



FLEXKB DOCUMENT
Version: HI.001.10242008.41661
Document generated: 10/24/2008

FRED HUTCHINSON CANCER RESEARCH CENTER (PCSIM)

FRED HUTCHINSON
CANCER RESEARCH CENTER
A LIFE OF SCIENCE

[Readers Guide](#)
[Model Overview](#)
[Assumption Overview](#)
[Parameter Overview](#)
[Component Overview](#)
[Output Overview](#)
[Results Overview](#)
[Validations Overview](#)
[Key References](#)

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

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 to ensure (improve?) model correctness.

Key References

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

Further Reading

These topics will provide an intermediate level view of the model. Consider these documents if you are interested gaining a working knowledge of the model, its inputs and outputs.

Advanced Reading

These topics denote more detailed documentation about specific and important aspects of the model structure



MODEL PURPOSE

SUMMARY

The FHCRC prostate cancer microsimulation is the product of extensive quantitative investigation into prostate cancer natural history, prostate-specific antigen (PSA) production, PSA testing, and disease-specific and other-cause mortality in the US population. This document summarizes FHCRC objectives in developing a prostate cancer microsimulation.

PURPOSE

The objective of the FHCRC prostate cancer model is to quantify the role of PSA screening in US prostate cancer incidence and mortality trends. Prostate cancer incidence and mortality in the US have been declining since the early 1990s. The role of PSA screening in these trends is a subject of intense debate. Information on the efficacy of PSA testing from controlled clinical trials is lacking, and researchers and the public are divided about how much information about the test can be gleaned from the observed trends.

To address the need for a quantitative approach to linking population PSA testing and prostate cancer trends, our primary specific aim is to develop a computer microsimulation model to project the impact of PSA screening on US prostate cancer incidence and mortality. The model will first project population prostate cancer incidence and mortality in the absence of PSA screening. The model will then superimpose dissemination of PSA screening and the modeled population trends will be compared with those observed.

Early detection of prostate cancer is affected not only by the extent of screening but also by the ability of the test to identify latent cancers. This depends on the growth of PSA in prostate cancer cases which has been estimated in several studies. Since these studies yield somewhat inconsistent results, part of our modeling work will be to estimate PSA growth trajectories based on data from retrospective stored-serum studies. The results of this analysis will be used to inform the microsimulation model about PSA growth in men with prostate cancer.



MODEL OVERVIEW

SUMMARY

This document describes the individual components of the microsimulation and discusses the insights to be gained by developing and using the FHCRC prostate cancer screening microsimulation.

PURPOSE

Our primary aim is to estimate the impact of PSA screening on US prostate cancer incidence and mortality. Our approach is to generate disease and clinical histories for individual subjects in both the absence and presence of PSA screening. Comparison of these histories quantifies the impact of PSA screening on prostate cancer overdiagnosis and mortality.

BACKGROUND

Prostate cancer is the most common non-dermatologic male malignancy in the US and the second leading cause of cancer-related mortality in men. Despite the uncertain efficacy of PSA measurement as a tool for early detection of prostate cancer, its use as such has increased dramatically since 1988. By 1994 approximately half of men aged 65 or older in 1987 had had a PSA test¹.

From 1992 to 2004, prostate cancer mortality in the US declined by 35% and the incidence of late-stage disease by 75%. However, while there is a general consensus that PSA screening explains much of the distant-stage decline, there is still considerable debate about its role in the observed mortality trends.

Many studies have explored the connection between PSA screening and prostate cancer mortality declines. Ecologic analyses have been widely used to compare prostate cancer mortality rates across geographic areas with different PSA utilization patterns. However, nearly all these efforts have yielded negative results. For example, prostate cancer mortality rates declined in both England and Wales, but PSA screening use is considerably lower in these countries than in the US. Another study found that prostate cancer death rates were virtually the same in Seattle and Connecticut even though PSA testing, biopsy, and treatment were much more common in Seattle. While concerns have been raised about the validity and interpretation of negative ecologic studies of PSA screening, there is no question that their persistently negative results have influenced both professional and public opinion about the value of the test.

Several investigators have suggested alternative explanations for declining rates of prostate cancer mortality. These include changes in treatment practices such as increases in curative therapy—surgery and radiation—for localized disease and hormone ablation therapy for localized disease or for early recurrence. In the US, the frequency of curative therapy has almost doubled since 1983, and studies have shown that the use of hormone therapy in conjunction with primary radiation therapy in the US increased substantially during the 1990s. Both of these treatment approaches have shown benefit in randomized studies. However, the role of treatment advances in explaining mortality declines also remains unclear.

The value of PSA screening is a pressing question because it carries high costs in terms of overdiagnosis and overtreatment. As results from two screening trials in the US and Europe are not expected for several years, important insights at present must rely on careful examination of the growing knowledge base concerning disease natural history, progression, and mortality. We use mathematical modeling to connect this information and quantify how much of the US prostate cancer mortality decline may plausibly be attributed to PSA screening.

MODEL DESCRIPTION

Dr. Etzioni and colleagues previously developed a model of serial PSA screening². The FHCRC prostate cancer model is an extension of this earlier work. The basic premise of the model is to distinguish cases from the total population simulated and to measure the benefit of stage shifting for the cases that are screen detected. A life history of a hypothetical case is presented in Figure 1.

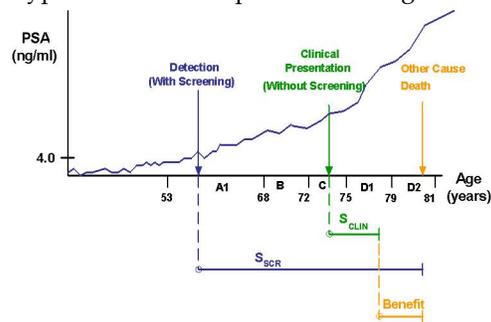


Figure 1. The life history of a hypothetical case, with disease transitions and major events in the absence and presence of screening marked. The difference in endpoints between survival from screen detection (S_{SCR}) and survival from clinical diagnosis (S_{CLIN}) produces the individual benefit due to screening.

The microsimulation generates clinical and disease histories for a hypothetical cohort of men beginning at age 30. The model comprises five basic modules.

Natural history

The *natural history module* generates independent:

1. clinical histories (year of birth, age/stage at diagnosis, age of other cause death), and
2. disease histories (age of asymptomatic onset, stage lengths for disease progression as described by Cowen³ and Whitmore⁵).

We combine data from the Surveillance, Epidemiology, and End Results (SEER) program, the US Census Bureau (USCB), and the National Center for Health Statistics (NCHS) to generate clinical histories. Disease histories are generated by combining data from Etzioni's asymptomatic onset study⁶ with Cowen's disease progression rates³.

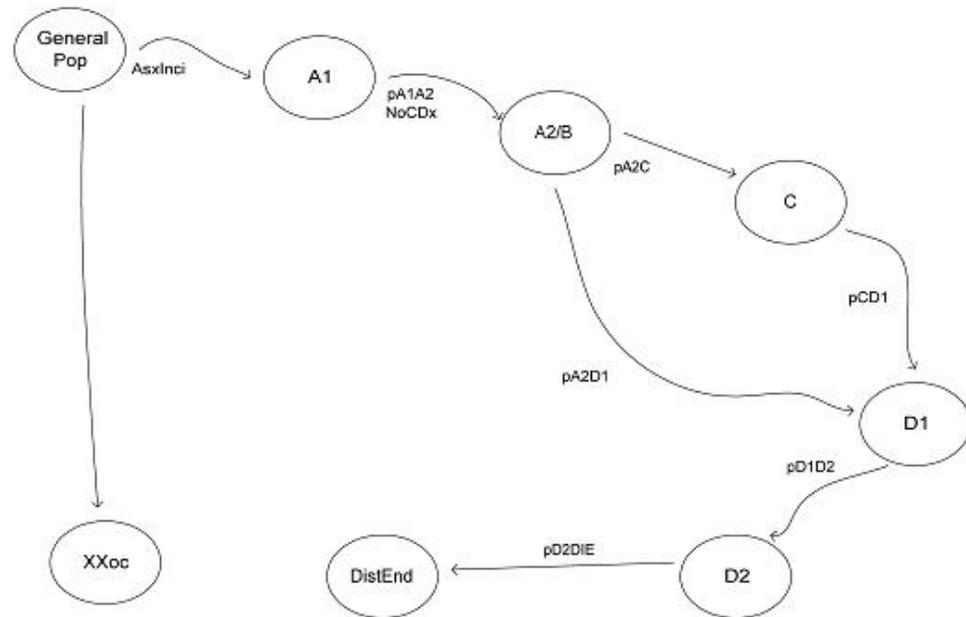


Figure 1. Markov Model diagram for Natural History of Prostate Cancer Onset and Progression. XXoc denotes death due to causes other than prostate cancer. AsxInci denotes asymptomatic incidence which occurs at the transition to stage A1. Transition probabilities (rate parameters for exponential dwelling-time distributions) between the American Urological Association (AUA) pathologic stages as defined by Cowen et al are prefixed with the letter p. NoCDx indicates that clinical diagnosis may be disallowed during the earliest part of stage A1.

Clinical diagnosis The *clinical diagnosis module* matches one disease history with each clinical history, thereby producing a complete disease profile for each hypothetical subject. We have explored several methods for matching disease and clinical histories and determined that uniform random matching, while slower, sidesteps artificial anomalies. The model projections of disease incidence prior to the PSA era (i.e., before 1988) are calibrated to match clinical incidence rates observed in the population.

Serial PSA screening The *screening module* assigns screening events to subjects. Subjects are eligible for a screen if they are alive and have not been previously diagnosed with prostate cancer. Screen dates are assigned based on Mariotto et al⁷. A positive test is defined as PSA > 4.0 ng/ml. We do not model digital rectal exam (DRE) testing.

PSA growth PSA trajectories have different growth rates, dependent on whether the subject is in a cancerous or non-cancerous state. Not all subjects experience disease onset in their lifetime. The PSA growth model is based on work by Inoue et al.⁸. Prior modeling work used the studies of Oesterling⁹ and Carter¹⁰.

Prostate cancer survival The survival module generates age at prostate cancer death for each subject based on his complete disease profile under screening and non-screening scenarios. We use SEER survival data from 1980 to 1987 to determine each case's age at death following prostate cancer diagnosis. Years of survival after diagnosis depend on age and stage; years are added to the age at clinical diagnosis, which is termed "lead-time delay." Model projections of disease-specific mortality rates prior to the PSA era are calibrated to match those observed in the population.



Disease-specific survival is irrelevant for latent subjects since, by definition, all latents die from some other cause before prostate cancer affects their lifespan.

CONTRIBUTORS

REFERENCES:

- ¹ Legler J, Feuer E, Potosky A, Merrill R, Kramer B "The role of Prostate-Specific Antigen testing patterns in the recent prostate cancer incidence decline in the USA" in *Cancer Causes Control* 1998; 9: 519-527
- ² Etzioni, Ruth, Cha, Raymond, Cowen, Mark E. "Serial Prostate Specific Antigen Screening For Prostate Cancer: A Computer Model Evaluates Competing Strategies" in *J Urol* 1999; 162: : 741-748
- ³ Cowen ME, Chartrand M, Weitzel WF "A Markov Model of The Natural History of Prostate Cancer" in *J Clin Epidemiol* 1994; 47: 1: 3-21
- ⁴ Whitmore WF "Background for screening: natural history and treatment. **EORTC Genitourinary Group Monograph 5: Progress and Controversies in Oncological Urology II.**" 1988; : 123-130
- ⁵ Whitmore, WF "Natural History of low-stage prostatic cancer and the impact of early detection." in *Urol Clin N Am* 1990; 17: 689-697
- ⁶ Etzioni R, Cha R, Feuer EJ, Davidov O "Asymptomatic Incidence and Duration in Prostate Cancer." in *American Journal of Epidemiology* 1998; 148: 775-785
- ⁷ Mariotto A, Etzioni R, Krapcho M, Feuer EJ "Reconstructing prostate-specific antigen (PSA) testing patterns among black and white men in the US from Medicare claims and the National Health Interview Survey" in *Cancer* 2007; in press:
- ⁸ Inoue LY, , Etzioni R, , Slate EH, , Morrell C, , Penson DF. "Combining longitudinal studies of PSA. " in *Biostatistics* 2004; 5: 3: 483-500
- ⁹ Oesterling JE Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, Lieber MM "Serum prostate-specific antigen in a community-based population of healthy men." in *JAMA* 1993; 270: 860-864
- ¹⁰ Carter HB, Morrell CH, Pearson JD, Brant LJ, et al. "Estimation of prostatic growth using serial Prostate-Specific Antigen measurements in men with and without prostate disease." in *Cancer Research* 1992; 52: 3323-3328

ASSUMPTION OVERVIEW

SUMMARY

The assumptions inherent in the FHCRC modeling approach are described below. When possible, we discuss the potential impact of these assumptions on our results.

BACKGROUND

Our model combines information on both the observed and latent aspects of the disease. Most of the assumptions made pertain to the latent natural history, but some also relate to the interface between the observed data and the latent disease history.

Our natural history model (onset and progression through disease stages) is based on two published studies: the Markov model of Cowen et al¹ and the asymptomatic onset and duration study of Etzioni et al². Our first main assumption is that these are accurate reflections of the frequency of disease onset and the rates of disease progression through the clinical stages of prostate cancer as defined by the American Urological Association (AUA, aka Whitmore-Jewitt) staging system.

Our second main assumption comes when we link natural histories with clinical diagnosis. We use a matching algorithm that randomly selects natural histories at the correct time so as to match observed age- and stage-specific clinical incidence. While the algorithm achieves the desired result, it also induces a structure on the natural histories that ultimately are selected to be clinically diagnosed; these end up having earlier ages at onset and shorter stage durations than those natural histories that do not have a corresponding date of clinical diagnosis (these “latent” histories are ultimately our candidates for overdiagnosis). See Figure 1. A further assumption concerning clinical incidence is that this would have remained constant at its pre-PSA level (the level observed in 1987) in the absence of screening.

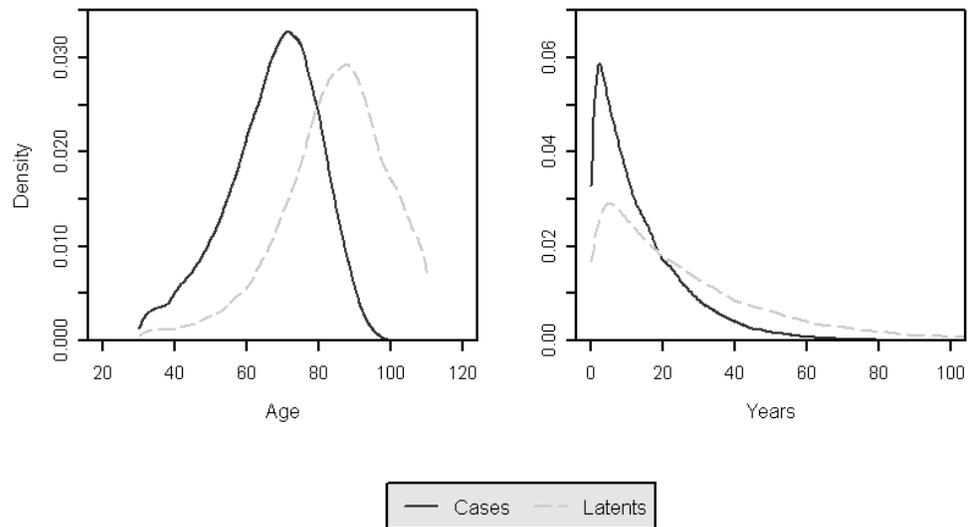


Figure 1. Age at disease onset (left) and stage A1 duration (right) distributions for cases



and latents resulting from the matching algorithm.

One of the hidden assumptions that is implicit in our matching algorithm is that stage D2 disease is always symptomatic.

Each individual is assigned a PSA growth trajectory that is based on a meta-analysis of stored serum data, conducted by Inoue et al³. This dataset provides information on PSA growth for clinical cases by stage at clinical diagnosis. We assume that the PSA growth for latent cases is on average approximately half that of the PSA growth for the local-regional clinical cases. We link PSA growth for an individual with his natural history as follows: the quantile in the distribution of PSA slopes across individuals is set to be one minus the individual's quantile in the distribution of stage A1 durations. Thus, those individuals with the longest stage A1 durations receive the lowest annual PSA growth rates and vice versa.

Our next major assumption relates to screening and biopsy practices in the population. One of our observed inputs is a set of screening histories that we use to assign individuals to screening tests. These inputs have been rigorously estimated based on data from the 2000 NHIS and the linked [SEER](#) -Medicare databases (Mariotto et al⁴). We assume that a PSA level of 4.0 ng/ml is the trigger for biopsy, which may not be an accurate reflection of practice. Based on this assumption, we use biopsy frequencies from the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial (by age and PSA level) to assign men to receive a biopsy. We also assume that biopsy accuracy increases over time, in accordance with increases in the number of cores typically sampled at biopsy. Until the late 1980s, four-core biopsies were standard; by the mid-1990s six-core biopsies were standard, and by the early 2000s, 8-12 and extended-core biopsies were standard. We have conducted a literature review and assume that for cases with stage A1 disease, 6-core biopsy accuracy is 80%, 4-core biopsy accuracy is 2/3 of this amount, and extended-core biopsies are 100% accurate. For cases with more advanced disease, biopsy accuracy is assumed to be 100%.

Our final major assumption is one that underlies all of the screening models in CISNET, namely that stage shift implies survival shift. A case who would have been detected clinically in late stage but is shifted by PSA screening to detection in local-regional stage has his survival from clinical diagnosis re-set to reflect that of a local-regional stage case. We assume that if the distant-stage survival is relatively good (or poor), then this will be the case with the local-regional survival as well. To achieve this correspondence, the quantile of the shifted survival within the local-regional stage distribution is set to be equal to the quantile of the individual's original distant-stage survival in its distribution.

The validity of these assumptions is not tested directly. The model is validated by comparing a results with published studies (see [Validations Overview](#)) and the model-projected prostate cancer incidence and mortality trends are calibrated against those observed in [SEER](#) prior to the PSA era.

ASSUMPTION LISTING



Mortality and clinical incidence:

- Age- and stage-specific clinical incidence rates would have remained at 1987 levels in the absence of screening. Thus, this assumption does not explicitly take into account changes in the frequency of transurethral resections of the prostate (TURPs) during the PSA era. TURPs were closely linked with increases in prostate cancer incidence during the 1980s (Merrill et al⁵), but use of this procedure declined sharply in the 1990s following the dissemination of medical approaches to manage benign prostatic hyperplasia. Telesca et al⁶ have recently estimated a background trend in incidence in the absence of PSA screening. This trend levels off after 1987 (i.e., it does not continue its historical increase), which is consistent with the constant secular trend in incidence assumed in the model.
- Age- and stage-specific incidence prior to 1973 is adequately approximated by the rates observed in 1973 to 1975.
- Stage D2 is symptomatic. Latents (individuals who are not clinically diagnosed in their lifetimes) must have an age at other-cause death that precedes their age at transition to AUA stage D2 (distant metastases).

Asymptomatic onset:

- Asymptomatic onset⁷ used in the model is estimated from autopsy studies performed in the US in the 1950s. The model assumes that these adequately reflect the prevalence of latent disease. Based on these data, we have estimated that approximately 36% of men develop prostate cancer in their lifetimes. It is likely that this is an underestimate of the true amount of latent disease in the population (newer biopsy studies using more modern technology have yielded higher age-specific prevalences), but this assumption still yields sufficient latent cases for our modeling purposes.

Disease progression and clinical presentation:

- A Markov model is used to describe the progression of disease through AUA stages. Stage transition rates are based on work by Cowen⁸.
- Disease progression rates are independent of patient age, race, and date of disease onset. Stage durations are exponentially distributed and are not correlated with each other.

PSA growth:

- Pre-cancerous PSA growth is based on Oesterling et al⁹. PSA increases by approximately 3% annually.
- Cancerous PSA growth is derived from a study by Inoue et al¹⁰. This study analyzed data on mostly clinical cases. The mean annual growth rate for cases destined to be diagnosed in distant stage is 60%, and for cases destined to be diagnosed in local-regional stage it is 15%. For latents, we assume that the annual increase in PSA is half that estimated by Inoue et al¹⁰ for local-regional cases.



- PSA growth accelerates at the time of entry into stage A1. It is also possible to specify a lag time (as a fraction of the stage A1 duration) until the start of PSA acceleration.
- PSA growth for an individual is inversely associated with the rate of disease progression from stage A1 to subsequent stages. An individual's quantile in the population distribution of PSA slopes is set to be one minus the individual's quantile in the population's distribution of stage A1 durations. Thus, those individuals with the longest stage A1 durations receive the lowest annual PSA growth rates and vice versa.

PSA test schedule:

- The PSA dissemination schedule is based on the work of Mariotto et al⁴. A positive test is defined as PSA > 4.0 ng/ml.
- We do not model digital rectal exam (DRE) testing. We effectively assume that the frequency of DRE screening remains at pre-PSA-era levels. Thus, we do not capture any possible increase in the frequency of DRE as a consequence of the increase in PSA use. If use of DRE testing increases during the PSA era (e.g., DRE may be routinely conducted in conjunction with PSA screening), then this may lead to underascertainment of cases at screening tests because we will not be capturing any increase in detection due to DREs with positive results in the absence of positive PSA test results. However, we anticipate these to be relatively small in number.

PSA test follow-up:

- Not all men with a positive PSA test will submit to a follow-up biopsy. The model assumes that the biopsy rate following a positive PSA test is similar to the one-year biopsy frequencies presented in Pinsky et al¹¹.
- No men with a PSA test
- Biopsy accuracy parameters for stage A1 cases are based on our assessment of trends in number of cores based on an extensive literature review. We have determined that 4-core biopsies (assumed accuracy 53%) were standard at the start of the PSA era, 6-core biopsies (assumed accuracy 80%) were standard in the mid 1990s, and higher numbers of cores (assumed accuracy 100%) were standard by the early 2000s.
- We assume that biopsy is 100% accurate when disease has progressed beyond stage A1.

Survival following diagnosis:

- The major survival benefit assumption for the model is that prostate cancer is a disease whose natural progression can be interrupted by intervention at an early stage; specifically, stage shift (from distant to local-regional) implies survival shift (from distant-stage survival to local-regional-stage survival).



- We do not model within-stage shifts, so a case shifted from regional to local or within local stage receives no survival benefit.
- We assume no improvements in survival during the PSA era due to treatment since we are trying to isolate the effect of the screening-induced stage shift on population mortality. Thus, in the absence of PSA testing, we assume that disease-specific survival observed for cases diagnosed from 1987 to 2000 would have been the same as the survival observed for cases diagnosed from 1980 to 1987.
- Among stage-shifted cases, the shifted survival begins declining only once the lead time has elapsed, i.e., at the time of clinical diagnosis. Thus, we explicitly disallow negative survival benefit under screening.
- The survival from clinical diagnosis without and survival with screening are correlated by quantile: the quantile of the shifted survival within the local-regional stage distribution is set to be equal to the quantile of the individual's original distant-stage survival in its distribution.

REFERENCES:

- ¹ Cowen ME, Chartrand M, Weitzel WF "A Markov Model of The Natural History of Prostate Cancer" in J Clin Epidemiol 1994; 47: 1: 3-21
- ² Etzioni R, Cha R, Feuer EJ, Davidov O "Asymptomatic Incidence and Duration in Prostate Cancer." in American Journal of Epidemiology 1998; 148: 775-785
- ³ Inoue LY, , Etzioni R, , Slate EH, , Morrell C, , Penson DF. "Combining longitudinal studies of PSA. " in Biostatistics 2004; 5: 3: 483-500
- ⁴ Mariotto A, Etzioni R, Krapcho M, Feuer EJ "Reconstructing prostate-specific antigen (PSA) testing patterns among black and white men in the US from Medicare claims and the National Health Interview Survey" in Cancer 2007; in press:
- ⁵ Merrill RM, Feuer EJ, Warren JL, Schussler N, Stephenson RA, "Role of transurethral resection of the prostate in population-based prostate cancer incidence rates" in Am J Epidemiol 1999; 150: 8: 848-60
- ⁶ Telesca D, Etzioni R, Gulati R "Estimating lead time and overdiagnosis associated with PSA screening from prostate cancer incidence trends" in Biometrics 2007; in press:
- ⁷ Etzioni R, Cha R, Feuer EJ, Davidov O "Asymptomatic Incidence and Duration in Prostate Cancer." in American Journal of Epidemiology 1998; 148: 775-785
- ⁸ Cowen ME, Chartrand M, Weitzel WF "A Markov Model of The Natural History of Prostate Cancer" in J Clin Epidemiol 1994; 47: 1: 3-21
- ⁹ Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, Lieber MM "Serum prostate-specific antigen in a community-based population of healthy men." in JAMA 1993; 270: 860-864
- ¹⁰ Inoue LY, , Etzioni R, , Slate EH, , Morrell C, , Penson DF. "Combining longitudinal studies of PSA. " in Biostatistics 2004; 5: 3: 483-500
- ¹¹ 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 2005; 173: 3: 746-50



PARAMETER OVERVIEW

SUMMARY

This page describes the model inputs with which we have developed the FHCRC prostate cancer microsimulation.

See the [Assumption Overview](#) for detailed assumptions associated with these model inputs.

BACKGROUND

PARAMETER LISTING OVERVIEW

The FHCRC microsimulation comprises five fundamental modules.

[Natural history and clinical presentation:](#)

- All-cause mortality data are based on Berkeley life tables containing annual mortality rates by birth cohort from birth year 1900 to 2000 by single year ages from 0 to 119. We use data provided by National Cancer Institute (NCI) to subtract out prostate cancer death rates from 1950 to 2000, yielding other cause (i.e., not due to prostate cancer) death rates. We use these to generate age at other-cause death.
- A cumulative distribution of age at asymptomatic onset is computed from the results of Etzioni et al¹ and is used to generate an age at disease onset for each individual. If the age at onset precedes other-cause death, the individual becomes asymptomatic during his lifetime.
- Stage transition rates from Cowen et al² are used to generate clinical stage durations from stage A1 through the end of stage D2.
- A year of birth distribution (uniform between 1895 and 1950) produces a multi-cohort population including men aged 50 to 84 for all years between 1980 and 2000. See Figure 1.
- The distribution of the lifetime probability of clinical incidence is created using [Dev Can](#) software provided by NCI. Inputs consist of [SEER](#) age-specific incidence rates from 1973 to 1987. We assume that incidence prior to 1973 is approximated by the rate observed in 1973 and that incidence after 1987 in the absence of PSA screening is approximated by that observed in 1987. We then use [Dev Can](#) to generate a cumulative distribution of age at clinical diagnosis in the absence of other-cause death for each birth cohort in the model. This is used to generate the clinical histories that correspond to the cases.
- The stage distribution at clinical presentation is based on [SEER](#) data. Prior to 1973 we assume the stage distribution to be approximated by that observed from 1973 to 1977. After 1987, we assume that the stage distribution in the absence of screening is approximated by the distribution observed from 1983 to 1987.

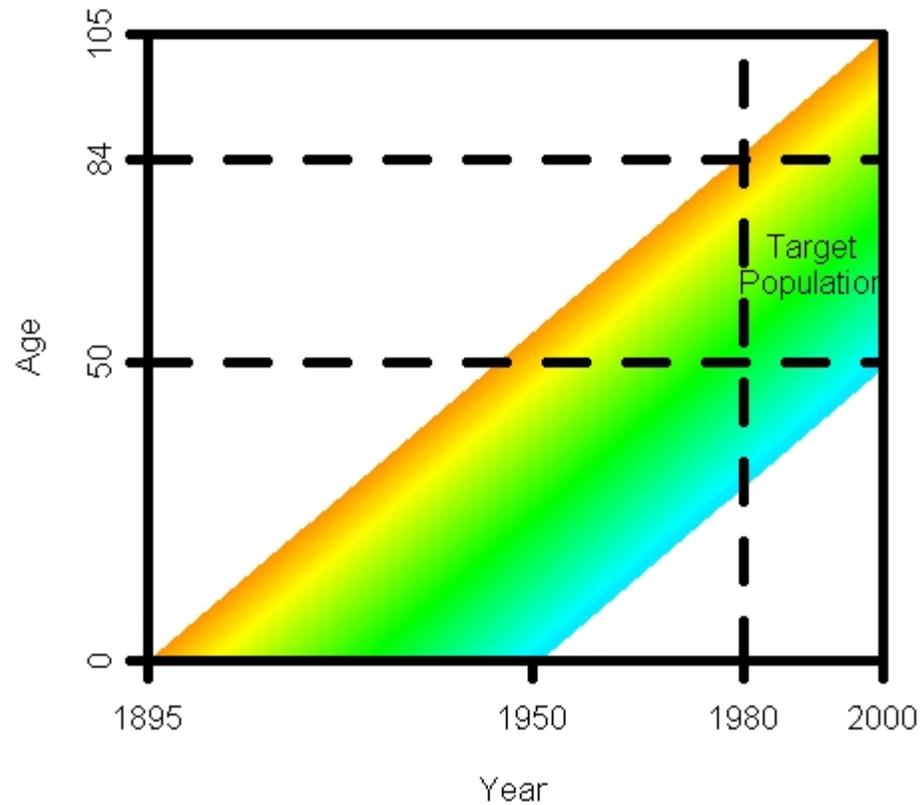


Figure 1. Illustration of birth years corresponding to target population for the ages (50-84) and years (1980-2000) of interest.

Screening: PSA testing and biopsy follow-up:

- A schedule for PSA testing is assigned to each subject based on the PSA dissemination model³ developed by IMS and provided to CISNET modelers by our collaborators at NCI.
- The probability of follow-up biopsy after a positive PSA result is based on data from Pinsky et al⁴, who estimated the likelihood of a biopsy within one year of a PSA test by PSA level, age, and calendar year in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial.
- Biopsy accuracy (ability to detect existing disease) for men with stage A1 disease is a function of the number of biopsy cores (4, 6, or more than 6). Based on an extensive review of the literature, we have estimated that prior to 1990, 4-core biopsies were standard, by 1995 6-core biopsies were standard, and by the early 2000s, 8- to 12-core biopsies were standard⁵. Following Presti et al⁶, we have utilized 80% as the sensitivity of 6-core biopsies, 100% as the sensitivity for extended-core biopsies, and 2/3 of 80% as the sensitivity for 4-core biopsies.

PSA growth:

- The distribution of PSA levels beginning at age 45 serves as an anchor point for the PSA growth curve. This is drawn from a lognormal distribution fit to the distribution of PSAs for 40 to 49 year olds in Oesterling et al⁷.
- Mean annual PSA growth rate for healthy subjects is 3% percent per year from Oesterling et al⁷.
- Within-person standard deviation of PSA level for healthy subjects is $\exp(\sqrt{0.05})$.
- Annual PSA growth rate after disease onset is modeled with an exponential growth⁸. Specifics of the model are:
 - Average annual percent change for distant-stage cases is 60%.
 - Average annual percent change for local/regional-stage cases is 15%.
 - Average annual percent change for latents is 6.5%.
 - After disease onset, between-individual standard deviation of annual percent change in PSA is 10% of mean growth rate.
 - Individual-specific annual percent change in PSA is determined by quantile q in the population distribution of PSA growth rates where $1 - q$ is the individual's quantile in the initial stage distribution.

Survival: Survival inputs consist of relative survival curves from SEER, by age, stage, and calendar year of diagnosis. Data from cases diagnosed between 1973 and 1987 are used, i.e., we end at the start of the PSA era. We split years of diagnosis into three calendar periods: 1973-1977, 1987-1982, 1983-1987. For diagnoses prior to 1973 we apply the 1973-1977 results and for diagnoses after 1987 we apply the 1983-1987 results. Thus we assume no improvement in age- and stage-specific survival from clinical diagnosis during the PSA era, i.e., we do not model any increases in survival that might be due to treatment changes.

REFERENCES:

- ¹ Etzioni R, Cha R, Feuer EJ, Davidov O "Asymptomatic Incidence and Duration in Prostate Cancer." in American Journal of Epidemiology 1998; 148: 775-785
- ² Cowen ME, Chartrand M, Weitzel WF "A Markov Model of The Natural History of Prostate Cancer" in J Clin Epidemiol 1994; 47: 1: 3-21
- ³ Mariotto A, Etzioni R, Krapcho M, Feuer EJ "Reconstructing prostate-specific antigen (PSA) testing patterns among black and white men in the US from Medicare claims and the National Health Interview Survey" in Cancer 2007; in press:
- ⁴ 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 2005; 173: 3: 746-50
- ⁵ Amling C "Personal communication" 2006;
- ⁶ Presti JCJ, Chang JJ, Bhargava V, Shinohara K "The optimal systematic prostate biopsy scheme should include 8 rather than 6 biopsies: Results of a prospective clinical trial" in J Urol 2000; 163: 1: 163-6
- ⁷ Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, Lieber MM "Serum prostate-specific antigen in a community-based population of healthy men." in JAMA 1993; 270: 860-864
- ⁸ Inoue LY, , Etzioni R, , Slate EH, , Morrell C, , Penson DF. "Combining longitudinal studies of PSA. " in Biostatistics 2004; 5: 3: 483-500

COMPONENT OVERVIEW

SUMMARY

For each major module of the microsimulation, implementation details are discussed in this section.

OVERVIEW

The FHCRC microsimulation comprises five fundamental modules; natural history, clinical diagnosis, PSA production, PSA screening, and survival. These modules are outlined in the figure below, and implementation details for each are discussed in broader detail in the Component Listing section. In addition, an output module collates the model results and creates summary output reports.

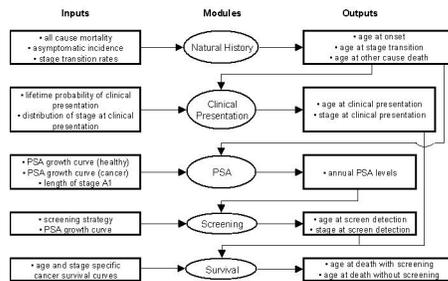


Figure 1. Overview of the model components

along with the inputs and outputs of each.

COMPONENT LISTING

The FHCRC microsimulation comprises five fundamental modules. Implementation details for each module are discussed in this section.

Natural history: This module generates N disease histories and N clinical histories that are later used in the clinical diagnosis module.

Disease histories

Generates age at asymptomatic disease onset and ages at stage transitions. We assume stage durations are distributed independently according to exponential distributions. Disease stage is converted from American Urological Association (AUA) staging to SEER historic stage using the mapping shown in the following table¹.

AUA Staging	SEER Historic Staging
A1, A2, B	Local
C, D1	Regional
D2	Distant

Clinical histories

Conditional on age of birth generate age of diagnosis in the absence of other-cause death and (independently) generate age at other-cause death. Two types of clinical



histories result: (1) histories that include an age at clinical diagnosis prior to the age at other-cause death and (2) histories that include only the age at other-cause death.

Clinical diagnosis:

Histories of the first type are matched to appropriate natural histories; for example, a natural history that has a birth year of 1920, disease onset at age 45, and progression to distant stage disease at age 60 might be matched to a clinical history from the 1920-1925 birth cohort that specifies local-regional diagnosis at age 58 in 1978. The matched clinical histories are called “cases.”

Histories of the second type are paired with the remaining unmatched natural histories so that, within each pair, the age at other-cause death in the clinical history precedes the age at transition to distant stage disease in the natural history. This operation effectively assumes that advanced prostate cancer is generally symptomatic and would not remain undetected during the lifetime of the patient. Matched histories of this type are labeled “latents.” The latents include both latent cases (those who have disease onset but not clinical diagnosis within their lifetimes) and healthy men (those who never have disease onset within their lifetimes—these men account for approximately 60% of the total population, in agreement with the autopsy studies).

Clinical histories and disease histories are processed in batches to control memory usage. Each subset of disease histories is searched for matches with the clinical histories in the current batch. Disease histories that do not match any of the current clinical histories are retained for comparison with subsequent batches of clinical histories. For each clinical history, one matching disease history is selected and removed from further consideration. This process is repeated until all possible clinical histories have been matched. Unmatched clinical and natural histories generally constitute less than 1% of the total and are dropped from the population.

PSA production: Assigns PSA levels to each individual's PSA screening events. PSA growth rates differ for cancerous and non-cancerous states, and by cancerous disease stage (local/regional or distant). Further details are on the [Parameter Overview](#) page.

Serial PSA screening: The screening module assigns screening schedules to subjects. Screening dissemination is based on the results of Mariotto et al², who used retrospective data from the linked [SEER](#) -Medicare database and the National Health Interview Survey.

Survival: This module applies only to cases as latents do not benefit from screening. The module generates three ages at death: age at death due to prostate cancer without screening (XXCaClin), age at death due to prostate cancer with screening (XXCaScrn), and age at death due to causes other than prostate cancer (XXoc).

A subject's age at death in the absence of screening is the smaller of XXoc and XXCaClin; his age at death in the presence of screening is the smaller of XXoc and the



larger of XXCaClin and XXCaScrn. Survival benefit is the difference between the age at death in the absence of screening and the age at death in the presence of screening.

Additional details are available in the [Screen Benefit Summary](#) page which can be accessed from the [Output Overview](#) page.

REFERENCES:

- ¹ Etzioni R, Legler JM, Feuer EJ, Merrill RM, Cronin KA, Hankey BF "Cancer Surveillance Series: Interpreting Trends in Prostate Cancer-Part III: Quantifying the Link Between Population Prostate-Specific Antigen Testing and Recent Declines in Prostate Cancer Mortality" in Journal of National Cancer Institute 1999; 91: 1033-1039
- ² Mariotto A, Etzioni R, Krapcho M, Feuer EJ "Reconstructing prostate-specific antigen (PSA) testing patterns among black and white men in the US from Medicare claims and the National Health Interview Survey" in Cancer 2007; in press:



OUTPUT OVERVIEW

SUMMARY

This page describes the principal outputs of the FHCRC prostate cancer microsimulation, and their importance in understanding prostate cancer trends in the US population.

OVERVIEW

The major outputs of the FHCRC model are as follows:

- Age-specific and (age-adjusted) stage-specific incidence of prostate cancer after 1987 in the absence and presence of PSA testing.
- Mean sojourn time (time from disease onset to clinical diagnosis). This can be computed for cases only, i.e., conditional on clinical diagnosis happening before other-cause death, in which case we refer to it as a “conditional sojourn time,” or it can be computed for all men with disease onset ignoring other-cause death, in which case we refer to it as an “unconditional sojourn time.” The sojourn time always starts at onset and ends at the date of clinical diagnosis.
- Mean lead time associated with PSA screening (time from screen to clinical detection). Like the sojourn time, this can be computed for cases only, i.e., conditional on clinical diagnosis happening before other-cause death, in which case we refer to it as a “conditional lead time,” or it can be computed for all screen-detected individuals, ignoring other-cause death, in which case we refer to it as an “unconditional lead time.” The lead time always starts at screen detection and ends at the date of clinical diagnosis.
- Age-specific and age-adjusted prostate cancer mortality rates after 1987 in the absence and presence of PSA screening. The difference between these two is our measure of screening benefit (see [Screen Benefit Computation](#)).

OUTPUT LISTING



RESULTS OVERVIEW

SUMMARY

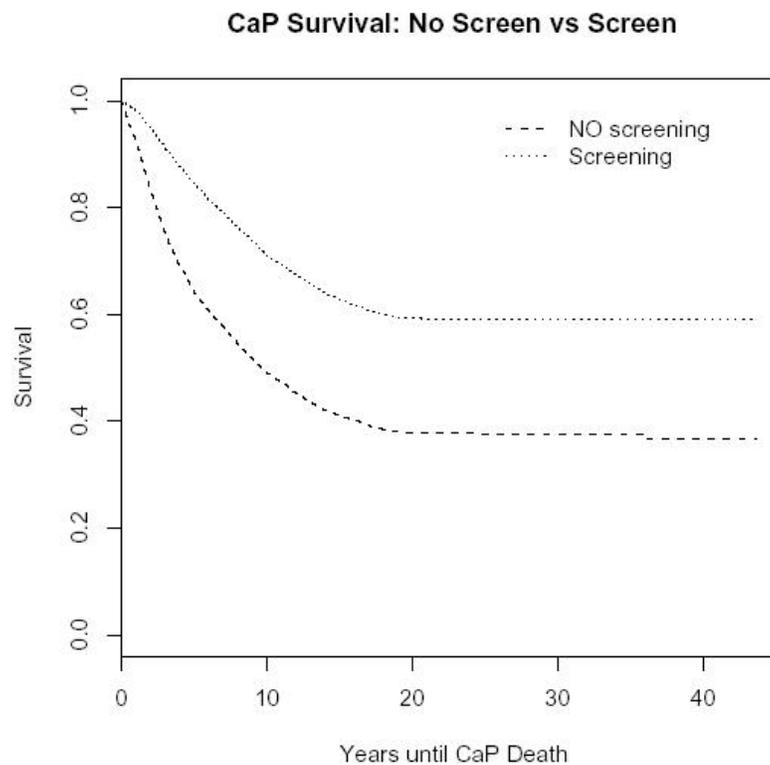
OVERVIEW

Selected numerical and graphical results from the microsimulation are explained below, including results for survival benefit, mortality and mortality reduction in the presence of screening, incidence in the presence of screening, and estimates for the mean lead-time.

RESULTS LIST

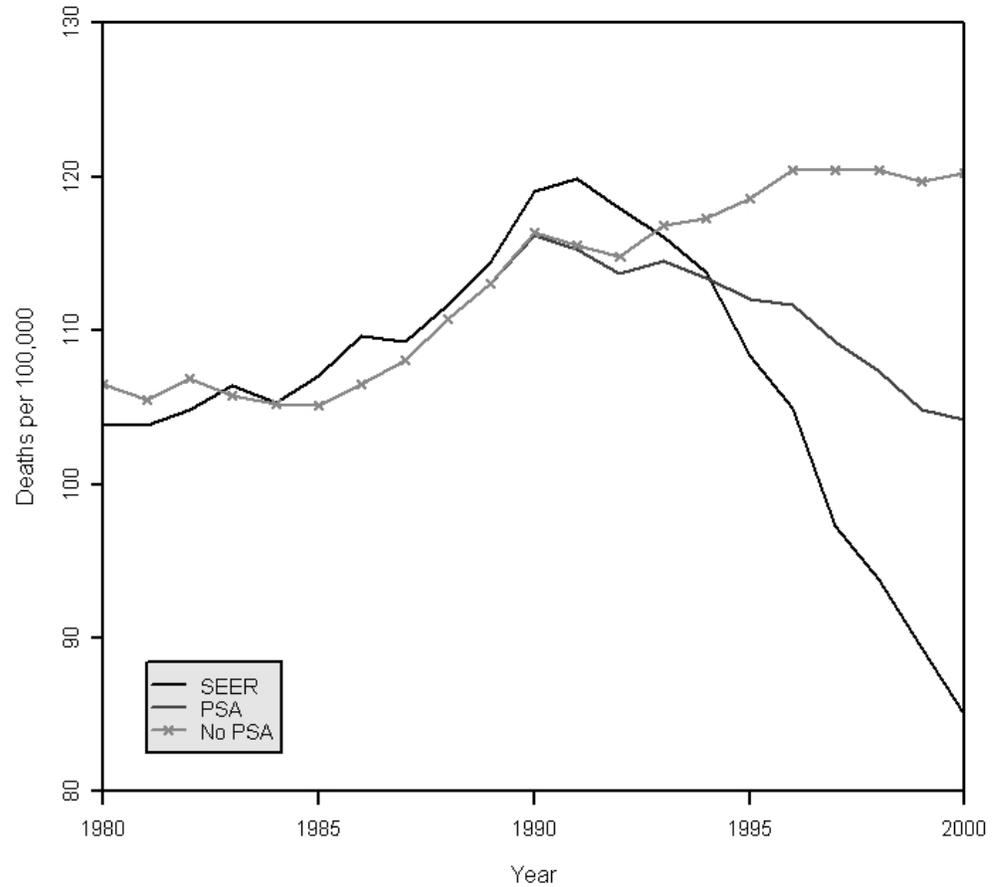
Survival benefit:

The model predicts a survival benefit from PSA screening. Screening and the corresponding stage shift imply a relative risk of 0.48. The following figure shows the relative survival among modeled cases with and without screening.



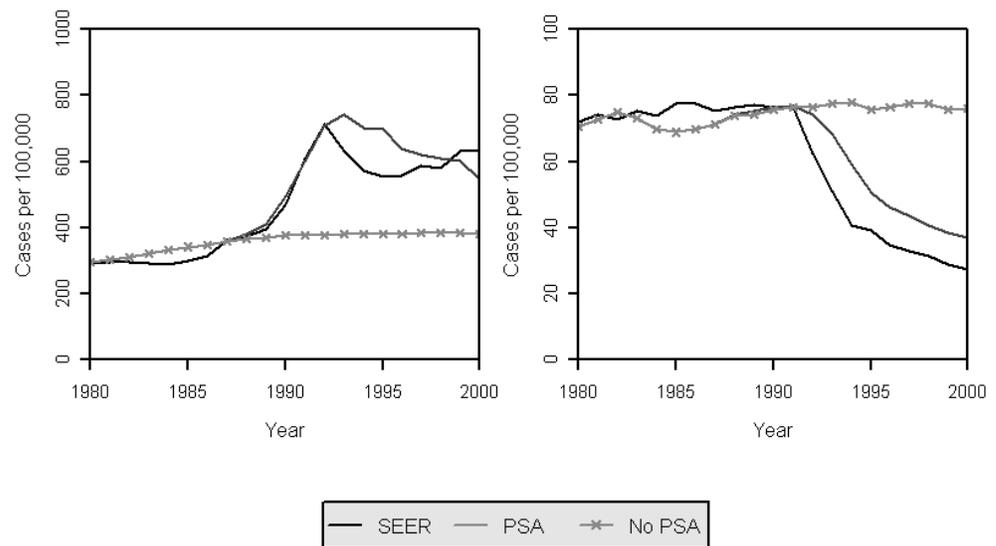
Mortality reduction:

In the absence of PSA testing, the model predicts that mortality due to prostate cancer would have increased throughout the 1990s. Model results indicate that PSA testing may be responsible for about half of the reduction in mortality.



Note: For the years 1980 to 1987, the figure shows model validation; results from 1988 to 2000 are model results.

Stage-specific incidence of prostate cancer:



Note 1: For the years 1980 to 1987, the figure shows model validation; results from 1988 to 2000 are model results.



to 2000 are model results.

Note 2: Stage-specific incidence is compared to a projection of incidence from SEER that assumes that the stage distribution among unstaged cases is equivalent to stage distribution among staged cases.

Sojourn and lead times associated with PSA testing:

Sojourn time is the length of time from preclinical disease onset to clinical diagnosis. Lead time is the length of time by which diagnosis is advanced by screening, or the difference between the age at screen diagnosis and age at diagnosis in the absence of screening. Table 1 shows min, mean, and max sojourn and lead time estimates (in years) from the model based on random samples of 1000 cases across 10 simulations. Sojourn times are by age group at onset and lead times are by age group at screen detection. Min (Max) times are the minimum (maximum) of the mean times across the 10 simulations, and \bar{n} is the mean number of subjects in each age group entering into calculations

Table 1. Sojourn and lead time estimates								
Age	Sojourn times				Lead times			
	Min	Mean	Max	\bar{n}	Min	Mean	Max	\bar{n}
50-59	12.9	13.7	14.5	164.8	8.8	11.3	13.8	11.5
60-69	8.7	9.1	9.6	287.7	5.5	7.2	8.6	24.3
70-79	6.3	6.6	6.9	324.4	4.4	5.3	6.0	26.1
80-84	4.4	5.1	5.4	102.2	2.6	4.3	5.4	9.3
Age-adjusted	8.3	8.6	8.8	—	5.5	6.8	7.6	—



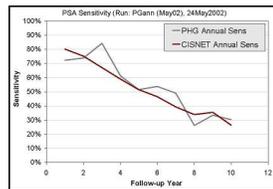
VALIDATIONS OVERVIEW

Model development requires many input parameters where reliable source data may not be available. This includes parameters describing disease natural history, the key points of which are generally not observable. Our model results are calibrated to prostate cancer incidence and mortality in the pre-PSA era and validated against data on PSA test characteristics, sojourn and lead times, and the cumulative probability of disease diagnosis in the presence of other-cause death.

Calibrations and Validations

- **Validation of PSA sensitivity in a case-control study.**

PSA sensitivity was validated by comparing results from the model to a retrospective case-control study by Gann et al¹. This study sampled men who had enrolled in the Physicians' Health Study and had provided a blood sample at the time of enrollment in 1980. Cases consisted of men diagnosed with prostate cancer within 10 years after enrollment; controls were age-matched to cases and had not been diagnosed with prostate cancer by the end of follow-up. The stored blood samples were retrospectively assayed for PSA and the sensitivity of PSA to detect disease diagnosed within k years (where k ranges from 1 to 10) was estimated. We simulated this study design and computed corresponding estimates of screen sensitivity by interval from test to clinical diagnosis.



- **Validation of model incidence to age 85 in presence of other-cause death**

The CISNET model takes as input estimates of the cumulative probability of clinical incidence in the absence of other-cause death. Disease cases consist of individuals whose clinical diagnosis precedes their other-cause death. Thus, as a validation exercise, we computed the model-generated probability of clinical diagnosis by age 85 by birth cohort and compared it with that produced by [Dev Can](#) software. This is shown below.

Birth cohort	Dev Can output	Model output
1900-1905	0.0905	0.0874
1905-1910	0.1000	0.0961
1910-1915	0.1114	0.1055
1915-1920	0.1217	0.1150
1920-1925	0.1284	0.1210
1925-1930	0.1321	0.1241
1930-1935	0.1346	0.1254

- **Validation of sojourn and lead time estimates produced by the model.**

Sojourn and lead times by birth cohort and calendar year of diagnosis, aggregated across 50 million subjects, are summarized in the [Results Overview](#). Sojourn time is the time from disease onset to clinical diagnosis and is computed for cases by age group at onset. Since the distribution of age at onset is the same for all birth cohorts, any between-cohort differences in sojourn times result from differences in clinical diagnosis rates. The lead time is the time from screen detection to clinical diagnosis and is computed for screen-detected cases by age group at detection.

Model estimates of mean sojourn and lead times validate well with other studies. Our overall, model-projected sojourn time is close to the estimate of 10 to 12 years obtained by Etzioni et al and slightly lower than the estimate of 12.7 years obtained by Draisma et al². The estimated mean lead time among clinical cases is between the 5 years obtained by Gann et al¹ and Telesca et al³ and the 7 years implied by Tsodikov et al⁴.

- **Calibration of the model to prostate cancer incidence and mortality prior to the PSA era.**

Calibration involves informal optimization in a high-dimensional parameter space, which is aided by an internal linear interpolation algorithm that smooths inputs provided by age group and calendar interval. In calibrating the model so that it replicates prostate cancer incidence and mortality levels prior to the PSA era, we vary the mean stage A1 duration, the minimum local-regional stage duration, the precise stage distribution at clinical diagnosis, the PSA growth rates for latents and for cases clinically diagnosed in distant stage, and the case-latent ratio in the modeled population. No formal estimation procedure is conducted to identify the best-fitting input values for these parameters. Regarding the case-latent ratio, this is set originally in the clinical diagnosis module, which uses [Dev Can](#) to compute the cumulative probability of clinical diagnosis—individuals with clinical diagnosis in their lifetimes become cases and the rest of the population become latents. Only 1 out of 12 latents is preserved for computational efficiency,



and the final model results upweight (i.e., inflate) any contributions from these latents by a factor of 12. However, for model calibration purposes we have found that a factor of 14 produces pre-PSA incidence and mortality rates that are considerably closer to those observed. Hence the incidence and mortality plots in the [Results Overview](#) use this as the latent inflation factor.

The calibrated model generates 5 million disease and screening histories and aggregates the resulting age- and stage-specific incidence rates over birth cohorts to produce results comparable to [SEER](#) rates, which are age-adjusted for the same age groups.

REFERENCES:

- ¹ Gann PH, Hennekens CH, Stampfer MJ "A prospective evaluation of plasma Prostate-Specific Antigen for detection of prostate cancer" in JAMA 1995; 273: 289-294
- ² Draisma G, Boer R, Otto SJ, van der Crujisen 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
- ³ Telesca D, Etzioni R, Gulati R "Estimating lead time and overdiagnosis associated with PSA screening from prostate cancer incidence trends" in Biometrics 2007; in press:
- ⁴ Tsodikov A, Szabo A, Wegelin J "A population model of prostate cancer incidence" in Stat Med 2006; 25: 16: 2846-66



Fred Hutchinson CRC (PCSIM)
SEER

SEER

The [Surveillance, Epidemiology, and End Results](#) program of the NCI :

[From the SEER website:](#)

"The [SEER Program](#) of the NCI is the most authoritative source of information on cancer incidence and survival in the United States. Information on more than 2.5 million cancer cases is included in the SEER database, and approximately 160,000 new cases are accessioned each year within the SEER catchment areas. SEER [data](#), [publications](#), and [resources](#) are available free of charge."

FRED HUTCHINSON
CANCER RESEARCH CENTER

A LIFE OF SCIENCE

[Readers Guide](#)

[Model Overview](#)

[Assumption Overview](#)

[Parameter Overview](#)

[Component Overview](#)

[Output Overview](#)

[Results Overview](#)

[Validations Overview](#)

[Key References](#)



Fred Hutchinson CRC (PCSIM)
USCB

USCB

The Bureau of the Census within the United States Department of Commerce

FRED HUTCHINSON
CANCER RESEARCH CENTER
A LIFE OF SCIENCE

- Readers Guide
- Model Overview
- Assumption Overview
- Parameter Overview
- Component Overview
- Output Overview
- Results Overview
- Validations Overview
- Key References



Fred Hutchinson CRC (PCSIM)
Nc Hs

Nc Hs

The [National Center for Health Statistics](#) is a division of the [CDC](#).

From the NCHS website:

"NCHS is the Federal Government's principal vital and health statistics agency. Since 1960, when the National Office of Vital Statistics and the National Health Survey merged to form NCHS, the agency has provided a wide variety of data with which to monitor the Nation's health. Since then, NCHS has received several [legislative mandates and authorities](#).

"The NCHS is a part of the [CDC, US Department of Health and Human Services](#). To meet priority data needs for public health, NCHS works closely with other Federal agencies as well as researchers and academic institutions.

"NCHS data systems include data on vital events as well as information on health status, lifestyle and exposure to unhealthy influences, the onset and diagnosis of illness and disability, and the use of health care. These data are used by policymakers in Congress and the Administration, by medical researchers, and by others in the health community."

FRED HUTCHINSON
CANCER RESEARCH CENTER

A LIFE OF SCIENCE

- Readers Guide
- Model Overview
- Assumption Overview
- Parameter Overview
- Component Overview
- Output Overview
- Results Overview
- Validations Overview
- Key References



Fred Hutchinson CRC (PCSIM)
Nc I

Nc I

The [National Cancer Institute](#), part of the [NIH](#).

[From the NCI website:](#)

"The [NCI](#) is a component of the [NIH](#), one of eight agencies that compose the Public Health Service (PHS) in the [US Department of Health and Human Services](#). The [NCI](#), established under the National Cancer Act of 1937, is the Federal Government's principal agency for cancer research and training. The National Cancer Act of 1971 broadened the scope and responsibilities of the [NCI](#) and created the National Cancer Program. Over the years, legislative amendments have maintained the NCI authorities and responsibilities and added new information dissemination mandates as well as a requirement to assess the incorporation of state-of-the-art cancer treatments into clinical practice.

"The National Cancer Institute coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer, rehabilitation from cancer, and the continuing care of cancer patients and the families of cancer patients."

FRED HUTCHINSON
CANCER RESEARCH CENTER

A LIFE OF SCIENCE

- [Readers Guide](#)
- [Model Overview](#)
- [Assumption Overview](#)
- [Parameter Overview](#)
- [Component Overview](#)
- [Output Overview](#)
- [Results Overview](#)
- [Validations Overview](#)
- [Key References](#)



Fred Hutchinson CRC (PCSIM)
Dev Can

FRED HUTCHINSON
CANCER RESEARCH CENTER

A LIFE OF SCIENCE

Readers Guide

Model Overview

Assumption Overview

Parameter Overview

Component Overview

Output Overview

Results Overview

Validations Overview

Key References

DEV CAN

Dev Can takes cross-sectional counts of incident cases from the standard areas of the Surveillance, Epidemiology, and End Results (SEER) Program conducted by the National Cancer Institute, and mortality counts for the same areas from data collected by the National Center for Health Statistics, and uses them to calculate incidence and mortality rates using population estimates from census data for these areas. These rates are converted to the probabilities of developing or dying from cancer for a hypothetical population.

Software to perform the calculations is maintained and available free of charge from NCI: <http://srab.cancer.gov/devcan/devcan.html>



SCREEN BENEFIT SUMMARY

SUMMARY

This section discusses how the FHCRC prostate cancer model computes survival benefit due to screening. The survival benefit computation compares a population strategy of PSA screening and diagnostic follow-up with a baseline strategy reflecting the level of diagnostic intervention in 1987, just prior to the start of the PSA era. This does not include PSA screening but may include other interventions that lead to detection of prostate cancer such as digital rectal exam (DRE) or trans-urethral resection of the prostate (TURP). We do not explicitly consider changes over time in these interventions.

OVERVIEW

Of screened subjects, only Cases (those who would have been clinically diagnosed in the absence of PSA) receive screening benefits. The primary mechanism to achieve benefit is by a shift from distant stage to regional or local-regional stage.

The model does not link pre-diagnosis progression rates with post-diagnosis prognosis. Thus it does not reflect any length bias that may be present in population screening.

Lead time bias is not an issue in our model because we generate survival beginning at clinical diagnosis in both the absence and presence of screening. Thus, if a case is shifted by screening from a distant to a local-regional stage, then his new (local-regional) survival time begins from his date of original clinical diagnosis.

BENEFIT: INPUT OR OUTPUT?

Individual screening benefit is an output calculated from three important parameters generated in the model:

- Age-at-death-due-to-clinically-diagnosed-disease (XXCaClin)
- Age-at-death-due-to-screen-diagnosed-disease (XXCaScrn)
- Death-due-to-other-causes (XXoc)

The screening benefit calculation looks like this:

If $XXCaClin > XXoc - XXCaClin$ and $XXoc > XXCaClin$; otherwise, if $XXoc > XXCaClin$
Population screening benefit is estimated from the disease-specific mortality curves generated by the model in the absence and presence of screening. For any given year, this is captured by the estimated percentage of the mortality decline attributable to PSA screening, given by $100 \times (M_a - M_p) / (M_a - M_o)$ where M_a and M_p denote mortality in the absence and presence of PSA and M_o is observed mortality.

BENEFIT: EXPLICIT OR IMPLICIT?

Benefit arises from the difference between explicitly modeled survival times for Cases with and without screening. Population screening benefit is estimated from the disease-specific mortality curves generated by the model in the absence and presence



of screening. For any given year, this is captured by the estimated percentage of the mortality decline attributable to PSA screening, given by $100 \times (M_a - M_p)/(M_a - M_o)$, where M_a and M_p denote mortality in the absence and presence of PSA and M_o is observed mortality.

ATTRIBUTES DRIVING SURVIVAL

We use survival curves from SEER for local, regional, and distant stage disease. The lookup parameters are year, age, and stage at diagnosis. The same tables are used for both clinical- and screened-detected subjects.

Clinical survival:

- Stage at clinical diagnosis
- Age at clinical diagnosis
- Calendar year periods of clinical diagnosis: 1973-1977 (used for diagnoses prior to 1973), 1978-1982, and 1983-1987 (used for diagnoses after 1987)

Screen survival:

- Stage at screen diagnosis
- Age at screen diagnosis

ATTRIBUTES CHANGED BY SCREENING

Age and stage at diagnosis may be changed by screening and may be used to recalculate disease-specific survival.

CORRELATION AND LINKING

The clinical and screen-diagnosed survivals for a given subject are computed at the same quantile of their respective survival distributions.

For the baseline model, benefit is not linked to any other attributes of the natural history model.

ISSUES AND ARTIFACTS

Individuals may not die of prostate cancer during their lead time or sojourn time. This is enforced by beginning disease-specific survival times at the original date of clinical diagnosis, whether in the absence or presence of screening. We refer to this as “lead time delay”; the survival under screening is delayed until the date of clinical diagnosis.

Latents (individuals with no clinical detection during their lifetimes) do by definition die of other causes within their sojourn and/or lead time.

OTHER ISSUES

What if XXCaScr is less than XXCaClin?

It can happen that, by “luck of the draw”, a case is given an age-at-death-due-to-screened-PCa that is less than age-at-death-due-to-clinical-PCa. In this case, we move XXCaScr to be at the same date as XXCaClin. This is a relatively rare occurrence because of the lead time delay and the linkage by quantile of the screen- and clinically-diagnosed survival times.



Fred Hutchinson CRC (PCSIM)
Screen Benefit Summary
Other Issues



Fred Hutchinson CRC (PCSIM)
Cd C

Cd C

The [Centers for Disease Control and Prevention](#), an agency of the US Department of Health and Human Services.

[From the CDC website:](#)

"The Centers for Disease Control and Prevention (CDC) is recognized as the lead federal agency for protecting the health and safety of people—at home and abroad, providing credible information to enhance health decisions, and promoting health through strong partnerships. CDC serves as the national focus for developing and applying disease prevention and control, environmental health, and health promotion and education activities designed to improve the health of the people of the United States.

"CDC, located in Atlanta, Georgia, USA, is an agency of the [US Department of Health and Human Services](#). [Dr. Jeffrey P. Koplan](#) is the Director."

FRED HUTCHINSON
CANCER RESEARCH CENTER

A LIFE OF SCIENCE

[Readers Guide](#)

[Model Overview](#)

[Assumption Overview](#)

[Parameter Overview](#)

[Component Overview](#)

[Output Overview](#)

[Results Overview](#)

[Validations Overview](#)

[Key References](#)



Fred Hutchinson CRC (PCSIM)
DHHS

DHHS

The [United States Department of Health and Human Services](#) comprises the following agencies:

FRED HUTCHINSON
CANCER RESEARCH CENTER

A LIFE OF SCIENCE

[Readers Guide](#)

[Model Overview](#)

[Assumption Overview](#)

[Parameter Overview](#)

[Component Overview](#)

[Output Overview](#)

[Results Overview](#)

[Validations Overview](#)

[Key References](#)

- [Office of the Secretary of Health and Human Services \(OS\)](#)
- [Administration for Children and Families \(ACF\)](#)
- [Administration on Aging \(AOA\)](#)
- [Agency for Healthcare Research and Quality \(AHRQ\)](#)
- [Agency for Toxic Substances and Disease Registry \(ATSDR\)](#)
- [Centers for Disease Control and Prevention \(CDC\)](#)
- [Centers for Medicare & Medicaid Services \(CMS\)](#)
- [Food and Drug Administration \(FDA\)](#)
- [Health Resources and Services Administration \(HRSA\)](#)
- [Indian Health Service \(IHS\)](#)
- [National Institutes of Health \(NIH\)](#)
- [Program Support Center \(PSC\)](#)
- [Substance Abuse and Mental Health Services Administration \(SAMHSA\)](#)



Fred Hutchinson CRC (PCSIM)
Ni H

Ni H

The [National Institutes of Health](#) is an agency of the [US Department of Health and Human Services](#).

[From the NIH website:](#)

"Begun as a one-room Laboratory of Hygiene in 1887, the [NIH](#) today is one of the world's foremost medical research centers, and the Federal focal point for medical research in the U.S.

"The [NIH](#) mission is to uncover new knowledge that will lead to better health for everyone. [NIH](#) works toward that mission by:

- conducting research in its own laboratories;
- supporting the research of non-Federal scientists in universities, medical schools, hospitals, and research institutions throughout the country and abroad;
- helping in the training of research investigators; and
- fostering communication of medical information.

"The [NIH](#) is one of eight health agencies of the Public Health Services which, in turn, is part of the [US Department of Health and Human Services](#). Comprising 27 separate components, mainly Institutes and Centers, [NIH](#) has 75 buildings on more than 300 acres in Bethesda, MD. From a total of about \$300 in 1887, the [NIH](#) budget has grown to more than \$20.3 billion in 2001."

FRED HUTCHINSON
CANCER RESEARCH CENTER

A LIFE OF SCIENCE

[Readers Guide](#)

[Model Overview](#)

[Assumption Overview](#)

[Parameter Overview](#)

[Component Overview](#)

[Output Overview](#)

[Results Overview](#)

[Validations Overview](#)

[Key References](#)



KEY REFERENCES

- (1995) GAUSS Mathematical and Statistical System Version 3.2.18.
- (1988) National Center for Health Statistics: Vital Statistics of the United States, 1986, Vol. II Mortality Part A. in *Public Health Service, Washington, U.S. Government Printing Office*
- Albertsen, PC** (1998) Editorial: Computer modeling-What should we look for? in *Journal of Urology* 159
- Amling C** (2006) Personal communication
- Babaian, R.J., Kojima, M., et al** (1996) Comparative Analysis of Prostate Specific Antigen and its Indexes in the Detection of Prostate Cancer. in *Journal of Urology* 156 : 2 , p 432-437
- Barry MJ , Fleming C , Coley CM , Wasson JH , Fahs MC, Oesterling JE** (1995) Should Medicare Provide Reimbursement for Prostate-Specific Antigen Testing for Early Detection of Prostate Cancer? Part IV: Estimating the Risks and Benefits of an Early Detection Program in *Urology* 4 : 46 , p 445-461
- Boring CC, Squires TS, Tong T, Montgomery S** (1994) Cancer Statistics, 1994 in *CA: A Cancer Journal for Clinicians* 44 , p 7-26
- Brown ML, Riley GF, Potosky AL, Etzioni RD** (1999) Obtaining long-term disease-specific costs of care: application to Medicare enrollees diagnosed with colorectal cancer. in *In press, Medical Care*
- Carter HB, Morrell CH, Pearson JD, Brant LJ, et al.** (1992) Estimation of prostatic growth using serial Prostate-Specific Antigen measurements in men with and without prostate disease. in *Cancer Research* 52 , p 3323-3328
- Carter HB, Piantadosi S, Isaacs JT** (1990) Clinical evidence for and implications of the multistep development of prostate cancer. in *J Urol* 143 , p 742-746
- Catalona WJ, Smith DS, Ratliff TL, Basler JW** (1993) Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. in *JAMA* , p 948-954
- Clark LC, Combs GF, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, Krongrad A, Leshner JL, Park HK, Sanders BB, Smith, CL, Taylor JR, and The Nutritional Prevention of Cancer Study Group** (1996) Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: A randomized clinical trial. in *JAMA* , p 1957-1963
- Coley, CM;, Barry, MJ;, Fleming, C;, Fahs, MC;, Mulley, AG** (1997) Early Detection of Prostate Cancer Part II: Estimating the Risks, Benefits, and Costs in *Ann Intern Med* 126 : 6 , p 468-479
- Cowen ME, Chartrand M, Weitzel WF** (1994) A Markov Model of The Natural History of Prostate Cancer in *J Clin Epidemiol* 47 : 1 , p 3-21
- Crawford ED, DeAntoni EP, Etzioni R, Schaefer VC, Olson RM, Ross CA , and the Prostate Cancer Education Council** (1996) Serum Prostate-Specific Antigen and Digital Rectal Examination for the early detection of prostate cancer in a national community-based program. in *Urology* 47 , p 863-869
- Cronin KA, Slate EH, Turnbull BW, Wells MT** (1994) Using the Gibbs sampler to detect changepoints: application to PSA as a longitudinal marker for prostate cancer. in *Computing Science and Statistics* 26 , p 314-318
- Draisma G, Boer R, Otto SJ, van der Crujisen IW, Damhuis RA, Schroder FH, de Koning HJ,** (2003) 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* 95 : 12 , p 868-78

- Dugan, JA, Bostwick, DG, Myers, RP, Qian, J, Bergstrahl, EJ, Oesterling, JE** (1996) The definition and preoperative prediction of clinically insignificant prostate cancer in *JAMA* 275 : 4 , p 288-294
- Etzioni R, Cha R, Feuer EJ, Davidov O** (1998) Asymptomatic Incidence and Duration in Prostate Cancer. in *American Journal of Epidemiology* 148 , p 775-785
- Etzioni R, Legler JM, Feuer EJ, Merrill RM, Cronin KA, Hankey BF** (1999) Cancer Surveillance Series: Interpreting Trends in Prostate Cancer-Part III: Quantifying the Link Between Population Prostate-Specific Antigen Testing and Recent Declines in Prostate Cancer Mortality in *Journal of National Cancer Institute* 91 , p 1033-1039
- Etzioni R, Pepe M, Longton G, Hu C, Goodman G** (1999) Incorporating the time dimension in receiver operating characteristic curves: A prostate cancer case study. in *Medical Decision Making* 19 , p 242-251
- Etzioni R, Ramsey SD, Berry K, Brown M** (1999) The impact of including future medical care costs when estimating the costs attributable to a disease: a colorectal cancer case study. in *In press, Health Economics*
- Etzioni R, Urban N, Baker M** (1996) Estimating the costs attributable to a disease with application to ovarian cancer in *Journal of Clinical Epidemiology* 49 , p 95-103
- Etzioni RD, Kadane JB** (1995) Bayesian statistical methods in public health and medicine. in *Annual Review of Public Health* 16 , p 23-41
- Etzioni, Ruth, Cha, Raymond, Cowen, Mark E.** (1999) Serial Prostate Specific Antigen Screening For Prostate Cancer: A Computer Model Evaluates Competing Strategies in *J Urol* 162 : , p 741-748
- Farkas A, Schneider D Perrotti M, Cummings KB, Ward WS** (1998) National Trends in the Epidemiology of Prostate Cancer, 1973 to 1994: Evidence for the Effectiveness of Prostate-Specific Antigen Screening. in *Journal of Urology* 52 , p 444-449
- Feuer EJ, Merrill RM, Hankey BF** (1999) Cancer Surveillance Series: Interpreting Trends in Prostate Cancer-Part II: Cause of Death Misclassification and the Recent Rise and Fall in Prostate Cancer Mortality. in *Journal of the National Cancer Institute* 2 : 91 , p 1025-1032
- Feuer EJ, Wun LM** (1992) How Much of the Recent Rise in Breast Cancer Incidence Can be Explained by Increases in Mammography Utilization: A Dynamic Population Approach. in *American Journal of Epidemiology* 136 , p 1423-1436
- Feuer, EJ, Wun, LM, Boring, CC** (1993) Probability of developing cancer. in *Cancer Statistics Review: 1973-1989, National Cancer Institute* , p 1-8
- Fleming, Craig, Wasson, JH, Albertsen, PC, Barry, MJ, Wennberg, JE** (1993) A Decision Analysis of Alternative Treatment Strategies for Clinically Localized Prostate Cancer in *JAMA* 269 : 20 , p 2650-2658
- Gann PH, Hennekens CH, Stampfer MJ** (1995) A prospective evaluation of plasma Prostate-Specific Antigen for detection of prostate cancer in *JAMA* 273 , p 289-294
- Gilliland FD, Welsh DJ, Hoffman RM, Key CR** (1995) Rapid rise and subsequent decline in prostate cancer incidence rates for New Mexico, 1989-1993 in *Cancer Epidemiology, Biomarkers and Prevention* 7 : 4 , p 797-800
- Gohagen JK, Prorok PC, Kramer BS, Cornett JE** (1994) Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian cancer screening trial of the National Cancer Institute. in *Journal of Urology* 152 , p 1905-1909

- Hankey BF, Feuer EJ, Clegg LX, Hayes RB, Legler JM, Prorok PC, Ries LA** (1999) Cancer Surveillance Series: Interpreting Trends in Prostate Cancer-Part I: Evidence of the Effects of Screening in Recent Prostate Cancer Incidence, Mortality, and Survival Rates. in *Journal of the National Cancer Institute* 2 : 1 , p 1017-1024
- Heston JR, Kelly JB, Meigs JW, et al** (1986) Forty-five years of cancer incidence in Connecticut 1935-1980. in *Natl Cancer Institute Monogr*
- Inoue LY, , Etzioni R, , Slate EH, , Morrell C, , Penson DF.** (2004) Combining longitudinal studies of PSA. in *Biostatistics* 5 : 3 , p 483-500
- Jacobsen SJ, Bergstralh EJ, Guess HA, Katusic SK, Klee GG, Oesterling JE, Lieber MM** (1996) Predictive Properties of Serum Prostate-Specific Antigen Testing in a Community-Based Setting. in *Archives of Internal Medicine* 156 , p 2462-2468
- Labrie F, Candas B, Dupont A, Cusan L, Gomez JL, Suburu RE, Diamond P, L'vesque J, Belanger A** (1998) Screening Decreases Prostate Cancer Death: First Analysis of the 1988 Quebec Prospective Randomized Controlled Trial in *The Prostate* 38 , p 83-91
- Laird NM, Ware JH** (1982) Random-effects models for longitudinal data. in *Biometrics* 38 , p 963-974
- Legler J, Feuer E, Potosky A, Merrill R, Kramer B** (1998) The role of Prostate-Specific Antigen testing patterns in the recent prostate cancer incidence decline in the USA in *Cancer Causes Control* 9 , p 519-527
- Lin DY, Feuer EJ, Etzioni R, Wax Y** (1997) Estimating medical costs from incomplete follow-up data. in *Biometrics* 53 , p 419-434
- Mariotto A, Etzioni R, Krapcho M, Feuer EJ** (2007) Reconstructing prostate-specific antigen (PSA) testing patterns among black and white men in the US from Medicare claims and the National Health Interview Survey in *Cancer* in press :
- Mccarthy** (1998) PSA screening said to reduce prostate-cancer deaths, or does it? in *The Lancet*
- Merrill RM, Feuer EJ, Warren JL, Schussler N, Stephenson RA,** (1999) Role of transurethral resection of the prostate in population-based prostate cancer incidence rates in *Am J Epidemiol* 150 : 8 , p 848-60
- Mettlin C, Murphy G, Babaian R, et al** (1996) The results of a five-year early prostate cancer detection intervention. in *Cancer* 1 : 77 , p 150-159
- Mettlin CJ, Murphy GP** (1998) Why is the prostate cancer death rate declining in the United States? in *Cancer* 2 : 82 , p 249-51
- Morrell CH, Pearson JD, Carter HB, Brant LJ** (1997) Estimating unknown transition times using a piecewise nonlinear mixed-effects model in men with prostate cancer. in *Journal of the American Statistical Association* 90 , p 45-53
- National Hospital Discharge Survey Web Page** Hospital Discharge and Ambulatory Surgery Data (Latest update - July 21, 1999). <http://www.cdc.gov/nchs/about/major/hdasd/nhds.htm>.
- Newman AJ Jr, Graham MA, Carlton CE Jr Lieman S** (1982) Incidental carcinoma of the prostate at the time of transurethral resection: importance of examining every chip in *Journal of urology* 128 , p 948-950
- Oesterling JE Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, Lieber MM** (1993) Serum prostate-specific antigen in a community-based population of healthy men. in *JAMA* 270 , p 860-864

- Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL, Valanis B, Williams JH, Barnhart S, Hammar S** (1996) Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. in *New England Journal of Medicine* 18 : 334 , p 1150-5
- Pearson JD, Morrell CH, Landis PK, Carter HB, Brant LJ** (1994) Mixed-effects regression models for studying the natural history of prostate disease. in *Statistics in Medicine* 13 , p 587-601
- Pienta K, Goodson J A, Esper S** (1996) Epidemiology of prostate cancer: molecular and environmental clues in *Urology* 5 : 48 , p 676-683
- Pinsky PF, Andriole GL, Kramer BS, Hayes RB, Prorok PC, Gohagan JK** (2005) Prostate biopsy following a positive screen in the Prostate, Lung, Colorectal and Ovarian cancer screening trial in *J Urol* 173 : 3 , p 746-50
- Potosky AL, Kessler L, Gridley G, Brown CC, Horm JW** (1990) Rise in prostatic cancer incidence associated with increased use of trans-urethral resection. in *Journal of National Cancer Institute* 82 , p 1624-1628
- Potosky AL, Miller BS, Kramer BS, Albertsen PC** (1995) The role of increasing detection in the rising incidence of prostate cancer. in *JAMA* 273 , p 548-552
- Potosky AL, Riley GF, Lubitz JD, Mentnech RM, Kessler LG** (1993) Potential for cancer related health services research using a linked Medicare-tumor registry database in *Medical Care* 8 : 31 , p 732-748
- Presti JCJ, Chang JJ, Bhargava V, Shinohara K** (2000) The optimal systematic prostate biopsy scheme should include 8 rather than 6 biopsies: Results of a prospective clinical trial in *J Urol* 163 : 1 , p 163-6
- Richie JP, et al** (1993) Effect of patient age on early detection of prostate cancer with serum Prostate-Specific Antigen and Digital Rectal Examination. in *Urology* 42 , p 365-374
- Roberts RO, Bergstralh EJ, Katusic SK, Lieber MM, Jacobsen SJ** (1999) Decline in prostate cancer mortality from 1980 to 1997, and an update on incidence trends in Olmsted County, Minnesota. in *Journal of Urology* 161 : 2 , p 529-33
- Slate EH, Clark LC** (1999) Using PSA to detect prostate cancer onset: An application of Bayesian retrospective and prospective changepoint identification. In: *Case Studies in Bayesian Statistics IV.* , p 511-534
- Smith Ds, Catalona WJ** (1994) The nature of prostate cancer detected through prostate-specific antigen based screening. in *Journal of Urology* 152 , p 1732-1736
- Stanford JL, Wicklund KG, McKnight B, Daling JR, Brawer MK** (1999) Vasectomy and Risk of Prostate Cancer in *Cancer Epidemiology* 8 , p 881-886
- Stanford JL, Stephenson RA, Coyle LM, Cerhan J, Correa R, Eley JW, Gilliland F, Hankey B, Kolonel LN, Kosary C, Ross R, Severson R, West D** (1999) Prostate Cancer Trends 1973-1995, Seer Program. in *National Cancer Institute*
- Telesca D, Etzioni R, Gulati R** (2007) Estimating lead time and overdiagnosis associated with PSA screening from prostate cancer incidence trends in *Biometrics* in press :
- Tsodikov A, Szabo A, Wegelin J** (2006) A population model of prostate cancer incidence in *Stat Med* 25 : 16 , p 2846-66
- Urban N, Drescher C, Etzioni R, Colby C** (1997) Use of a stochastic simulation model to identify an efficient protocol for ovarian cancer screening in *Controlled Clinical Trials* 18 , p 251-270
- Weiss NS, Rossing MA** (1996) Healthy screenee bias in epidemiologic studies of cancer incidence in *Epidemiology* 3 : 7 , p 319-22



- Whitmore WF** (1988) Background for screening: natural history and treatment. **EORTC Genitourinary Group Monograph 5: Progress and Controversies in Oncological Urology II.** , p 123-130
- Whitmore, WF** (1990) Natural History of low-stage prostatic cancer and the impact of early detection. in *Urol Clin N Am* 17 , p 689-697
- Whittemore AS, Lele C, Friedman GD, Stamey T, Vogelmann JH, Orentreich N** (1995) Prostate-specific antigen as predictor of prostate cancer in black men and white men. in *Journal of the National Cancer Institute* 87 , p 354-360
- Whittemore, AS, Keller, JB, Betensky, R** (1991) Low grade latent prostate cancer volume: predictor of clinical cancer incidence? in *Journal of the National Cancer Institute* 83 , p 1231-1235
- Wun LM, Merrill RM, Feuer EJ** (1998) Estimating lifetime and age-conditional probabilities of developing cancer in *Lifetime Data Analysis* 4 , p 169-186

[Core Docs](#)