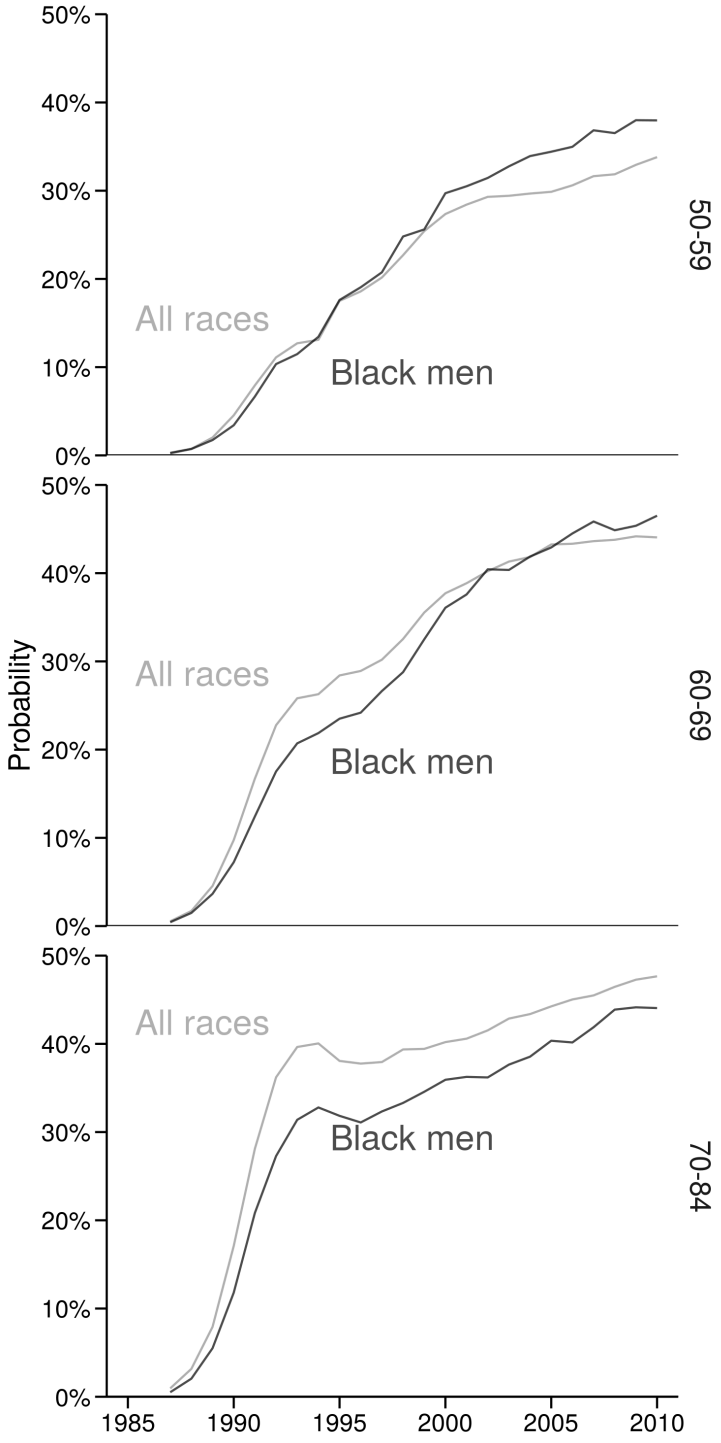
Figure 1. Probability of at least one PSA test reconstructed using a model fit to data from the National Health Interview Survey for age at first test and the linked Surveillance, Epidemiology, and End Results and Medicare 5% random sample of the cancer-free population for intervals between tests by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

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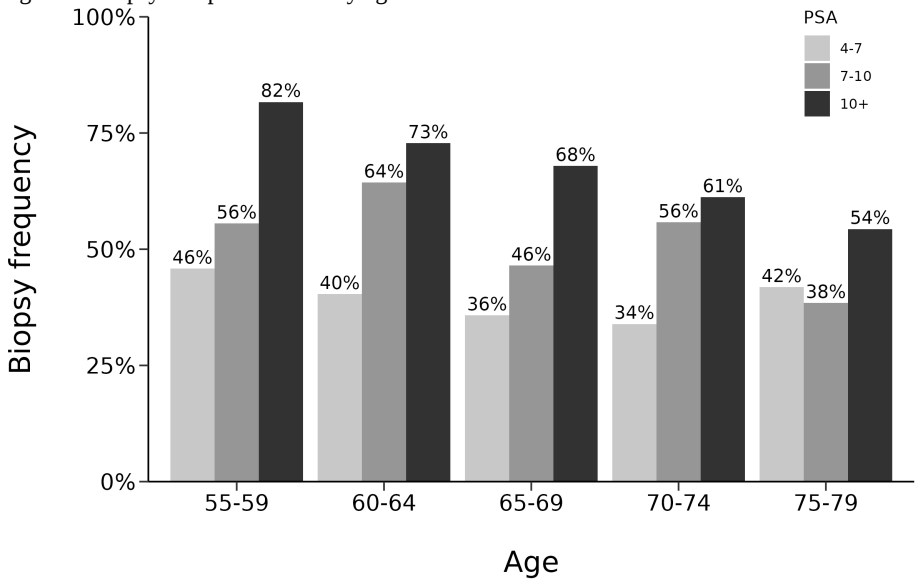
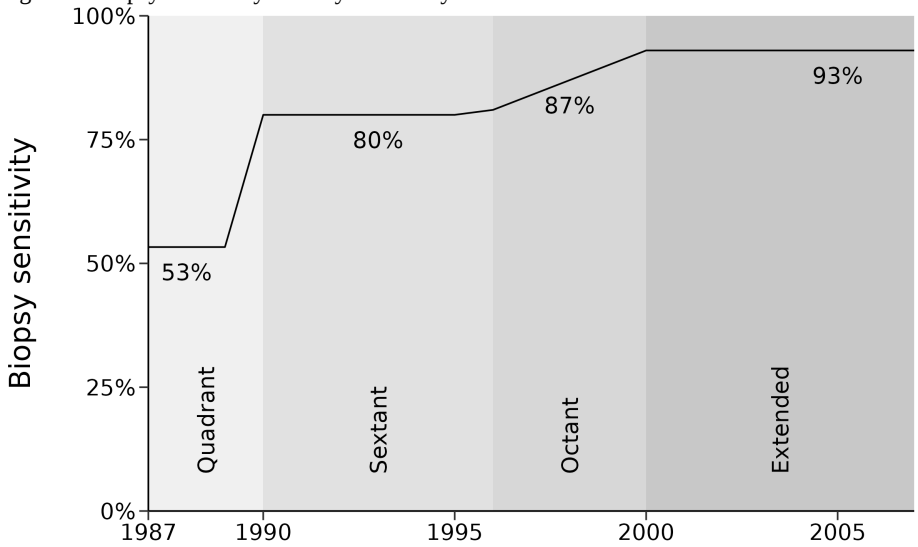
patterns. These studies also explicitly modeled receipt of digital rectal exam (DRE) tests when applicable.[10-12]Specifically, DRE sensitivity to detect latent disease in men with negative PSA test results was based on a ERSPC study[13] that found DRE sensitivity is approximately 20% for PSA below 3.0 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

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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.

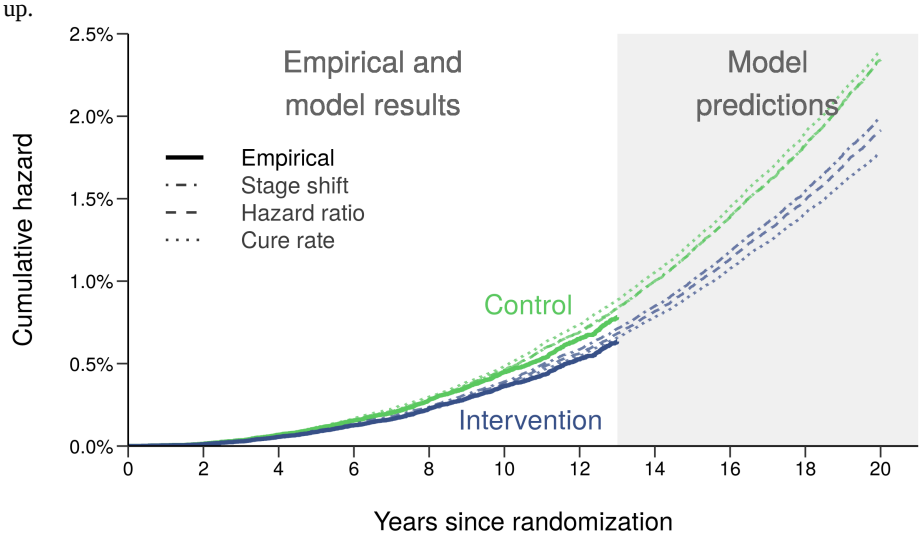
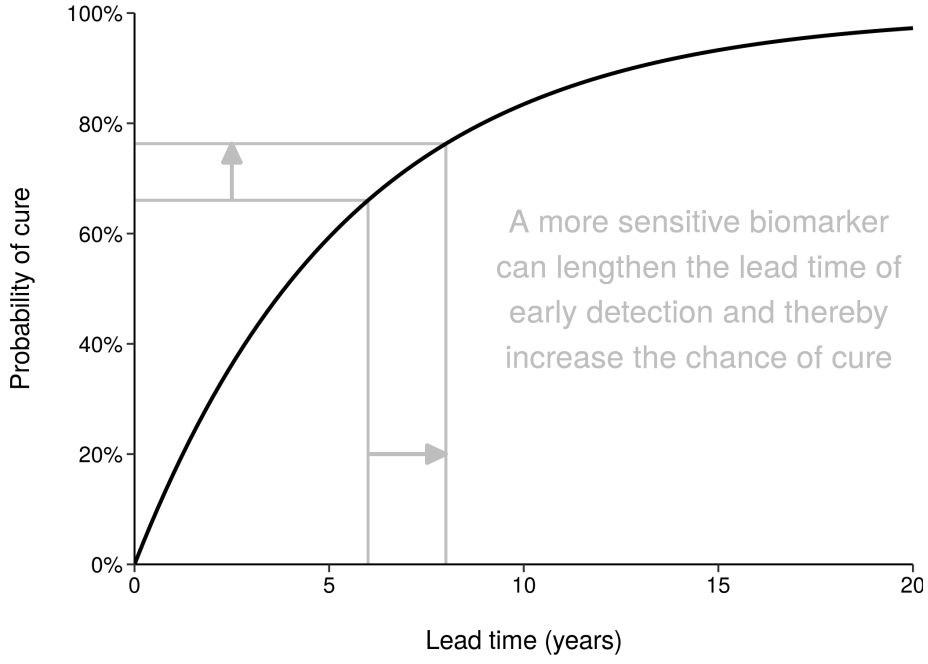


Figure 5 shows schematically how a flexible cure fraction depends on an individual's lead time.[15]

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



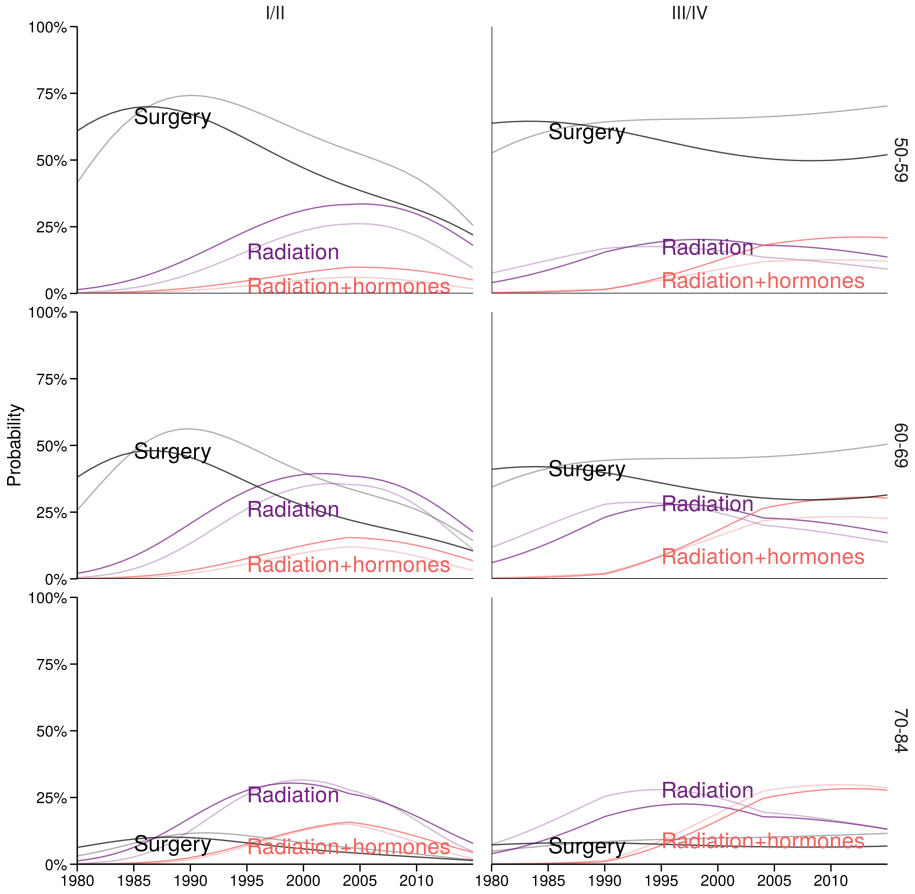
Primary treatment

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

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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.

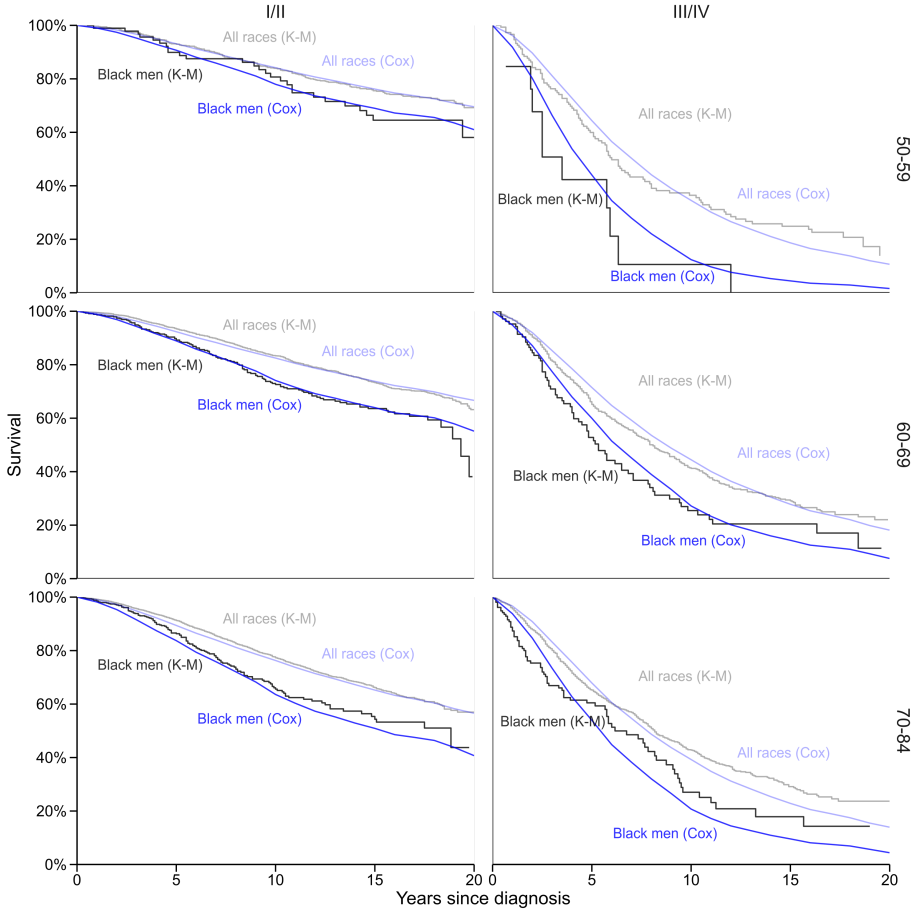
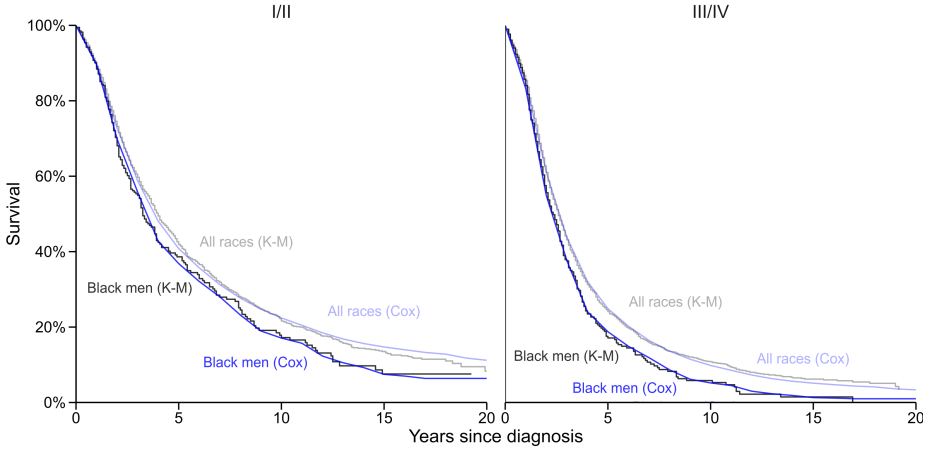


Figure 8. Probability of not dying from prostate cancer estimated using Cox regression (“Cox”; blue lines) and stratified Kaplan-Meier (“K-M”; black lines) for untreated cases diagnosed in the Surveillance, Epidemiology, and End Results program in 1980--1986 with distant stage prostate cancer by disease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

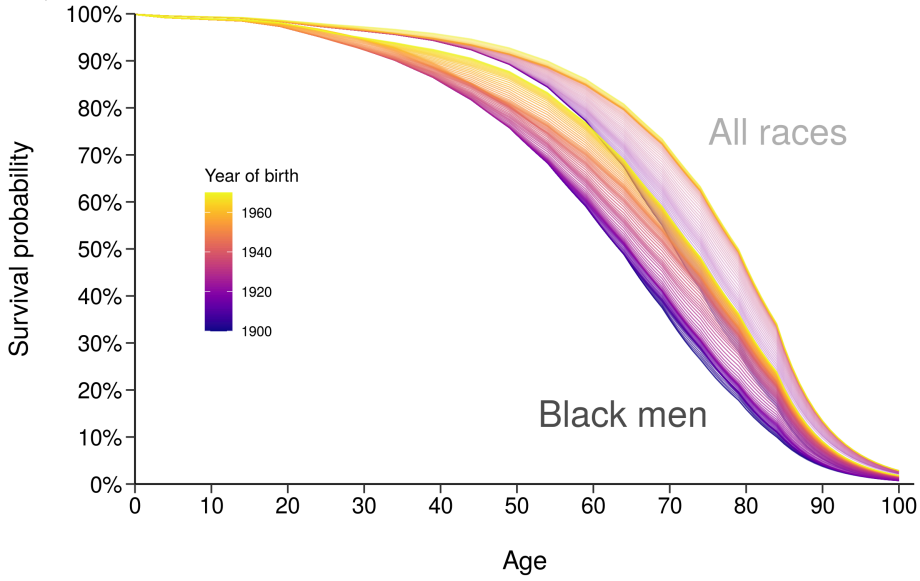


These models extend earlier Poisson regressions fit to pre-PSA SEER data for untreated cases. Those fitted models agreed closely with long-term empirical estimates.[31] The extended models used Cox instead of Poisson regressions and incorporated race.

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.

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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).

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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.

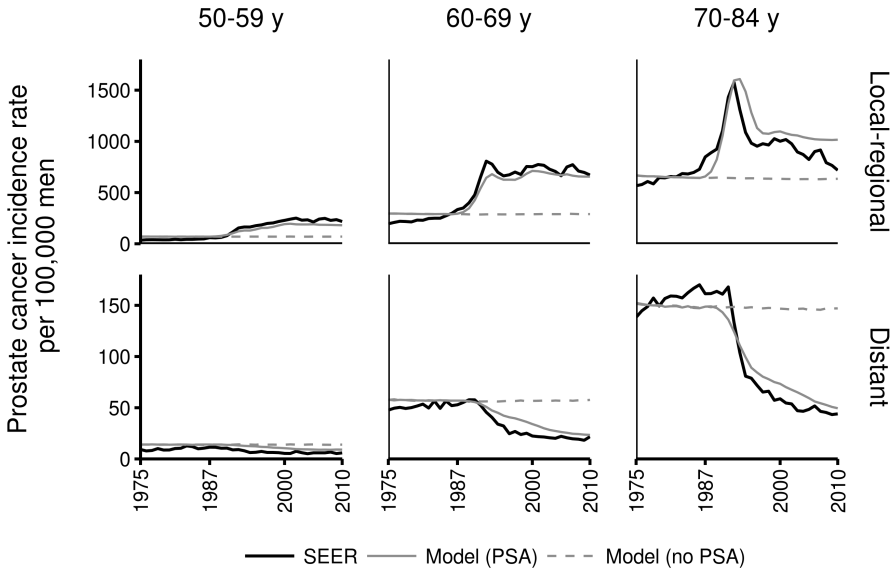

Figure 2 shows observed and projected incidence rates by age at diagnosis, for all races combined and for Black men, with projections partitioned into overdiagnosed and non-overdiagnosed cases.[2]

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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.

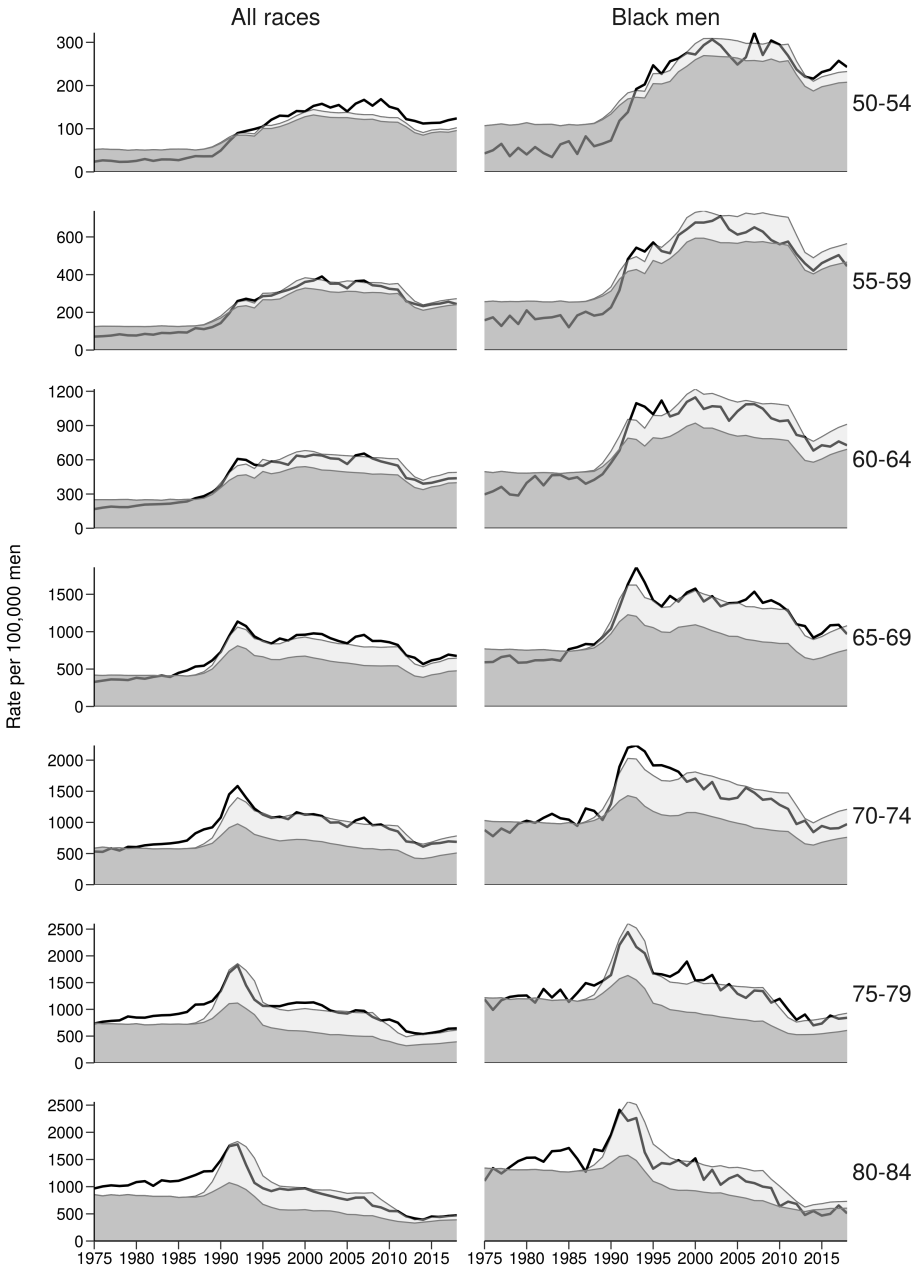

Figure 3 shows observed prostate cancer mortality rates from the National Center for Health Statistics (NCHS) and projections from the PSAPC model with and without screening or changes in care. Because the model does not attempt to replicate the transitory increase in mortality in the early 1990s, modeled 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.

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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.

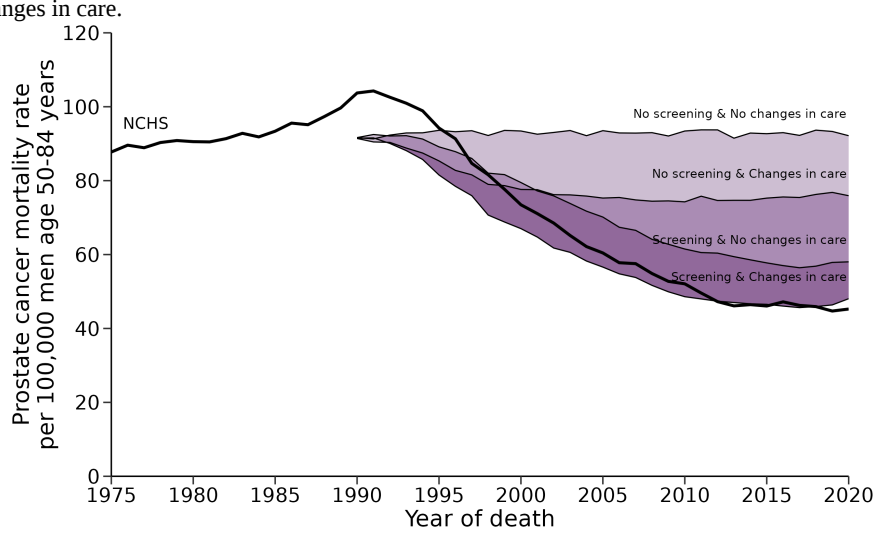

Figure 4 shows observed prostate cancer incidence rates from Surveillance, Epidemiology, and End Results (SEER) and prostate cancer mortality rates from the NCHS and projections from the PSAPC model by race. Model projections for all races were systematically replaced with inputs for Black men to quantify 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.

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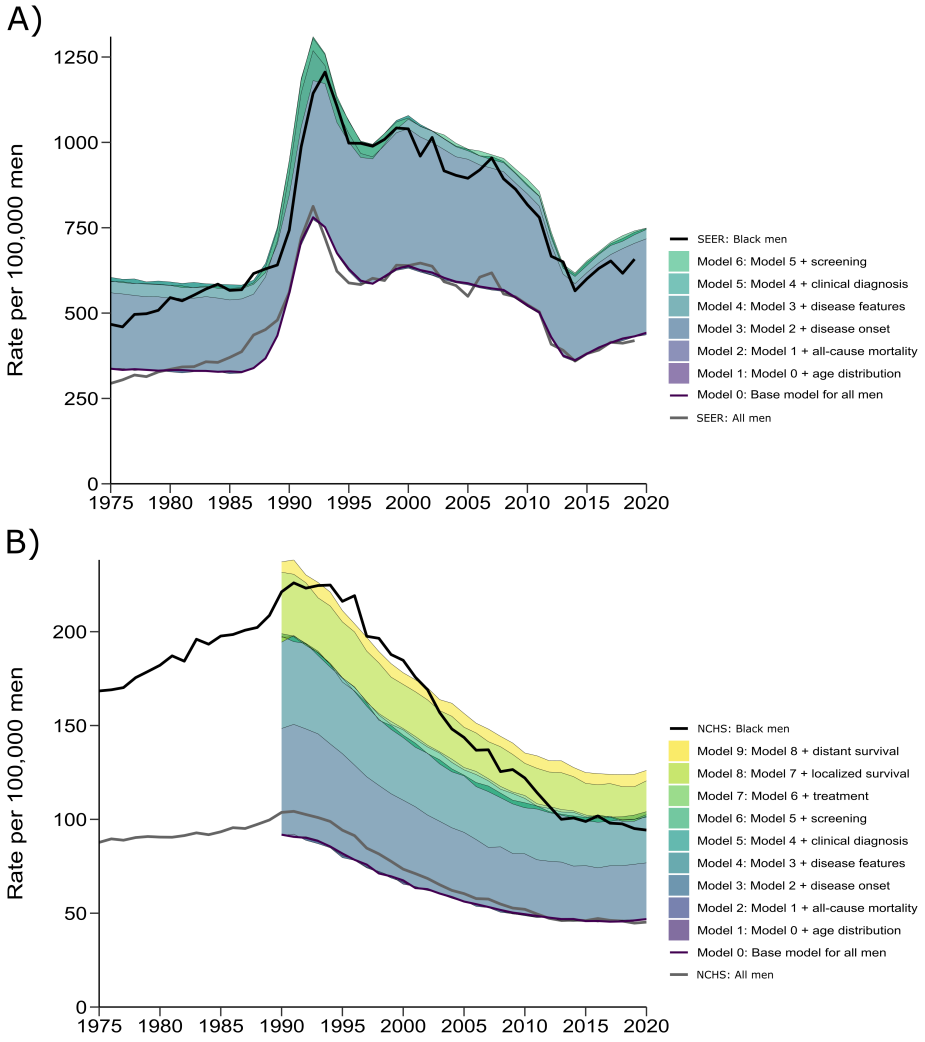
Figure 4. Prostate cancer A) incidence and B) mortality rates for all races and for Black men aged 40-84 years at diagnosis from the Surveillance, Epidemiology, and End Results program and corresponding model projections after sequentially replacing model components for all men with components for Black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

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

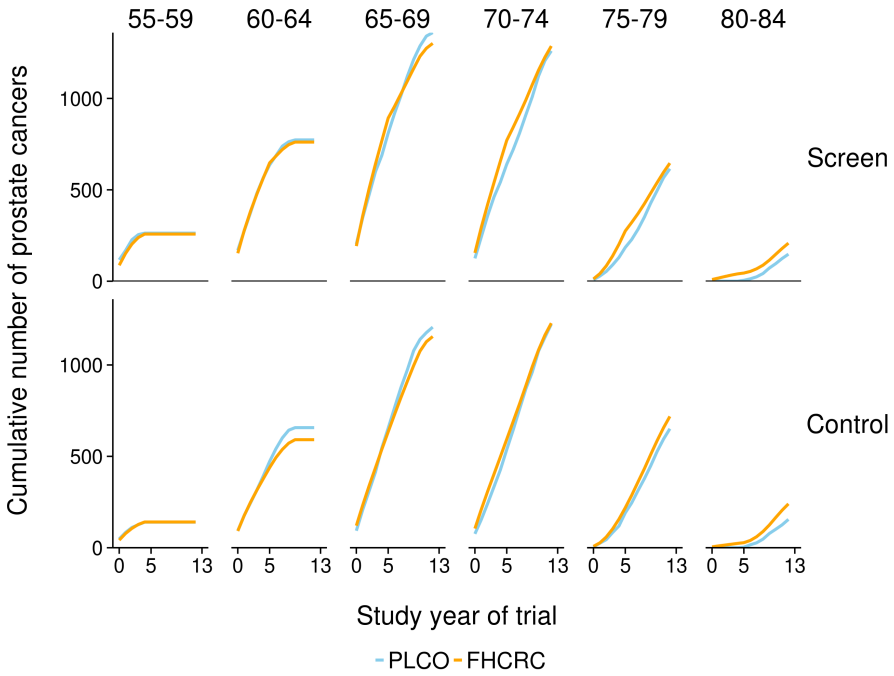
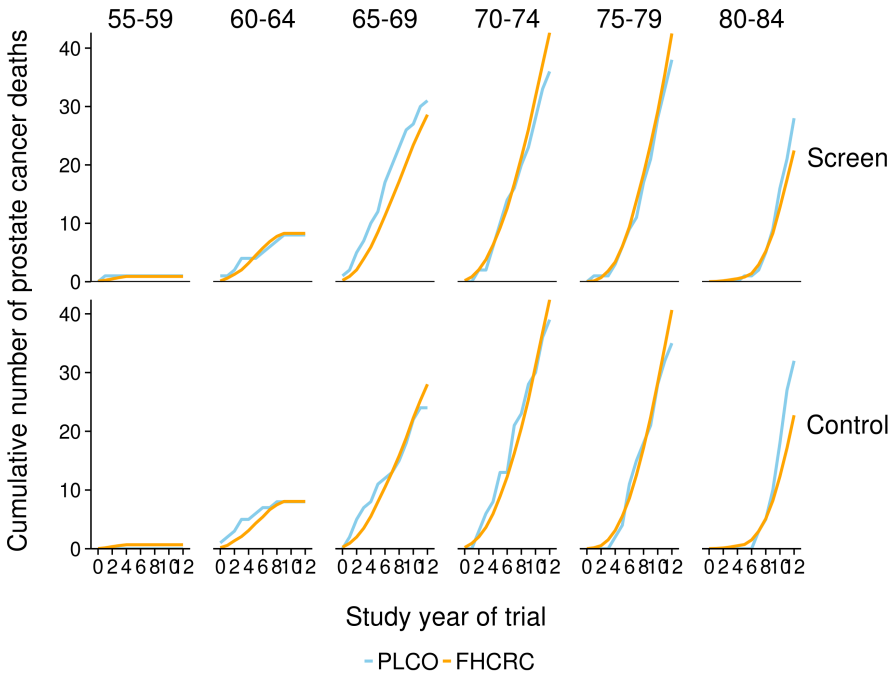


Figure 6 shows observed and projected prostate cancer deaths by arm and age at randomization.

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.

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

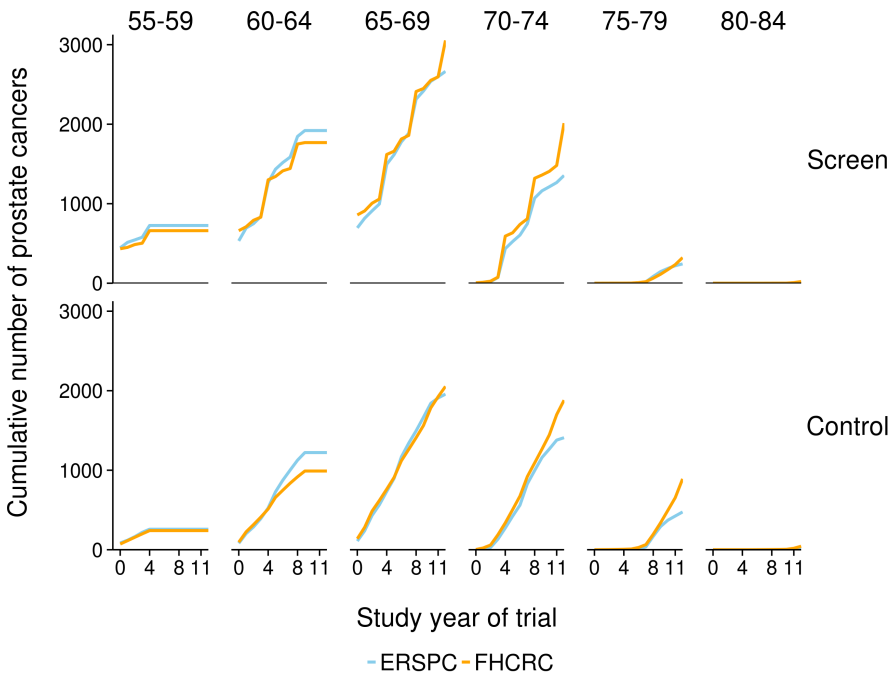
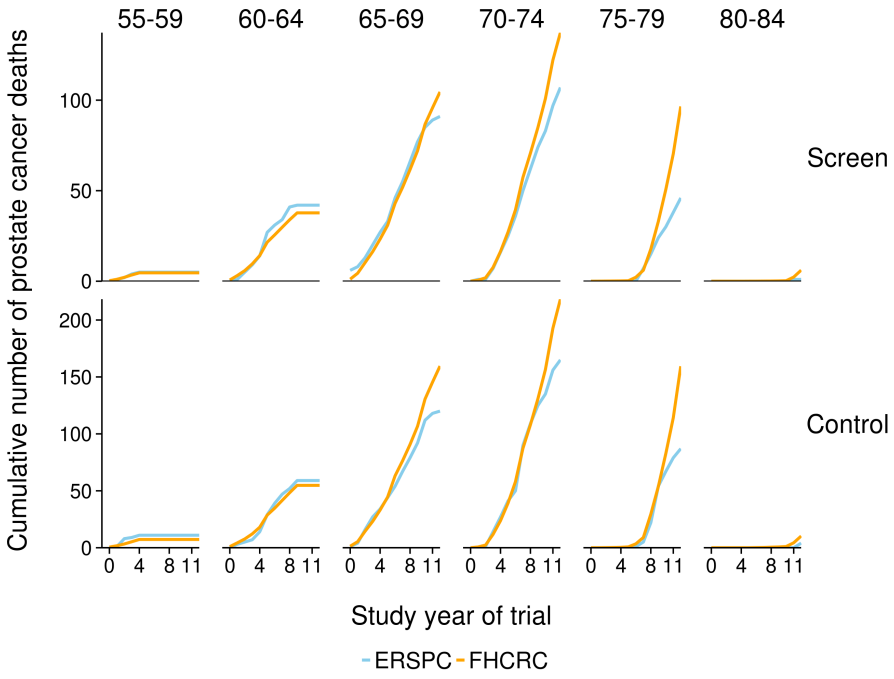


Figure 8 shows observed and projected prostate cancer deaths by arm and age at randomization.

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

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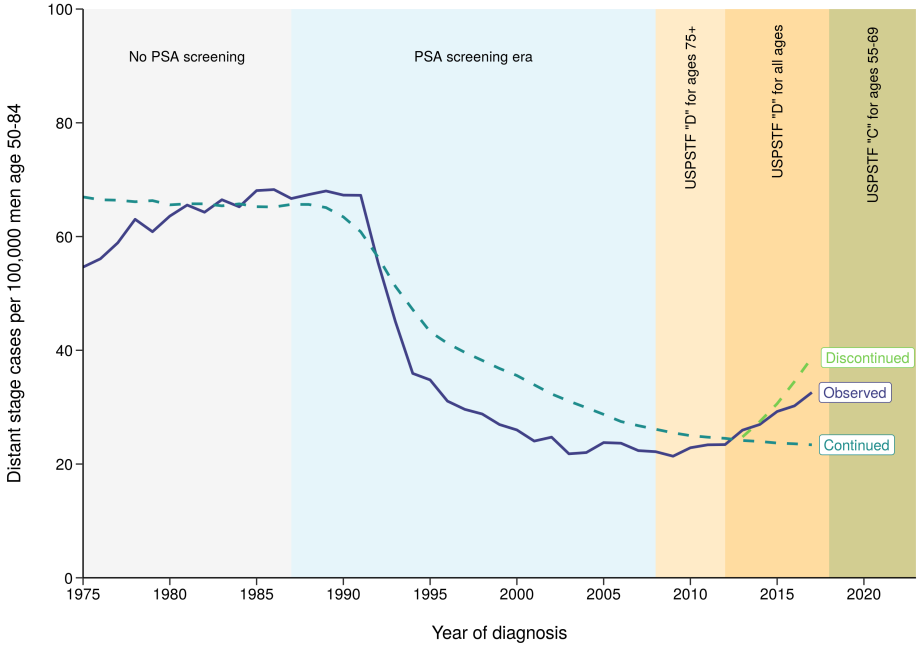
and under completely discontinued screening.[5] A later study examined the plausible role of decreased screening in the subsequent increasing trend in de novo metastatic disease.[6] Figure 9 shows that observed incidence of de novo metastatic disease fell midway between the previously projected extremes.

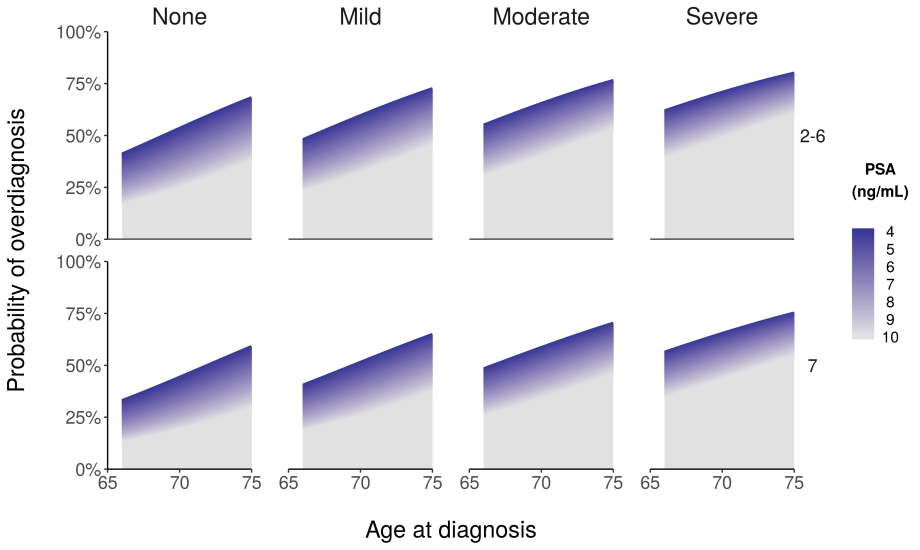
Figure 9. Metastatic prostate cancer incidence rates for men aged 50-84 years from the Surveillance, Epidemiology and End Result program and projections from the PSAPC model under a continuation of historical screening and discontinued screening beginning January 1, 2013.



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.

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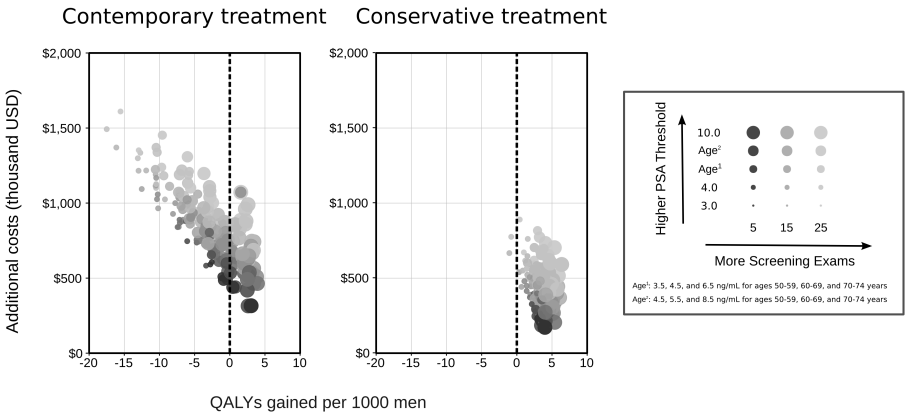
Cost-effectiveness of screening and treatment strategies

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.

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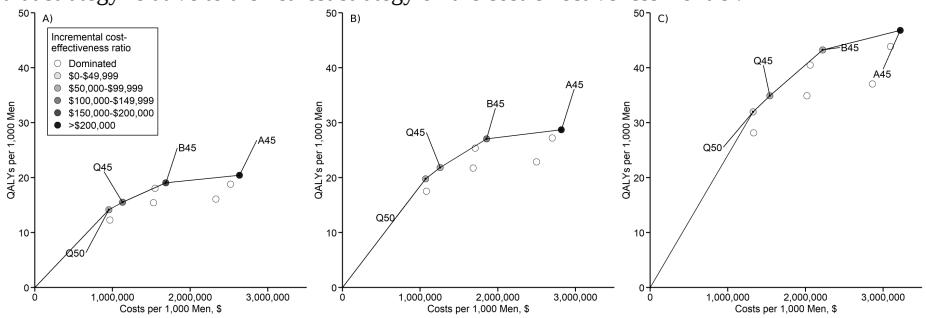
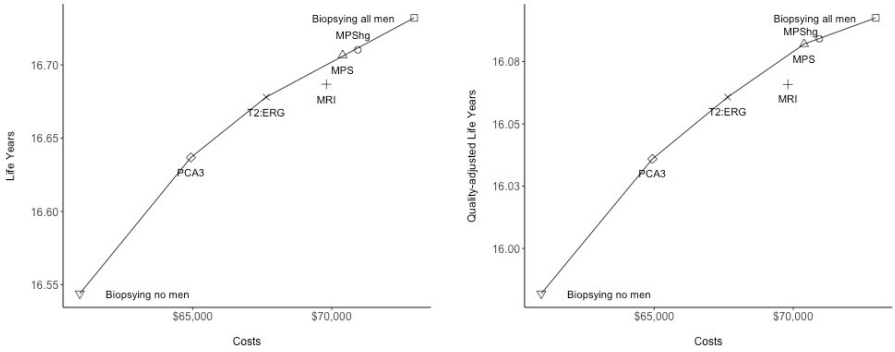
Figure 13. Costs and quality-adjusted life years (QALYs) gained for screening strategies for A) low-, B) intermediate-, and C) high-risk men relative to no screening. Strategy labels indicate frequency (Q=quadrennial, B=biennial, A=annual) and starting age. Only nondominated strategies are labeled; the 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.

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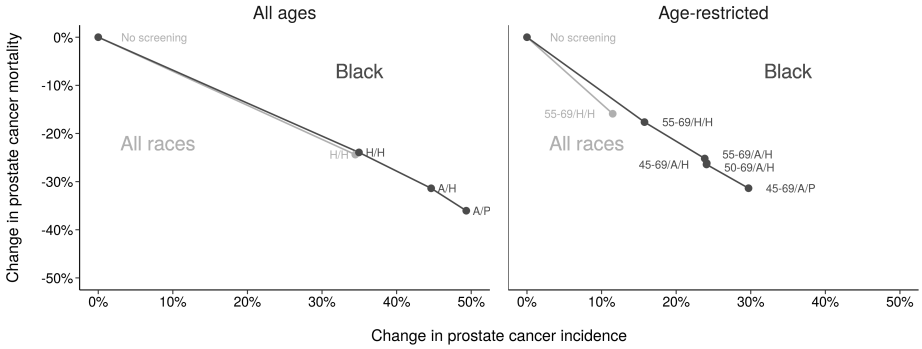
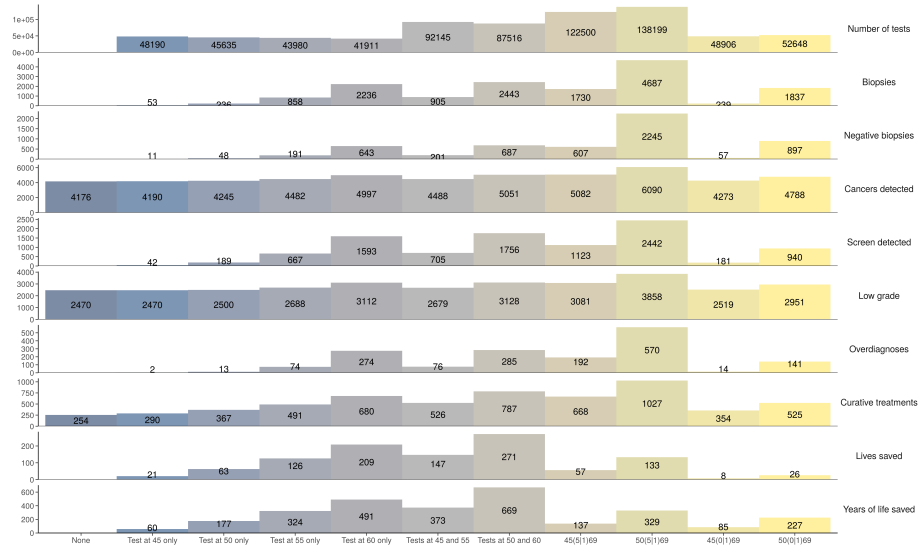
Figure 15. Changes in prostate cancer incidence (overdiagnosis) and mortality under no screening and historical early detection strategies for all races (light gray) and under no screening, historical, and intensified early detection strategies for Black men (dark gray) projected by the PSAPC model. 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.

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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.

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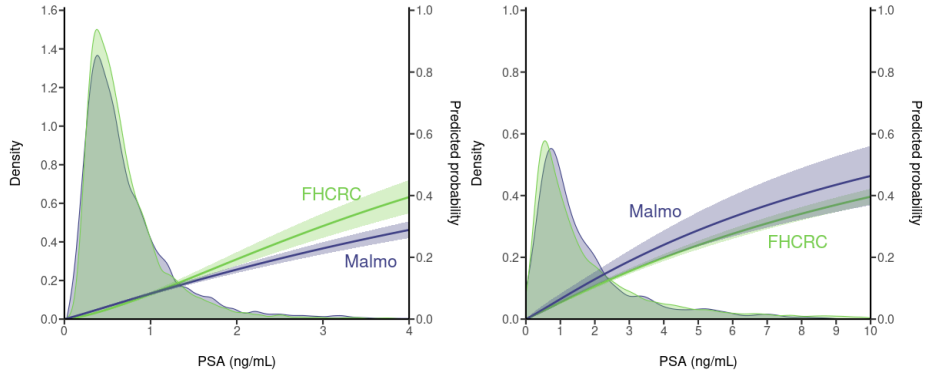
Figure 1. Observed PSA distributions for men ages 44–50 (left) and 60 (right) years at venipuncture and predicted 25-year risk of prostate cancer diagnosis based on empirical analysis of Malmo Preventive Project and corresponding projections from the PSAPC model in the absence of screening.



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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