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 a intermediate level view of the model. Consider these documents if you are interested gaining in 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 test.1

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 screening\(^2\). 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](image.png)

**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 Cowen\(^3\) and Whitmore\(^5\)).

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 study\(^6\) with Cowen’s disease progression rates\(^3\).
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 al. 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. Prior modeling work used the studies of Oesterling and Carter.

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

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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


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


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:


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 al.\(^1\) and the asymptomatic onset and duration study of Etzioni et al.\(^2\). 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 al\textsuperscript{3}. 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 al\textsuperscript{4}). 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.
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 populations 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 al. 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 al.

• 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:


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:


11 Pinsky PF, Andriole GL, Kramer BS, Hayes RB, Prorok PC, Cohagan 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 al\(^1\) 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 al\(^2\) 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 model\(^3\) 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 al\(^4\), 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 standard\(^5\). Following Presti et al\(^6\), 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.
• 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 al\(^7\).

• Mean annual PSA growth rate for healthy subjects is 3% percent per year from Oesterling et al\(^7\).

• 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 growth\(^8\). 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:**


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:

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5 Amling C “Personal communication” 2006;

6 Presti JC, 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


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.

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 table:\(^1\).

<table>
<thead>
<tr>
<th>AUA Staging</th>
<th>SEER Historic Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1, A2, B</td>
<td>Local</td>
</tr>
<tr>
<td>C, D1</td>
<td>Regional</td>
</tr>
<tr>
<td>D2</td>
<td>Distant</td>
</tr>
</tbody>
</table>

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 al\(^2\), 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 XXCaScr. 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:


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.

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>
<thead>
<tr>
<th>Age</th>
<th>Sojourn times</th>
<th>Lead times</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Min</td>
<td>Mean</td>
</tr>
<tr>
<td>50-59</td>
<td>12.9</td>
<td>13.7</td>
</tr>
<tr>
<td>60-69</td>
<td>8.7</td>
<td>9.1</td>
</tr>
<tr>
<td>70-79</td>
<td>6.3</td>
<td>6.6</td>
</tr>
<tr>
<td>80-84</td>
<td>4.4</td>
<td>5.1</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>8.3</td>
<td>8.6</td>
</tr>
</tbody>
</table>
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 al\(^1\). 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.

![Diagram of PSA sensitivity by interval from test to clinical diagnosis](image)

- **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.

![Graph showing model-generated probability of clinical diagnosis by age 85](image)
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 al. The estimated mean lead time among clinical cases is between the 5 years obtained by Gann et al and Telesca et al and the 7 years implied by Tsodikov et al.

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:


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."
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."
NCI

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.”
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 XXCaClin and XXoc XXCaClin; otherwise, if XXoc

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 \(100 \times \frac{(M_a - M_p)}{(M_a - M_o)}\) 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 \(100 \times \frac{(M_a - M_p)}{(M_a - M_o)}\) 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

**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 XXCaScrn 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 XXCaScrn 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.
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."
The United States Department of Health and Human Services comprises the following agencies:

- 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)
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."
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