FRED HUTCHINSON CANCER RESEARCH CENTER (PSAPC)

Important note: This document will be updated periodically. The most current version is available at http://cisnet.cancer.gov/profiles. Note that unlike most PDF documents, the CISNET model profiles are not suitable for printing as they are not typically written or read in sequential fashion.

We recommend you let your interests guide you through this document, using the navigation tree as a general guide to the content available.

The intent of this document is to provide the interested reader with insight into ongoing research. Model parameters, structure, and results contained herein should be considered representative but preliminary in nature.

We encourage interested readers to contact the contributors for further information.

Go directly to the: Reader's Guide.

READERS 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

Definitons and methodologies for the basic model outputs.

Results Overview

A guide to the results obtained from the model.

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

Key References

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

MODEL PURPOSE

SUMMARY

The PSAPC microsimulation model extends our earlier modeling studies of prostate cancer natural history, prostate-specific antigen (PSA) screening, and disease-specific and other-cause mortality in the US population. The extension involves a new modeling approach and an additional component that models the effects of trends in primary treatment on disease-specific mortality. This document describes the main objective of the PSAPC model.

PURPOSE

Our primary objective behind modeling prostate cancer trends is to disentangle the roles of PSA screening and changes in primary treatment patterns in US prostate cancer incidence and mortality trends. While both prostate cancer incidence and mortality rates have continued to fall since the early 1990s, the relative contributions of screening and treatment to the observed declines remain intensely debated.

Early results of two randomized clinical trials of PSA screening were recently released, and unfortunately their findings may have only added to the confusion. 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. The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial involving eight European countries 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; an even greater benefit is observed among men who actually underwent screening. Reconciling the results of these studies will be an important area of future research.

In contrast, only limited information is available concerning the comparative efficacy of primary treatments--conservative management, radical prostatectomy, and radiation therapy with or without androgen deprivation therapy.

In this context, drawing inference about the value of screening versus treatment from observed trends is very challenging. However, the number of people whose lives are directly or indirectly affected by prostate cancer screening and/or diagnosis every day underscores the potential value to be gained from modeling efforts.

MODEL OVERVIEW

SUMMARY

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

BACKGROUND

The original FHCRC CISNET prostate model (PCSIM) provided a direct link between prostate cancer progression and PSA growth. However, while intuitively reasonable, the link could not be tested empirically. In addition, the cross-model dependence of its components and the large number of parameters (over 30) made systematic estimation intractable. 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 original FHCRC CISNET motivated an overhaul and the adoption of a new, simpler, unified, statistically coherent model framework. At its core, the new PSAPC model continues to exploit a linkage between prostate cancer progression and PSA growth. In contrast with the original model formulation, this link can now be examined via formal statistical methods since model parameters that determine disease natural history explicitly depend on PSA levels. 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.

MODEL DESCRIPTION

Data from the Prostate Cancer Prevention Trial[1] and Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial[2] inform the model about individual PSA growth rates. These rates determine individual PSA trajectories and are linked to hazards of cancer progression events in a simulated population. The hazards of cancer progression represent a natural history model that accounts for clinical diagnosis, while the PSA trajectories together with screening dissemination and biopsy patterns account for screen detections. By comparing the total projected number of new cases to observed incidence, we simultaneously estimate the natural history parameters linking PSA with event hazards and calibrate the model to the US population. Once calibrated, we then systematically remove an intervention (or combination of interventions) and compare projected mortality in its presence and its absence to quantify its impact on mortality.

CONTRIBUTORS

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REFERENCES:

[1] Thompson, IM, Goodman, PJ, Tangen, CM, Lucia, MS, Miller, GJ, Ford, LG, Lieber, MM, Cespedes, RD, Atkins, JN, Lippman, SM, Carlin, SM, Ryan, A, Szczepanek, CM, Crowley, JJ, Coltman, CA Jr. "The influence of finasteride on the development of prostate cancer" in N Engl J Med 2003; 349: 3: 214-24

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ASSUMPTION OVERVIEW

SUMMARY

This document describes the core assumptions of prostate cancer natural history in the PSAPC model.

BACKGROUND

The main idea behind the PSAPC model is to link PSA growth with prostate cancer progression. The model is similar to models linking disease progression with tumor growth, but the PSAPC model replaces tumor volume with an observable biomarker, namely PSA. The model consists of two main components: longitudinal PSA growth and transitions between natural history disease states (i.e., healthy, preclinical, clinical, localized, metastatic). The hazards of transitioning from one state to the next are dependent on age or PSA growth.

ASSUMPTION LISTING

PSA GROWTH

We assume:

- PSA growth is log-linear in age
- A changepoint occurs at onset
- PSA growth rates are heterogeneous across individuals

More precisely, we assume PSA grows as follows:

$$\log(y_i(t)) = \beta_{0i} + \beta_{1i}t + \beta_{2i}(t - t_{oi})I(t > t_{oi}) + \varepsilon$$

where

- i indexes subjects
- $y_i(t)$ is PSA at age t
- $I(A)$ is 1 if A is true and 0 otherwise
- $\beta_{0i} \sim N(\mu_0, \sigma_0^2)$
- $\beta_{ki} \sim N(\mu_k, \sigma_k^2)I(\beta_{ki} > 0), k = 1, 2$
- $\varepsilon \sim N(0, \tau^2)$

Note that $N(\mu_k, \sigma_k^2)I(\beta_k > 0)$ represents a truncated normal distribution disallowing negative PSA growth. Estimated PSA growth rates together with between-individual truncated normal distributions are illustrated below. These plots are based on parameters estimated from the control group of the Prostate Cancer Prevention Trial[1] and tuned to validate against results of the initial screening round of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.[2]
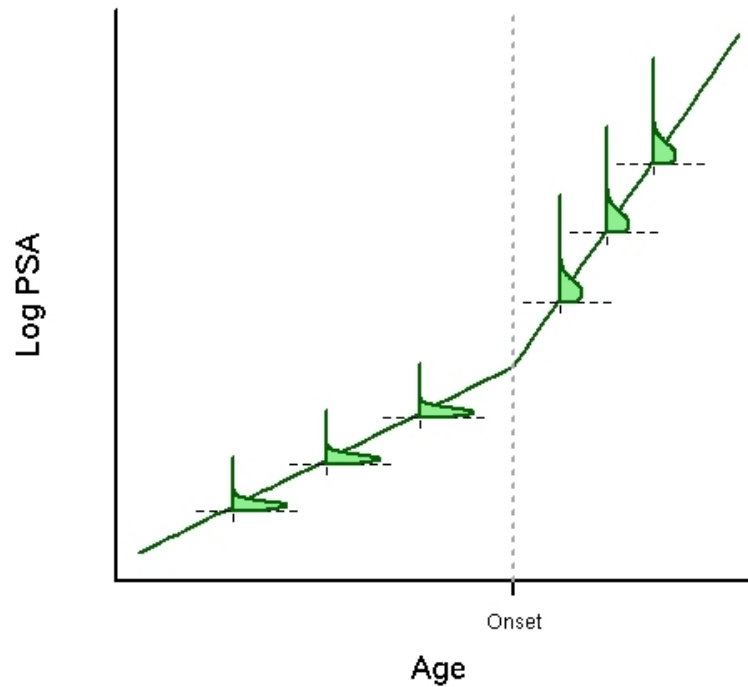

Figure 1. Log-linear PSA growth with truncated normal slopes and changepoint at disease onset.

NATURAL AND CLINICAL HISTORY EVENT HAZARDS

DISEASE ONSET

The hazard of prostate cancer onset is proportional to age:

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

A variant of the model allows this hazard to increase exponentially with age.

Figure 2. Hazard of disease onset.

DISEASE METASTASIS

The hazard of transition from localized to metastatic cancer is:

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

where $\tilde{y}_i(t) = \exp\{\beta_{0i} + \beta_{1i}t + \beta_{2i}(t - t_{oi})I(t > t_{oi})\}$ denotes the individual-specific mean PSA trajectory.
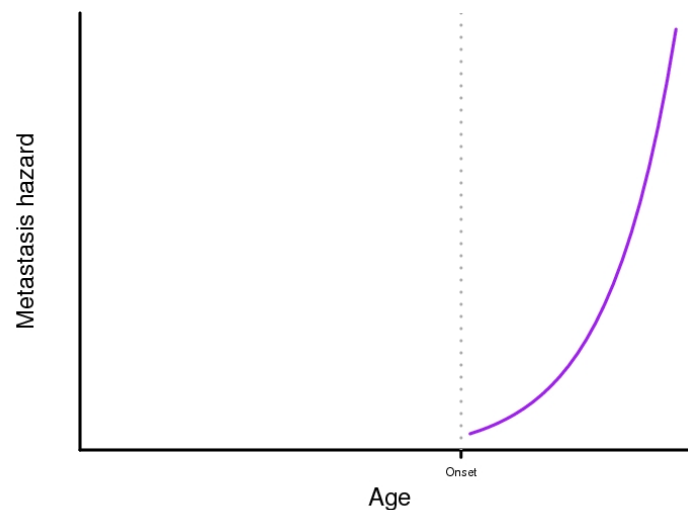

Figure 3. Hazard of progression to advanced stage.

CLINICAL DIAGNOSIS

The hazard of clinical diagnosis before metastasis is:

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Assumption Overview
Additional variants of natural and clinical
history event hazards

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

and after metastasis is:

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

This specification allows for a greater chance that an individual with metastatic cancer will present symptoms and be diagnosed than one with localized disease.
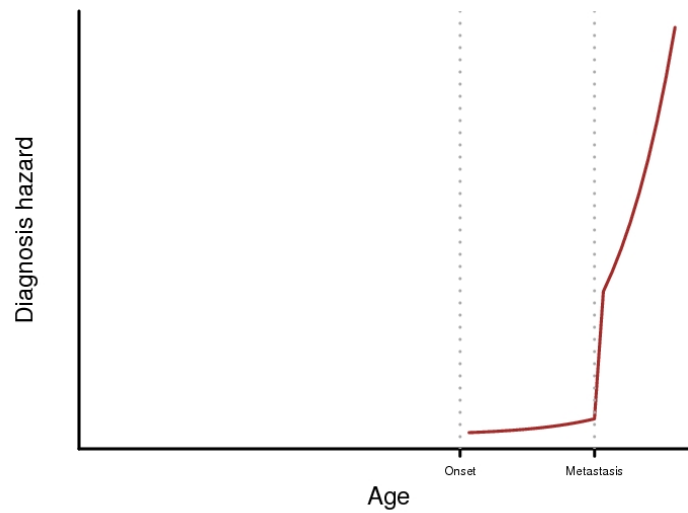

Figure 4. Hazard of clinical diagnosis.

ADDITIONAL VARIANTS OF NATURAL AND CLINICAL HISTORY EVENT HAZARDS

An extended version of the model incorporates disease grade, categorized as low-moderate (Gleason score 2-7) versus high (Gleason score 8-10). This version has the following additional assumptions:

- PSA growth after disease onset differs for cases with high-grade versus low-grade disease, i.e., the distribution of individual-specific PSA growth rates differs for high- versus low-grade cases
- Disease grade is determined at onset and does not change over time
- The transition rate from localized to metastatic disease, given PSA level, depends on grade category. Thus, the hazard of transition from localized to metastatic cancer for low-grade tumors is:

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

and for high-grade tumors is:

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

- The transition rate from preclinical disease to clinical diagnosis given PSA depends on both grade and stage. Thus, the hazard of clinical diagnosis for low-grade tumors before metastasis is:

$$\lambda_c(t) = \gamma_{c_1}\tilde{y}_i(t)$$

for high-grade tumors before metastasis is:

$$\lambda_c(t) = \gamma_{c_2}\gamma_{c_1}\tilde{y}_i(t)$$

for low-grade tumors after metastasis is:

$$\lambda_c(t) = \theta_{c_1}\tilde{y}_i(t)$$

and for high-grade tumors after metastasis is:

$$\lambda_c(t) = \theta_{c_2}\theta_{c_1}\tilde{y}_i(t)$$

REFERENCES:

[1] Thompson, IM, Goodman, PJ, Tangen, CM, Lucia, MS, Miller, GJ, Ford, LG, Lieber, MM, Cespedes, RD, Atkins, JN, Lippman, SM, Carlin, SM, Ryan, A, Szczepanek, CM, Crowley, JJ, Coltman, CA Jr. "The influence of finasteride on the development of prostate cancer" in N Engl J Med 2003; 349: 3: 214-24

[2] Andriole, GL, Levin, DL, Crawford, ED, Gelmann, EP, Pinsky, PF, Chia, D, Kramer, BS, Reding, D, Church, TR, Grubb, RL, Grubb, RL, Izmirlian, G, Ragard, LR, Clapp, JD, Prorok, PC, Gohagan, JK, PLCO Project Team "Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: Findings from the initial screening round of a randomized trial" in J Natl Cancer Inst 2005; 97: : 433-8

PARAMETER OVERVIEW

SUMMARY

This document describes parameters in the PSAPC model.

BACKGROUND

In compiling data for estimating model parameters, our main goal was to obtain data that reflects the US population. For this reason, PSA growth rate parameters are input based on data from the PCPT[1] and PLCO[2], natural and clinical history parameters are estimated via calibration to SEER incidence data, screening dissemination parameters are input based on the NHIS-Medicare PSA data, treatment dissemination data are based on SEER, and biopsy compliance is based on data from the PLCO. All of these data sources reflect either large, population-based surveys or registries or large, population-based trials. Since we do not have large trials in the US comparing initial treatments for prostate cancer, we use data from the Scandinavian trial[3] on radical prostatectomy and selected observational studies to set cause-specific hazard ratios associated with different initial treatment choices. Finally, we base our estimates of biopsy accuracy on a review of relevant literature (see Biopsy Compliance And Accuracy).

PARAMETER LISTING OVERVIEW

PARAMETERS

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

- PSA growth parameters (input; based on analysis of longitudinal PSA data from the PCPT and PLCO)

    ◦ PSA growth intercept (value at age 35) mean and variance across individuals (μ_0, σ_0^2)
    ◦ Pre-onset PSA growth slope mean and variance (μ_1, σ_1^2)
    ◦ Post-onset PSA growth slope mean and variance (μ_2, σ_2^2)
    ◦ PSA noise or within-individual error (τ^2)

- Natural and clinical history parameters (fitted)

    ◦ Onset hazard (γ_o)
    ◦ Metastasis hazard (γ_m)
    ◦ Pre-metastasis clinical diagnosis hazard (γ_c)
    ◦ Post-metastasis clinical diagnosis hazard (θ_c)

- Grade-based model: Additional PSA growth parameters (input)

  ◦ Post-onset PSA growth slope mean and variance for low-grade cases
  ◦ Post-onset PSA growth slope mean and variance for high-grade cases

- Grade-based model: Additional parameters (fitted)

  ◦ Probability a tumor is low grade at onset
  ◦ Metastasis hazard for low-grade cases
  ◦ Metastasis hazard for high-grade cases
  ◦ Pre-metastasis clinical diagnosis hazard for low-grade cases (γ_{c_1})
  ◦ Pre-metastasis clinical diagnosis hazard for high-grade cases (γ_{c_2})
  ◦ Post-metastasis clinical diagnosis hazard for low-grade cases (θ_{c_1})
  ◦ Post-metastasis clinical diagnosis hazard for high-grade cases (θ_{c_2})

- Biopsy parameters (input)

  ◦ Likelihood of referral to biopsy if PSA is below 4.0 ng/ml
  ◦ Biopsy compliance rate, i.e., probability a biopsy is performed if referred; frequencies depend on PSA level and age
  ◦ Biopsy accuracy rate, i.e., probability that a biopsy will detect a tumor if it is present; increases across calendar years
  ◦ Biopsy compliance and accuracy increase to 100% for individuals within δ years of transitioning to metastatic disease

- Survival parameters (input)

  ◦ Hazard of non-prostate cancer death
  ◦ Baseline prostate cancer survival in the absence of treatment
  ◦ Hazard ratios associated with initial treatments, i.e., radical prostatectomy, radiation therapy, and radiation therapy combined with hormones

- Dissemination parameters (input)

  ◦ Screening dissemination: Annual probability of having a PSA test
  ◦ Treatment dissemination: Annual probability of initial treatment choice

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[1] Thompson, IM, Goodman, PJ, Tangen, CM, Lucia, MS, Miller, GJ, Ford, LG, Lieber, MM, Cespedes, RD, Atkins, JN, Lippman, SM, Carlin, SM, Ryan, A, Szczepanek, CM, Crowley, JJ, Coltman, CA Jr. "The influence of finasteride on the development of prostate cancer" in N Engl J Med 2003; 349: 3: 214-24

[2] Andriole, GL, Levin, DL, Crawford, ED, Gelmann, EP, Pinsky, PF, Chia, D, Kramer, BS, Reding, D, Church, TR, Grubb, RL, Grubb, RL, Izmirlian, G, Ragard, LR, Clapp, JD, Prorok, PC, Gohagan, JK, PLCO Project Team "Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial: Findings from the initial screening round of a randomized trial" in J Natl Cancer Inst 2005; 97: : 433-8

[3] Bill-Axelson, A, Holmberg, L, Ruutu, M, Häggman, M, Andersson, SO, Bratell, S, Spångberg, A, Busch, C, Nordling, S, Garmo, H, Palmgren, J, Adami, HO, Norlén, BJ, Johansson, JE, Scandinavian Prostate Cancer Group Study No. 4 "Radical prostatectomy versus watchful waiting in early prostate cancer" in N Engl J Med 2005; 352: 19: 1977-84

COMPONENT OVERVIEW

SUMMARY

This document describes the main components of the PSAPC simulation model in detail.

OVERVIEW

The general steps in estimating the natural history parameters and calibrating the model to the US population are as follows.

- A simulated population of individuals is generated to match observed male population counts by age and year. As a consequence of the generation scheme, each simulated individual has a date of birth and a date of all-cause death. Simulated individuals are then randomly assigned PSA growth rates, ages at natural and clinical history events, ages at which PSA screening occurs, and screen-specific biopsy compliance and sensitivity indicators.

- Simulated individual natural and clinical history time courses are followed to determine whether they are screen detected, clinically diagnosed, or neither. In other words, individuals are aged forward and undergo disease progression and screening with each event determining future possible event paths (so that, for example, individuals that are clinically diagnosed do not undergo subsequent screening). Screened individuals are recommended to biopsy if their PSA exceeds 4.0 ng/ml; biopsy occurs based on a biopsy compliance indicator, and the biopsy detects cancer in individuals who have had disease onset based on a biopsy sensitivity indicator. Diagnosed individuals are assigned an initial treatment and, as a consequence of the treatment assignment, a new age at death due to prostate cancer is generated. The earlier of the individual's ages at all-cause and cause-specific death is taken as the true age at death.

- Counts of individuals that are screen detected or clinically diagnosed are then tallied by age, year, and stage at diagnosis. Similarly, counts of prostate cancer death and all-cause death are tallied by age and year at death.

- Projected counts are compared with observed incidence counts by age, year, and stage at diagnosis in a Poisson likelihood. A variant of the Nelder-Mead algorithm for stochastic maximum likelihood[1] is used to estimate model parameters and to calibrate the model to observed incidence data. To account for Monte Carlo error, model parameters are re-estimated for multiple random number seeds.

COMPONENT LISTING

POPULATION GENERATION, PSA GROWTH, AND NATURAL/CLINICAL HISTORY

- Population Generation
- All Cause Mortality
- Psa Growth
- Natural And Clinical History

PSA AND DRE SCREENING

- Biopsy Compliance And Accuracy
- Dre Detections

CLINICAL PRESENTATION AND SCREEN DETECTION

- Treatment Distributions
- Cause Specific Mortality
- Treatment Efficacy

CLINICAL PRESENTATION AND SCREEN DETECTION

- Model Estimation

REFERENCES:

[1] Spall, J "Introduction to stochastic search and optimization: Estimation, simulation, and control" 2003;

OUTPUT OVERVIEW

SUMMARY

This document describes the main outputs of the PSAPC microsimulation model.

OVERVIEW

The main outputs of the PSAPC model are as follows:

- Projected incidence by age, year, stage, grade, and mode of detection.
- Overdiagnosis rates by age and year of diagnosis. An individual is overdiagnosed if he is screen detected but would not have been clinically diagnosed in his lifetime.
- Mean lead time (time from screen detection to clinical diagnosis). We calculate three definitions of lead times:

  ◦ **Relevant** lead times are calculated only for non-overdiagnosed individuals, i.e., individuals for which age at clinical diagnosis precedes age at death.

  ◦ **Censored** lead times are 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 are calculated for both non-overdiagnosed individuals and for overdiagnosed individuals. The lead times for overdiagnosed individuals are not censored at death from other causes.

- Mean sojourn time (time from disease onset to clinical diagnosis) for the three corresponding definitions.
- Five-, 10-, 15-, and 20-year survival by age and stage at diagnosis for men diagnosed in 2000.
- Mortality by age and year at death and cause of death. Mortality projected under basecase settings compared with that under a given intervention (or combination of interventions) is the main way in which we quantify the intervention's impact.

RESULTS OVERVIEW

SUMMARY

This document outlines PSAPC results.

RESULTS LIST

- Projected Incidence

- Lead And Sojourn Times

- Over Diagnosis

BIOPSY COMPLIANCE AND ACCURACY

BIOPSY COMPLIANCE

Each subject is assigned a profile of discrete uniform random draws that indicate whether he will comply with referral to biopsy and whether a biopsy is sensitive enough to detect existing cancer at each screen.

Biopsy compliance rates vary by age and PSA level based on PLCO trial data illustrated below.[1] Note that to reflect the use of diagnostic PSA testing for metastatic and symptomatic cases, we force biopsy compliance to be 100% when an individual is within $\delta = 2$ years of transitioning to metastatic disease.
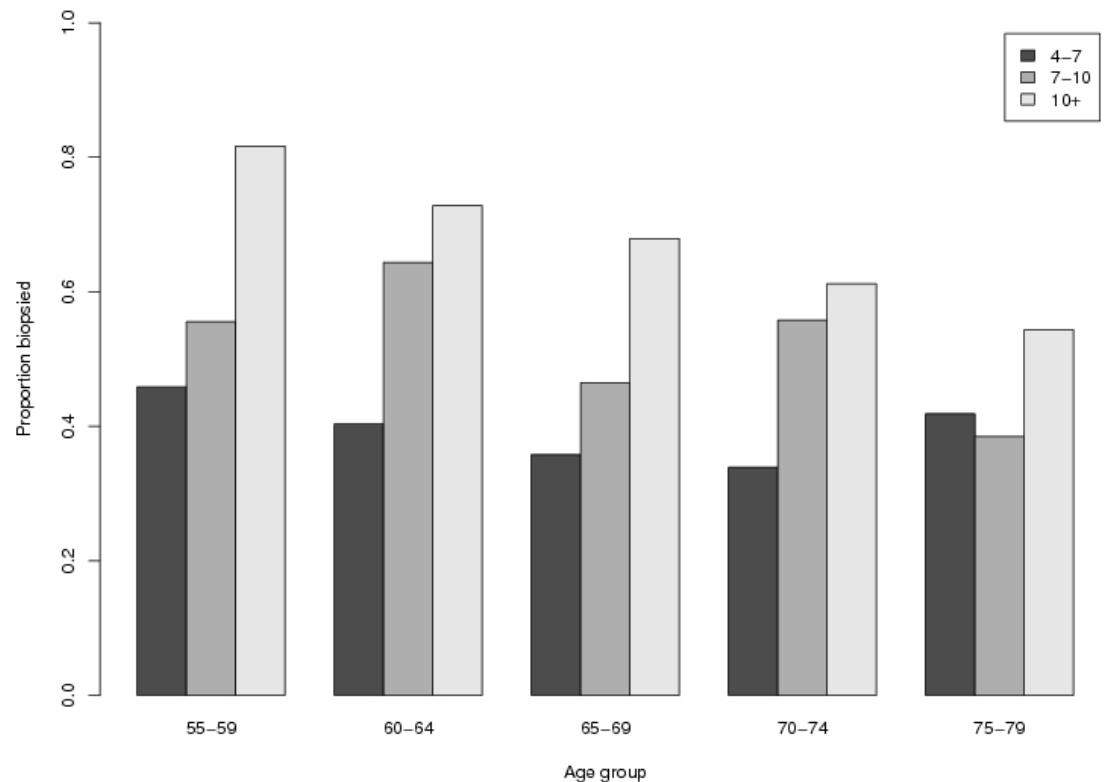

Figure 7. Biopsy compliance rates by age and PSA level.

BIOPSY SENSITIVITY

Biopsy sensitivity is based on a literature review of how biopsy schemes have changed over the time period considered.[8] Based on these studies we assume:

- Sensitivity increases linearly with the number of cores

- 6-core sensitivity is 80% sensitive

- 8+ cores are 100% sensitive

- The proportion of 6-core scheme decreases linearly after 1995 in favor of 8+ cores

The middle blue line pictured below reflects average biopsy sensitivity rates. (The other lines represent alternative sensitivity patterns to be considered when investigating the robustness of model projections.) As for biopsy compliance, to reflect the use of diagnostic PSA testing for metastatic and symptomatic cases, we force biopsy sensitivity to be 100% when an individual is within $\delta = 2$ years of transitioning to metastatic disease.
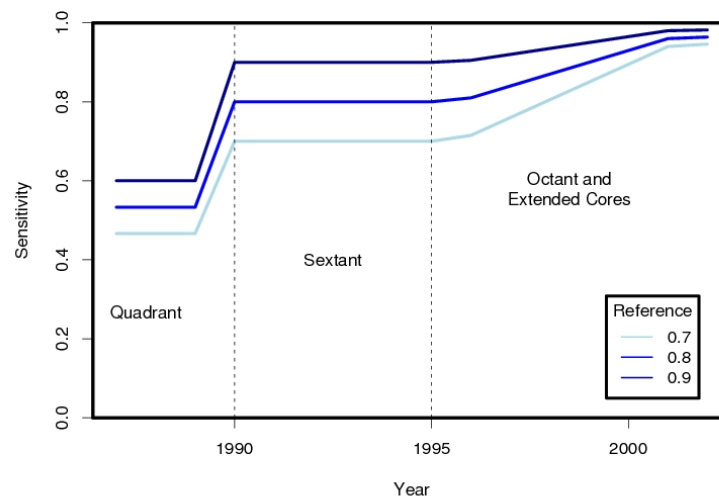

Figure 8. Biopsy sensitivity rates by calendar year.

REFERENCES:

[1] Pinsky PF, Andriole GL, Kramer BS, Hayes RB, Prorok PC, Gohagan JK "Prostate biopsy following a positive screen in the Prostate, Lung, Colorectal and Ovarian cancer screening trial" in J Urol 200 173: 3: 746-50

[2] Hodge KK,, McNeal JE,, Terris MK,, Stamey TA "Random systematic versus directed ultrasound guid transrectal core biopsies of the prostate" in J Urol 1989; 142: : 71-5

[3] Stamey TA "Making the most out of six systematic biopsies" in Urology 1995; 45: 1: 2-12

[4] Norberg M,, Egevad L,, Holmberg L,, Sparen P,, Norlen BJ,, Busch C "The sextant protocol for ultrasound-guided core biopsies of the prostate underestimates the presence of cancer" in Urolog 1997; 50: : 562-6

[5] Babaian RJ,, Toi A,, Kamoi K,, Troncoso P,, Sweet J,, Evans R,, Johnston D,, Chen M "A comparative analysis of sextant and an extended 11-core multisite directed biopsy strategy" in J Urol 2000; 16. 152-7

[6] Klein EA,, Zippe CD "Editorial: Transrectal ultrasound guided prostate biopsy—defining a new standard" in J Urol 2000; 163: 179-80

[7] Presti JCJ, Chang JJ, Bhargava V, Shinohara K "The optimal systematic prostate biopsy scheme shoul include 8 rather than 6 biopsies: Results of a prospective clinical trial" in J Urol 2000; 163: 1: 163-6

[8] Eichler K,, Hempel S,, Wilby J,, Myers L,, Bachmann LM,, Kleijnen J "Diagnostic value of systematic biopsy methods in the investigation of prostate cancer: A systematic review" in J Urol 2006; 175: 1605-12

POPULATION GENERATION

POPULATION GENERATION

The target population for drawing inference is SEER 9 men (all races) aged 50-84 in 1975-2000 by single-year age group and calendar year. However, we also model younger ages (i.e., 20-49) and earlier years (i.e., 1950-1974) in order to improve the quality of the model calibration to the target population trends.

The population is generated by creating simulated individuals to populate observed male counts in the observed age-year table one birth year cohort at a time. For each individual in each cohort, we generate a cohort-specific age at all-cause death derived from US life tables. While alive, the individual ages along the cohort-specific diagonal strip of the table contributing to the counts in those cells (birth year 1895 is shown in the figure below). This generation process is repeated until the count in the first calendar year matches the observed total. The process continues along the diagonal with deficits between generated and observed totals filled by new individuals. In practice, we observe only deficiencies and no surpluses, reflecting net immigration into the SEER 9 catchment areas.
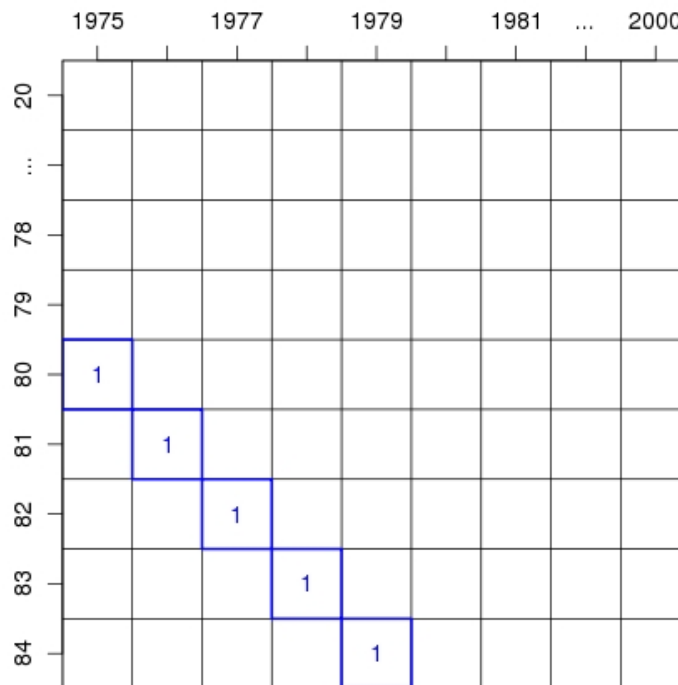

Figure 5. Generating individuals to match observed population counts.

In practice, observed counts are partitioned into many (typically 100) subpopulations that sum to the observed counts. This multi-subpopulation representation allows us to simulate the full SEER 9 population while constraining the number of simulated individuals in memory at any point in time.
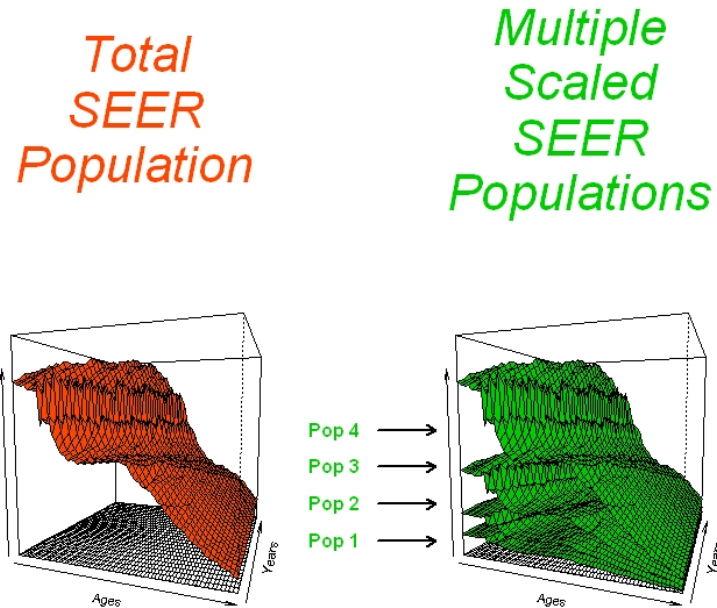

Figure 6. Partitioning full population into sub-populations.

ALL CAUSE MORTALITY

ALL-CAUSE MORTALITY

All-cause annual mortality from NCI (based on US life tables from the Berkeley Mortality Database) for ages $0\text{-}119$ and years $1950\text{-}2000$ were converted to cohort tables for birth years $1900\text{-}2000$. Birth-year-specific annual hazards ($h_y(t)$) were then converted to cumulative distribution functions ($F_y(t)$) using the standard relationship:

$$F_y(t) = 1 - \exp\left\{-\sum_{k=0}^{t} h_y(k)\right\}$$

where $y = 1900, \ldots, 2000$. The CDF for year 1900 ($F_{1900}(t)$) was then assumed for years $1865\text{-}1899$. To ensure death by age 120 we set $F_y(120) = 1$.

PSA GROWTH

PSA GROWTH

Each subject is assigned a profile of normal and truncated normal random draws that determine his PSA at a reference age, PSA growth rates, and PSA noise at screen and natural and clinical history events.

PSA growth

One normally distributed random draw is used to generate PSA at age 35; this serves as the intercept for log-linear PSA growth over his lifetime; mean PSA at this age is 0.2 ng/ml. A series of normally distributed random draws are used to generate PSA noise at each screen and at each natural and clinical history event.

Long lists ($n = 50000$) of truncated normally distributed draws are randomly sampled and assigned to represent individual-specific PSA growth rates. The means and variances of these random variates are based on a Bayesian mixed model fit to longitudinal PSA growth curves from the Prostate Cancer Prevention Trial (PCPT).[1] We use PCPT interim case data for individuals with at least 3 PSA tests.

REFERENCES:

[1] Inoue, L, Etzioni, R, Morrell, C, Muller, P "Modeling disease progression with longitudinal markers" in Journal of the American Statistical Association 2008; 103: : 259-70

NATURAL AND CLINICAL HISTORY

NATURAL AND CLINICAL HISTORY

Each subject is assigned a profile of continuous uniform random draws that determine ages at natural and clinical history events.

Ages at onset, at transition to metastasis, and at clinical presentation are generated using random uniform draws evaluated in inverted survivor functions corresponding to each hazard function (a standard analogue of the well-known inverse CDF method). For example, to generate age at onset, the survivor function is:

$$S_o(t) = \exp\left(-\int_0^t \gamma_o s\, ds\right) = \exp\left(-\frac{\gamma_o}{2}t^2\right)$$

We obtain age at onset for individual i by evaluating the inverted survivor function at random uniform draw u_{oi}:

$$t_{oi} = S_o^{-1}(u_{oi}) = \sqrt{-\frac{2}{\gamma_o}\log(u_{oi})}$$

Given his age at onset, we obtain his PSA at onset using his PSA growth rate parameters and random noise:

$$\tilde{y}_i(t_{oi}) = \exp\left(\beta_{0i} + \beta_{1i}t_{oi} + \varepsilon\right)$$

where the β_{ki} are the individual-specific PSA growth rates and ε is PSA noise at age t_{oi}. Similarly, to generate his age at metastasis, the survivor function is:

$$S_m(t) = \exp\left(-\int_{t_{oi}}^t \gamma_m \tilde{y}_i(s)\, ds\right) = \exp\left\{-\frac{\gamma_m}{\beta_{1i} + \beta_{2i}}\left[\tilde{y}_i(t) - \tilde{y}_i(t_{oi})\right]\right\}$$

and we obtain an age at metastasis corresponding to random uniform draw u_{mi} as:

$$t_{mi} = S_m^{-1}(u_{mi}) = \frac{1}{\beta_{1i} + \beta_{2i}}\left\{\log\left[\tilde{y}_i(t_{oi}) - \frac{\beta_{1i} + \beta_{2i}}{\gamma_m}\log(u_{mi})\right] - (\beta_{0i} + \beta_{2i}t_{oi})\right\}$$

Age and PSA at clinical presentation are generated analogously.

DRE DETECTIONS

DRE DETECTIONS

In one variant of the model, we account for DRE detections by randomly assigning individuals with negative PSA test results to biopsy. The frequency of referral to biopsy among men with PSA below 4 is based on a study by Schröder et al (1998) which found that the sensitivity of DRE is approximately 20% for PSA below 3.0 ng/ml and 40% for PSA from 3.0 to 3.9 ng/ml.[1] Men with a negative PSA who are referred to biopsy are assumed to comply with a frequency that is similar to that among men with a moderately elevated PSA (PSA between 4.0 and 7.0 ng/ml).

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TREATMENT DISTRIBUTIONS

TREATMENT DISTRIBUTIONS

Empirical distributions for treatment choices conservative management (None), radical prostatectomy (RP), and radiation therapy (RT) provide the basis for multinomial random assignment of treatments among individuals diagnosed with local-regional stage disease by grade at diagnosis (Gleason score 2-7 and Gleason 8-10). Similarly, empirical proportions of men receiving androgen deprivation therapy (ADT) form the basis for binomial random assignment by age, year, and grade at diagnosis.[1]

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[1] Tsodikov, A, Solomon, C "Generalized self-consistency: Multinomial logit model and Poisson likelihood" in J Stat Plan Inference 2008; 138: 8: 2380-97

CAUSE SPECIFIC MORTALITY

CAUSE-SPECIFIC MORTALITY

We used Poisson regression models to estimate survival curves for untreated cases. Cause-specific SEER 9 actuarial survival data from SEER*Stat for men diagnosed at ages 50-84 in 1983-1986 were considered as representative of pre-PSA-era survival. Model covariates included age, treatment decisions (None, RT, or RP), stage (local-regional or distant), grade (SEER categories I-II, III-IV, or unknown) at diagnosis, and selected interactions. The models provide reasonable agreement with observed survival and the projected survival curves for men treated conservatively (i.e., not with RP or RT) agree closely with the curves of Albertsen et al. (2005).[1] These survival curves are used as the baseline cause-specific survival for untreated cases. This baseline survival is adjusted using hazard ratios that reflect treatment-specific efficacy for treated cases.

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[1] Albertsen, PC, Hanley, JA, Fine J "20-year outcomes following conservative management of clinically localized prostate cancer" in JAMA 2005; 293: 17: 2095-101

TREATMENT EFFICACY

TREATMENT EFFICACY HAZARD RATIOS

To reflect the benefits of treatment, survival for untreated cases is inflated by hazard ratios to obtain survival for treated cases. For RP we assume a hazard ratio of 0.56 both with and without androgen deprivation therapy.[1] For RT, we conducted an informal survey of expert clinicians. We found general agreement that RT+ADT is believed to be similarly efficacious as RP. RT alone, however, remains worse than RP despite improvements in the early 1990s.

Based on these results, we fix treatment basecase RT+ADT efficacy at 0.56 and set RT efficacy at 0.9 before the 1990s and linear decrease to 0.7 by 1995, where it remains to 2000. RT efficacy trends are summarized in the figure below.
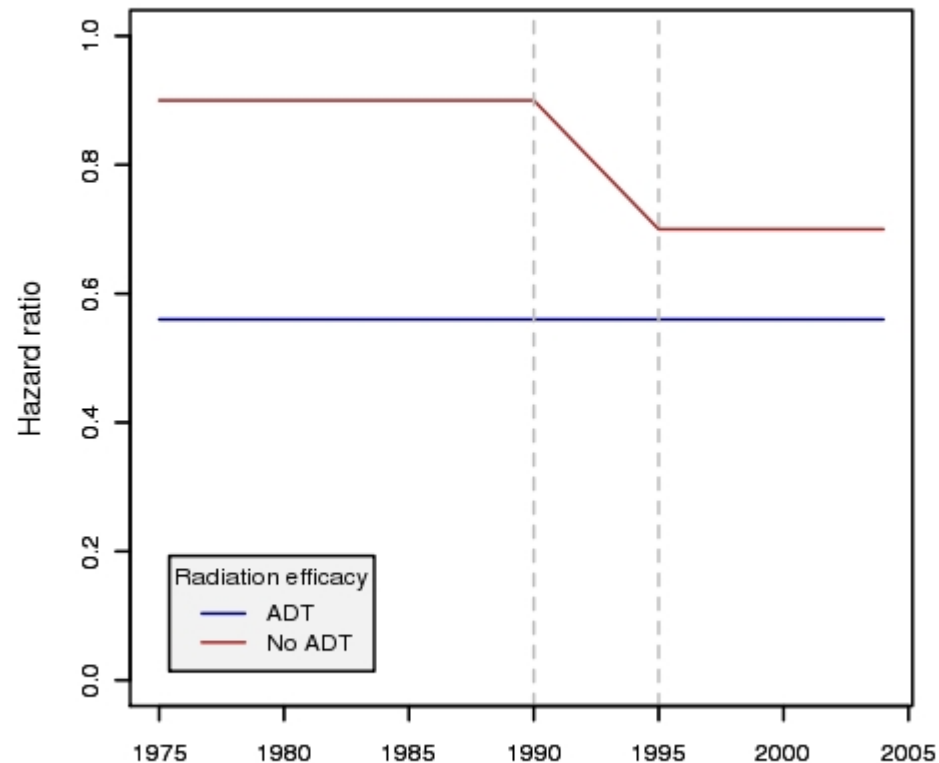
Figure 9. Efficacy of radiation therapy with and without androgen deprivation therapy by calendar year.

REFERENCES:

[1] Bill-Axelson, A, Holmberg, L, Ruutu, M, Häggman, M, Andersson, SO, Bratell, S, Spångberg, A, Busch, C, Nordling, S, Garmo, H, Palmgren, J, Adami, HO, Norlén, BJ, Johansson, JE, Scandinavian Prostate Cancer Group Study No. 4 "Radical prostatectomy versus watchful waiting in early prostate cancer" in N Engl J Med 2005; 352: 19: 1977-84

MODEL ESTIMATION

MODEL ESTIMATION

Subjects' PSA trajectories, disease natural histories, and screening experience yield projected incidence counts by age, year, and stage. Comparing with corresponding observed counts, we estimate parameters by maximizing the log Poisson likelihood:

$$\log L(\mathbf{\Theta} \mid \mathbf{O}, \mathbf{E}) = \sum_{ays} \left[O_{ays} \times \left(1 + \log \frac{E_{ays}}{O_{ays}} \right) - E_{ays} \right]$$

where

- $\mathbf{\Theta} = (\mu_0, \mu_1, \mu_2, \sigma_0^2, \sigma_1^2, \sigma_2^2, \tau^2, \gamma_O, \gamma_A, \gamma_C, \theta_C) \cup \mathbf{\Omega}$
- $\mathbf{\Omega} =$ grade-specific or other model-variant-specific parameters
- $\mathbf{O} =$ SEER 9 observed counts
- $\mathbf{E} =$ model-projected counts
- $a = 20, \ldots, 84$ indexes ages
- $y = 1975, \ldots, 2000$ indexes calendar years
- $s =$ local-regional or distant stages

Maximization is performed using the Nelder-Mead algorithm adapted for stochastic likelihoods[1] based on Bhat, a suite of optimization routines generously provided by Dr. Georg Luebeck.[2]

Note that observed local-regional and distant stage incidence counts are inflated to account for cases with unknown stage. Such unstaged cases are allocated to local-regional or distant stage according to their relative proportions in each age group and calendar year.

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[1] Spall, J "Introduction to stochastic search and optimization: Estimation, simulation, and control" 2003;

[2] Luebeck, G "Bhat: General likelihood exploration"

PROJECTED INCIDENCE

SUMMARY

This documents summarizes projected incidence from the basecase PSAPC model.

RESULT TYPE

Target Simulation

OVERVIEW

Incidence projections reflect the successfulness of calibration of the model to the US population. Our goal is to match as closely as possible observed incidence patterns.

METHODS

Age-adjusted observed and projected incidence trends are presented by stage. Results are based on averages across 20 random seeds and re-estimated natural and clinical history parameters.
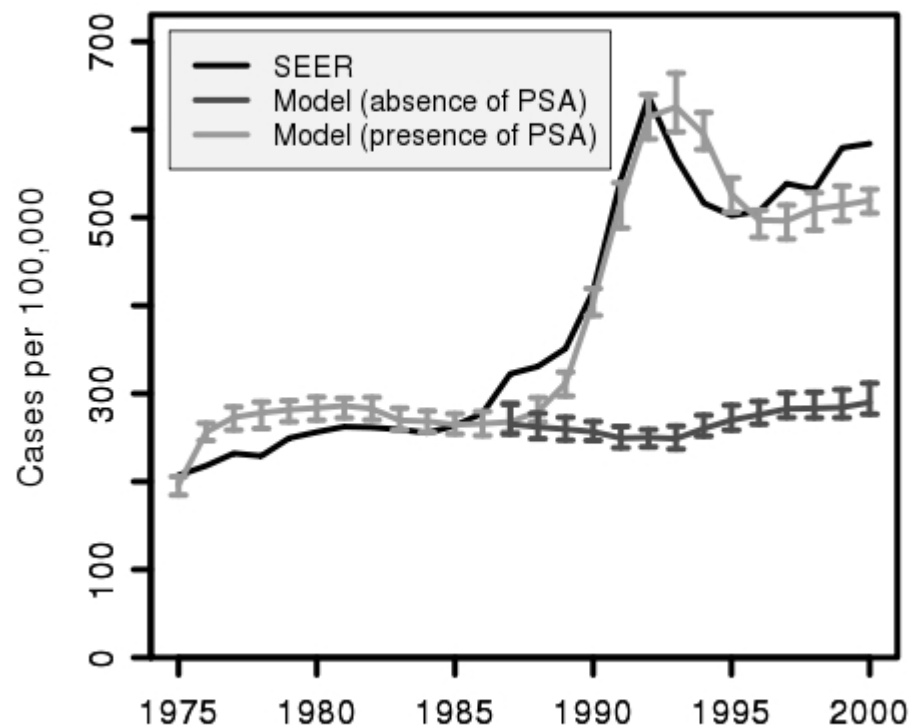
RESULT

Figure 10. Age-adjusted observed and projected local-regional stage incidence.
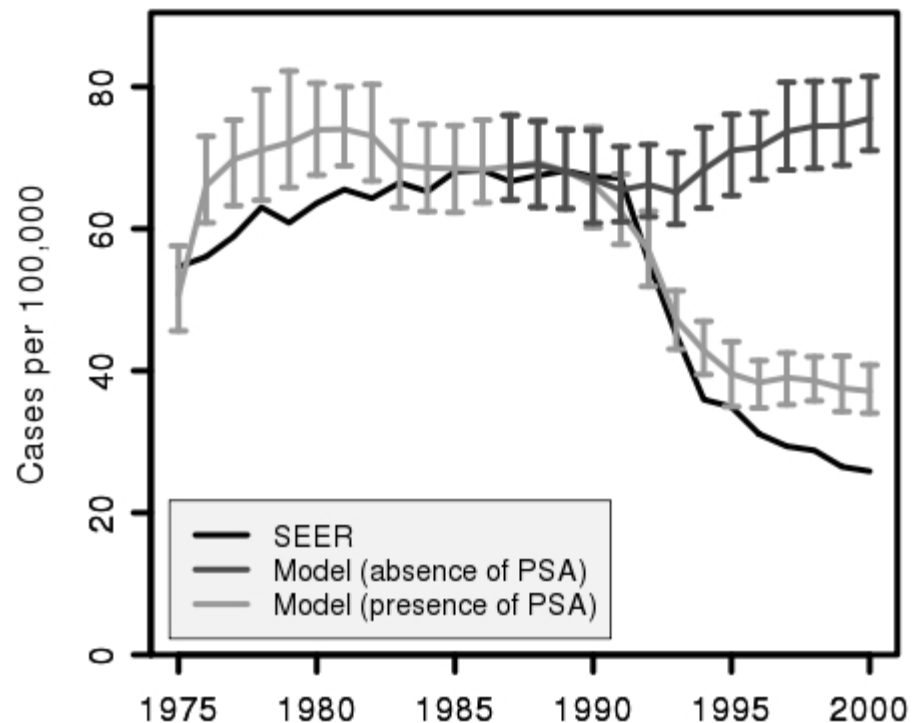
Figure 11. Age-adjusted observed and projected distant stage incidence.

DISCUSSION

Projected incidence matches the general shape of observed incidence rather well. The model overprojects local-regional stage incidence in the pre-PSA era, and the spike following early PSA dissemination is less peaked than observed. The model underprojects distant stage incidence in the late 1980s, then fails to fall as quickly as observed. Difficulty attaining the observed decline in distant stage incidence has been experienced in other modeling frameworks as well.[1]

CONCLUSION

Model projections are imperfect but reasonable considering the simplicity of its assumptions.

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[1] Etzioni R, Gulati R, Falcon S, Penson DF "Impact of PSA screening on the incidence of advanced stage prostate cancer in the United States: A surveillance modeling approach" in Med Decis Making 2008; 28: 3: 323-31

LEAD AND SOJOURN TIMES

SUMMARY

This documents summarizes projected lead and sojourn time results from the basecase PSAPC model.

RESULT TYPE

Validation

OVERVIEW

Lead time represents an important measure of the benefit of screening since it represents the time by which diagnosis is advanced by screening. Since detection of cancer at an earlier stage confers a survival benefit (this is the main argument behind early detection programs), lead times quantify the potential benefit in the context of the cancer's natural history. Sojourn time, reflecting duration of pre-diagnosis disease progression in the absence of screening, provides valuable information concerning this natural history.

METHODS

Note that mean lead and sojourn times are projected based on the basic model variant that excludes DRE screening to avoid confounding PSA screening with DRE screening. *Lead time* is defined as the time interval from screen detection to clinical diagnosis. *Sojourn time* is defined as the time interval from disease onset to clinical diagnosis. Results reported here are averages over 10 runs.

RESULT

Mean lead times by age at PSA detection

Mean lead times by age at PSA detection

Age	Censored	Relevant	Uncensored
50-54	7.77	7.88	8.17
55-59	7.90	8.00	8.67
60-64	7.62	7.70	8.96
65-69	6.98	6.91	8.96
70-74	6.42	6.20	9.31
75-79	6.30	5.44	12.25
80-84	4.59	3.18	11.46
Adjusted	7.13	6.97	9.27
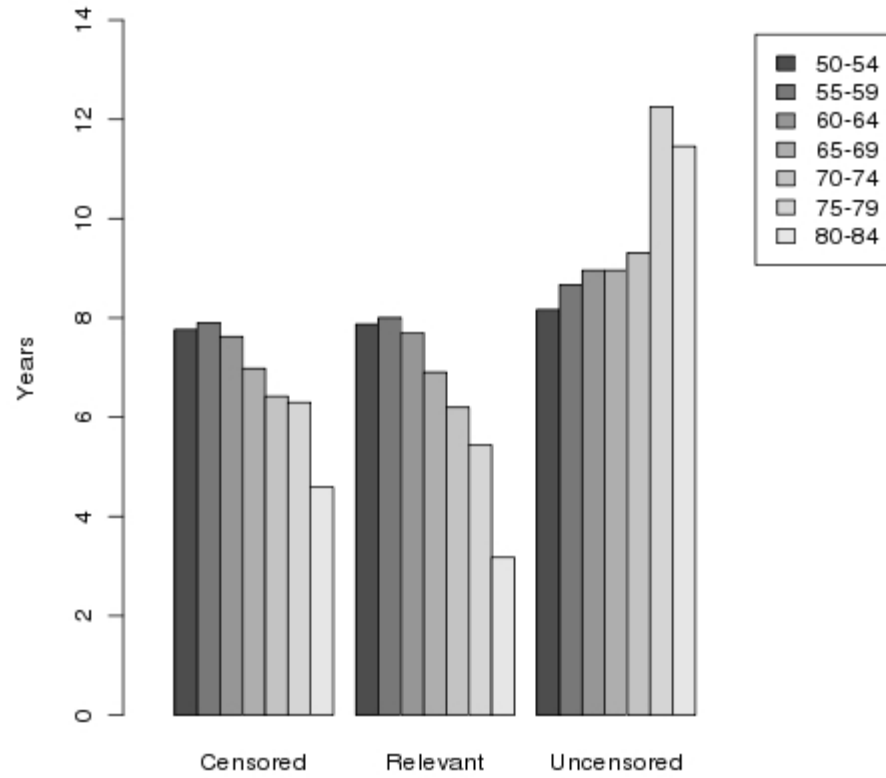
Figure 12. Mean lead times by age group and definition.

	Mean sojourn times by age at onset		
Age	Censored	Relevant	Uncensored
50-54	19.18	18.29	16.84
55-59	16.74	16.27	14.67
60-64	14.30	14.12	12.18
65-69	11.99	11.91	9.66
70-74	9.79	9.62	7.97
75-79	7.69	7.33	6.15
80-84	5.78	5.11	4.51
Adjusted	13.80	13.36	11.77
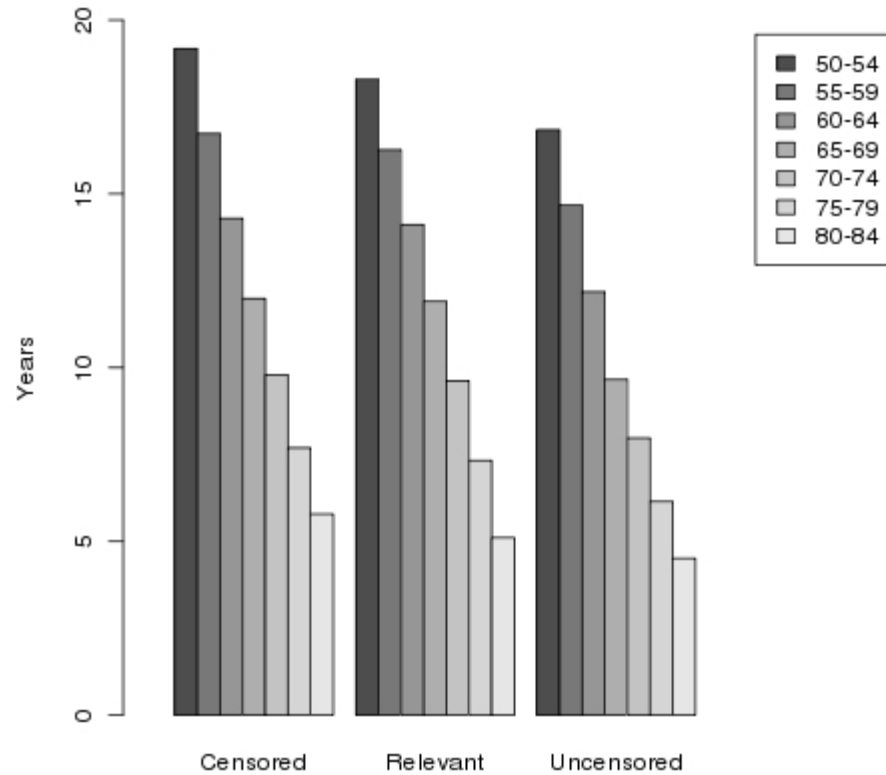
Figure 13. Mean sojourn times by age group and definition.

Mean local-regional stage durations by age at onset			
Age	Censored	Relevant	Uncensored
50-54	12.20	21.53	22.52
55-59	9.70	19.33	19.86
60-64	7.23	16.90	16.70
65-69	5.05	14.41	13.41
70-74	3.58	11.76	11.21
75-79	2.28	8.97	8.77
80-84	1.32	6.17	6.51
Adjusted	7.23	15.95	16.07

Figure 14. Mean local-regional stage durations by age group and definition.

DISCUSSION

Relevant mean lead times are longer for younger men than for older men since the possible intervals until diagnosis narrows with age. Our projections are modestly higher than estimates reported by Gann et al.[1] an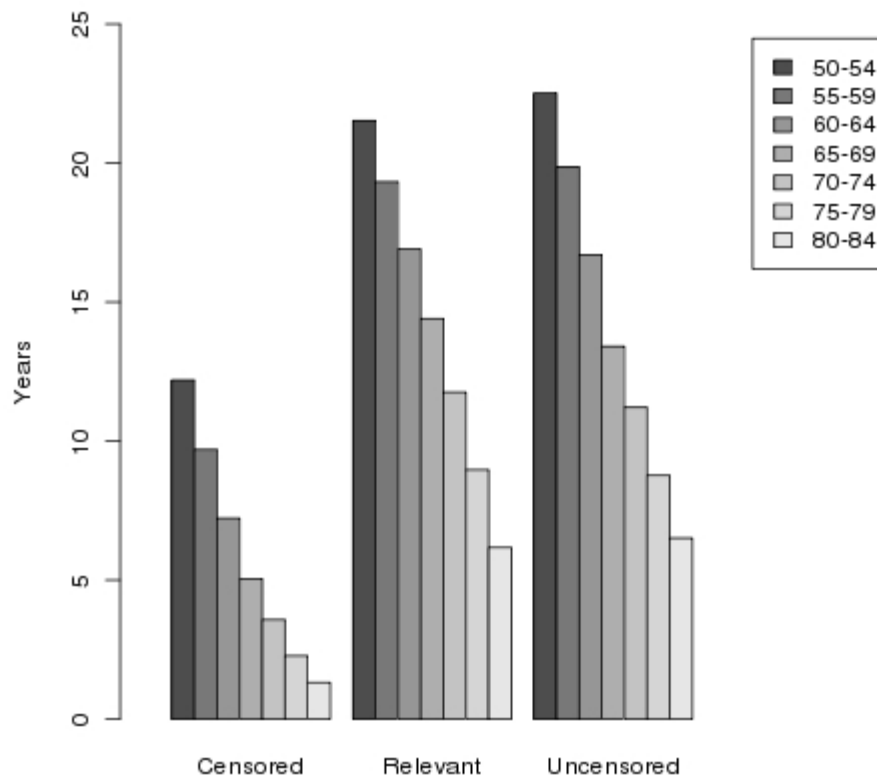d Telesca et al.[2] but considerably lower than those presented by Draisma et al.[3] However, we note that estimates based on data from a European screening trial differ in important ways from the US population setting.[4]

Relevant mean sojourn times around 12 years are consistent with earlier estimates obtain with the original version of the CISNET FHCRC model.[5]

Mean local-regional stage durations for relevant cases is estimated to be approximately 16 years. This estimate is difficult to validate since published literature tend to use a finer staging system than what is available in SEER. These results are nonetheless reported here for completeness.

CONCLUSION

Model-projected mean lead and sojourn times are generally consistent with previously published studies.

RELEVANT PARAMETERS

Validation of lead and sojourn times serves as a check of several model parameters, including the hazard of disease onset and the rate of transitioning to clinical disease.

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[1] Gann PH, Hennekens CH, Stampfer MJ "A prospective evaluation of plasma prostate-specific antigen for detection of prostate cancer" in JAMA 1995; 273: 289-94

[2] Telesca D, Etzioni R, Gulati R "Estimating lead time and overdiagnosis associated with PSA screening from prostate cancer incidence trends" in Biometrics 2008; 64: 1: 10-9

[3] Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RA, Schroder FH, de Koning HJ, "Lead times and overdetection due to prostate-specific antigen screening: Estimates from the European Randomized Study of Screening for Prostate Cancer" in J Natl Cancer Inst 2003; 95: 12: 868-78

[4] Draisma, G, Etzioni, R, Tsodikov, A, Mariotto, A, Wever, E, Gulati, R, Feuer, E, de Koning, H "Lead time and overdiagnosis in prostate-specific antigen screening: Importance of methods and context" in J Natl Cancer Inst 2009; 101: 6: 374-83

[5] Etzioni R, Cha R, Feuer EJ, Davidov O "Asymptomatic incidence and duration in prostate cancer" in Am J Epidemiol 1998; 148: 775-85

OVER DIAGNOSIS

SUMMARY

This documents summarizes projected overdiagnosis rates from the basecase PSAPC model.

RESULT TYPE

Validation

OVERVIEW

An individual is *overdiagnosed* if he is screen detected but would not have been diagnosed in the absence of PSA screening. Overdiagnosis rates represent one of the main drivers of costs associated with PSA screening.

METHODS

The PSAPC counts simulated individuals who are screen-detected but whose date of clinical diagnosis exceeds his date of other-cause death. These overdiagnosis counts are recorded by age, year, and stage. Overdiagnosis rates are calculated by dividing these counts by all diagnoses or by screen detections in each age, year, and stage, aggregating across stages, then age-adjusted to the 2000 US standard million for ages 50-84. Reported overdiagnosis rates are averages over 20 random seeds with re-estimated natural and clinical history parameters.
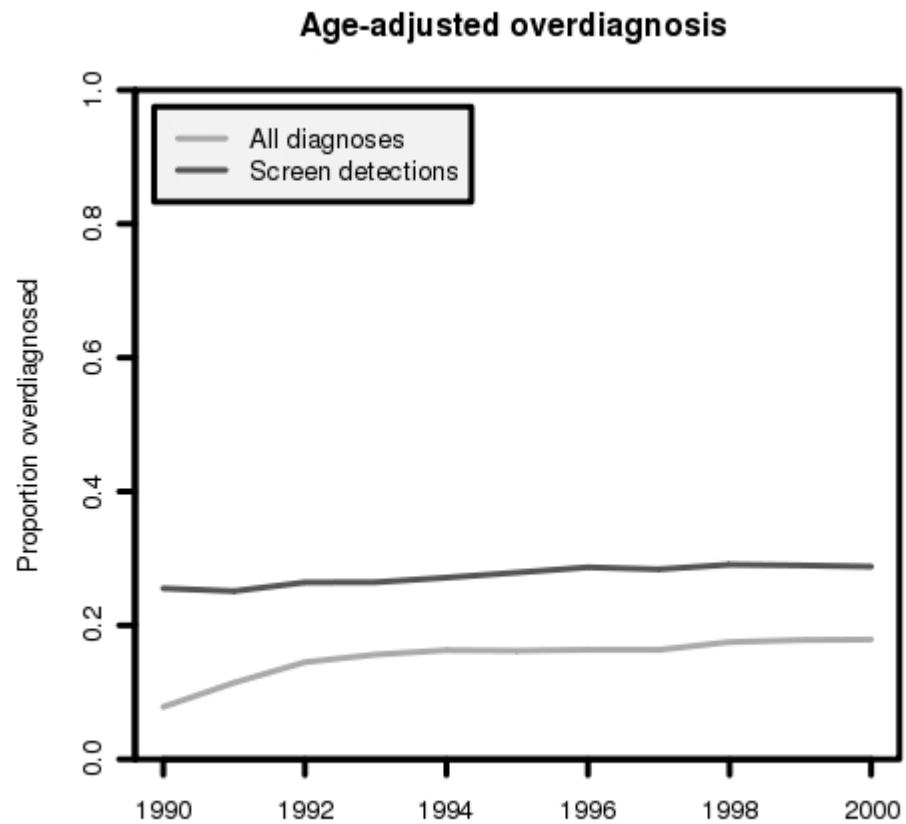
Age-adjusted overdiagnosis
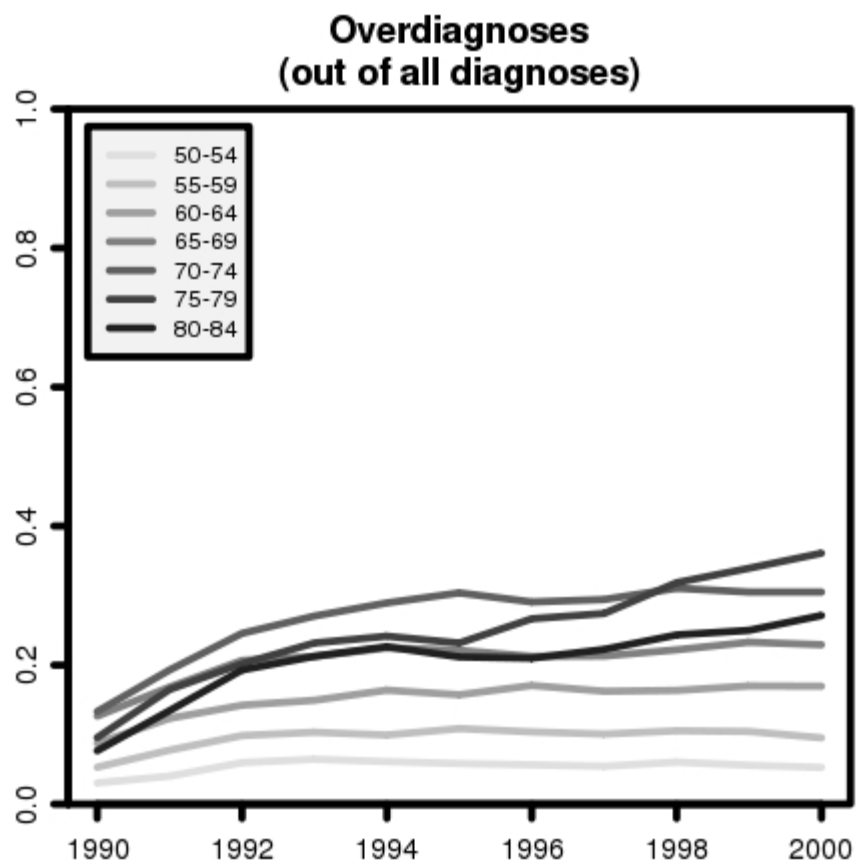

Figure 13. Age-adjusted overdiagnosis rates by calendar year.

Figure 14. Overdiagnosis as fraction of all detections by age group and calendar year.

Overdiagnoses
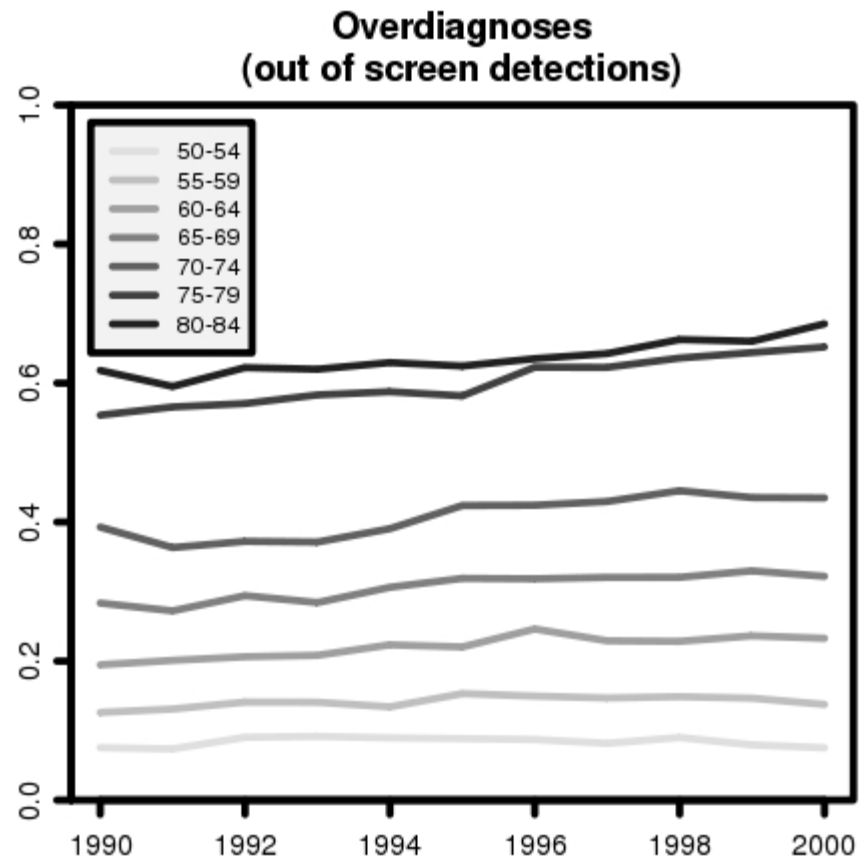## (out of screen detections)

Figure 15. Overdiagnosis as fraction of screen detections by age group and calendar year.

DISCUSSION

Age-adjusted overdiagnosis rates are relatively flat after 1992, about when PSA screening stabilized in the US population. The model projects that each year about 18% of new cases (29% of new screen-detected cases) are overdiagnosed.

The age-specific projections illustrate two intuitive patterns. First, overdiagnosis rates as fractions of screen detections are constant across years, while overdiagnosis rates as fractions of all diagnoses follow PSA dissemination trends, increasing as screening disseminates into the population in the early years then stabilizing in later years. Second, higher overdiagnosis rates are associated with older age groups; this is expected since older men face higher risk of other-cause death each year, so that when these men are detected by screening, it is more likely that other-cause death occurs before they would have presented clinically.

CONCLUSION

Overdiagnosis results exhibit intuitive general features and are consistent with values reported in the literature for the US population.

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