Impact of PSA Screening on the Incidence of Advanced Stage Prostate Cancer in the United States: A Surveillance Modeling Approach

Ruth Etzioni, PhD, Roman Gulati, MS, Seth Falcon, MS, David F. Penson, MD, MPH

Background and objective. *Both the detection and the treatment of prostate cancer have undergone important clinical advances. Simultaneously, both distant stage incidence and disease-specific mortality have fallen in the United States. A recent study suggests that if prostate-specific antigen (PSA) testing explains the decline in distant stage incidence, then it may be largely responsible for the decline in mortality. The objective was to quantify this link between PSA screening and the decline in distant stage incidence.* ***Methods.*** *A fixed-cohort simulation model of prostate cancer progression and screening was adapted to a population-based model that integrates new data on trends in testing and biopsy practices. The model was calibrated to pre-PSA incidence and then screening was superimposed, obtaining incidence projections in the absence and presence of testing. This approach permits calculation of clinically relevant measures for model validation and direct assessment of the role of testing in the distant stage incidence decline.* ***Results.*** *The model validated well with prior studies of natural history, and the sensitivity analysis indicated that the findings were robust to variation in model parameters. Model results indicate that PSA screening accounts for approximately 80% of the observed decline in distant stage incidence.* ***Conclusions.*** *PSA screening contributed to the observed declines in distant stage incidence and mortality in the 1990s. However, additional factors, such as increasing awareness of prostate cancer and advances in treatment, have probably also played a role in these trends.* ***Key words:*** *public health; prostatic neoplasms; prostate-specific antigen; computer simulation.* ***(Med Decis Making 2008;28:323–331)***

Prostate cancer may be one of the greatest contemporary success stories in the fight against cancer. Since 1992, prostate cancer death rates in the United States have declined by one-third, from 39 to 26 per 100,000.[1] Advanced stage or metastatic tumors, which in 1980 constituted 25% of newly diagnosed and staged cases, have become a rarity: by 2002, only 4% of prostate cancer cases were metastatic at the time of diagnosis.

The role of prostate-specific antigen (PSA) screening in these dramatic trends remains unclear. The PSA test was first approved by the US Food and Drug Administration in 1986 to monitor established disease but was rapidly adopted for early detection purposes in the late 1980s and early 1990s. The widespread use of this test in the early 1990s led to a doubling of disease incidence and to extensive speculation that it might be responsible for the mortality declines that began in 1992. However, many public health professionals have been openly skeptical about the efficacy of PSA screening for several reasons.[2–4]

First, the downturn in prostate cancer mortality in the United States began in 1992, just 1 year after the frequency of first PSA tests peaked and just 3 years after PSA screening began to be performed at non-negligible levels. Etzioni and others[5] showed that this reversal in prostate cancer mortality could only be due to PSA screening under extreme assumptions about the efficacy and lead time associated with the test. Second, ecologic studies comparing prostate cancer mortality rates across areas with different intensities of PSA use have been almost uniformly negative. For example, PSA use has been quite heterogeneous in different areas of the Surveillance Epidemiology and End Results (SEER) registry, but

Received 29 December 2006 from the Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington (RE, RG, SF); and the Norris Cancer Center, University of Southern California, Los Angeles, California (DFP). Research supported by the Cancer Intervention and Surveillance Modeling Network U01 from the National Cancer Institute. Revision accepted for publication 19 September 2007.

Address correspondence to Ruth Etzioni, PhD, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N, M2-B230, PO Box 19024, Seattle WA 98109-1024; e-mail: retzioni@fhcrc.org.

DOI: 10.1177/0272989X07312719

studies comparing prostate cancer mortality in high- versus low-use areas revealed that the mortality trends in these areas are very similar.[6,7] Finally, treatment for prostate cancer has also shown significant advances, beginning before and continuing through the PSA era. Given the established benefits of both surgery[8] and hormonal therapy,[9] it is plausible that treatment advances may have contributed to, or even been chiefly responsible for, the declines in prostate cancer mortality.

Rather than directly investigating how screening activity might have impacted prostate cancer mortality, Feuer and others[10] modeled the link between mortality and the dramatic decline in distant stage incidence observed since the early 1990s. Under the assumption that screen-detected local-regional cases have the same prognosis as patients with clinically detected local-regional disease, the model-projected decline in prostate cancer mortality from 1990 to 1999 was 18% whereas the observed mortality decline was 21%. Thus, if PSA screening accounts completely for the drop in distant stage incidence observed since 1990, their results imply that screening could plausibly explain much of the decline in prostate cancer mortality. However, the link between PSA screening and distant stage incidence trends has not been formally confirmed. Although it is plausible that PSA accounts for much of the stage shift, changing prostate-related patterns of care and greater public awareness of the disease may also have played a role in nonscreen diagnoses and in distant stage incidence trends.

In previous work[11] we developed a model of PSA screening for prostate cancer and its likely impact on survival. In this article, we describe the adaptation of the original fixed-cohort model to a population-based model that reflects the likely impact of PSA screening on advanced stage prostate cancer incidence in the United States from its introduction to 2000. The adapted model investigates whether our accumulated knowledge of prostate cancer natural history, together with our best estimates of screening dissemination and biopsy characteristics in the United States, is sufficient to explain the observed drop in distant stage incidence.

METHODS

Our model builds on the single-cohort microsimulation model of serial PSA screening developed by Etzioni and others[11] to explore the costs and benefits of different screening strategies and frequencies. The adapted model extends the single-cohort framework

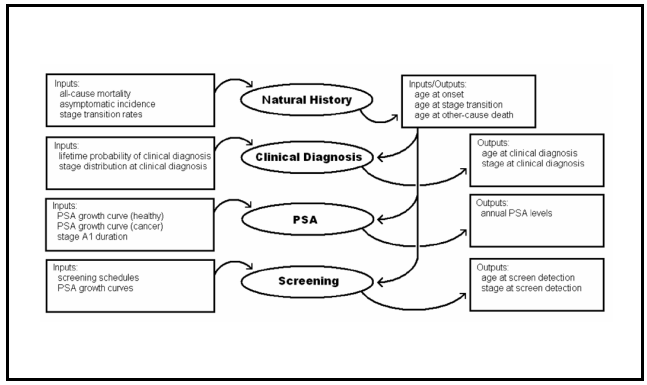

Figure 1 Prostate-specific antigen (PSA) screening simulation model structure.

and simulates life histories for the US population of men aged 50 to 84 years between 1980 and 2000, corresponding to birth cohorts 1895–1900, 1900–1905, . . ., and 1945–1950. PSA testing is superimposed on a background of prostate cancer natural history and clinical diagnosis in the absence of screening. Figure 1 summarizes the structure of the model, which consists of 4 modules. (A detailed description of the model is also available at: http://cisnet.cancer.gov/profiles/.)

Natural History Module

The natural history module generates, for each subject, age at disease onset and ages at transitions through clinical stages of disease. The age-specific incidence of latent disease is based on disease prevalence data from autopsy studies.[12] Approximately 40% of the simulated population enters the preclinical stage before their dates of other-cause death, which are generated in the clinical diagnosis module. Disease progresses through pathologic stages based on the Markov model of Cowen and others[13] from American Urological Association stage A1 (mean duration, 24.5 years), through A2/B (12 years) and C (2.8 years), to D1 and D2 (combined duration, 5.7 years). Direct progression from A2/B to D1 is also allowed, with a mean waiting time before transition of 9.5 years. The pathologic stages are converted to equivalent clinical stages (local-regional or distant) using the conversion algorithm described in Etzioni and others.[11]

Clinical Diagnosis Module

The clinical diagnosis module generates age and stage at clinical diagnosis (i.e., in the absence of

screening) and age at other-cause death. Thus, this module generates a simulated population of clinical case histories and pairs each case history with a natural history to match the age- and stage-specific incidence of prostate cancer prior to the introduction of PSA testing. We first describe how the case histories are generated and then detail the matching algorithm used to pair the case histories and natural histories.

Each clinical case history contains a date of other-cause death from birth-cohort-specific life tables provided to all Cancer Intervention and Surveillance Modeling Network (CISNET) groups, and an age and stage at clinical diagnosis. The age and stage at clinical diagnosis are generated based on disease incidence rates from the SEER registry. For the calendar interval 1973–1987, we use empirical age- and stage-specific incidence data from SEER but extrapolate incidence from the 1973–1975 interval to years before 1973 and from the 1985–1987 interval to years after 1987. Thus, we assume that stage-specific disease incidence remained constant at the 1987 level in the absence of screening. This assumption is supported by Telesca and others.[14] In practice, we input disease incidence corresponding to a few index calendar years and invoke a linear interpolation algorithm that smoothes the input data and provides trend results by single calendar year and age intervals.

Age-specific incidence rates from SEER are converted to cumulative probabilities of disease diagnosis in the absence of other-cause death using DevCan[15] software provided by the Statistical Research and Applications Branch of the National Cancer Institute. The probability of clinical diagnosis by age 85 in the absence of other-cause death ranges from 13% for the 1895–1900 cohort to 20% for the 1940–1945 cohort. Clinical case histories in the absence of other-cause death are generated from these cumulative curves. Dates of other-cause death are then generated independently and applied to the clinical histories.

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. 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). Unmatched clinical and natural histories generally constitute less than 1% of the total and are dropped from the population.

PSA Module

The PSA module generates serial PSA levels for both healthy men and men with prostate cancer. In the absence of disease, PSA levels grow at an annual rate of 3.2% per year.[16] Following disease onset, PSA growth is based on the results of Inoue and others[17] who retrospectively analyzed PSA samples from 3 stored-serum studies and found an average annual increase of 15% in men who were later clinically diagnosed with nonmetastatic tumors and 60% in men later clinically diagnosed with advanced disease. Latent cases (i.e., those who have disease onset but not clinical diagnosis in their lifetimes) are assigned an average annual PSA growth rate of 6.5%, approximately half the growth rate among men clinically diagnosed with local-regional disease. Although estimates of PSA growth for latent cases are difficult to obtain empirically, these individuals are more likely to have a low histologic grade, and they are only detected in the prospective screening setting. This assumption is also consistent with Etzioni and others,[18] who estimated that low-grade cases in the annual screening setting of the Prostate Cancer Prevention Trial had an annual growth rate between 6% and 9%.

The assigned rate of PSA growth is individual-specific and varies across, but not within, individuals. Between-individual variability in PSA growth is based on the results of Inoue and others.[17] The quantile of the individual-specific growth rate in its relevant distribution (clinically local-regional, clinically distant, or latent) is taken to be 1 minus the quantile of the individual's stage A1 duration, so that cases

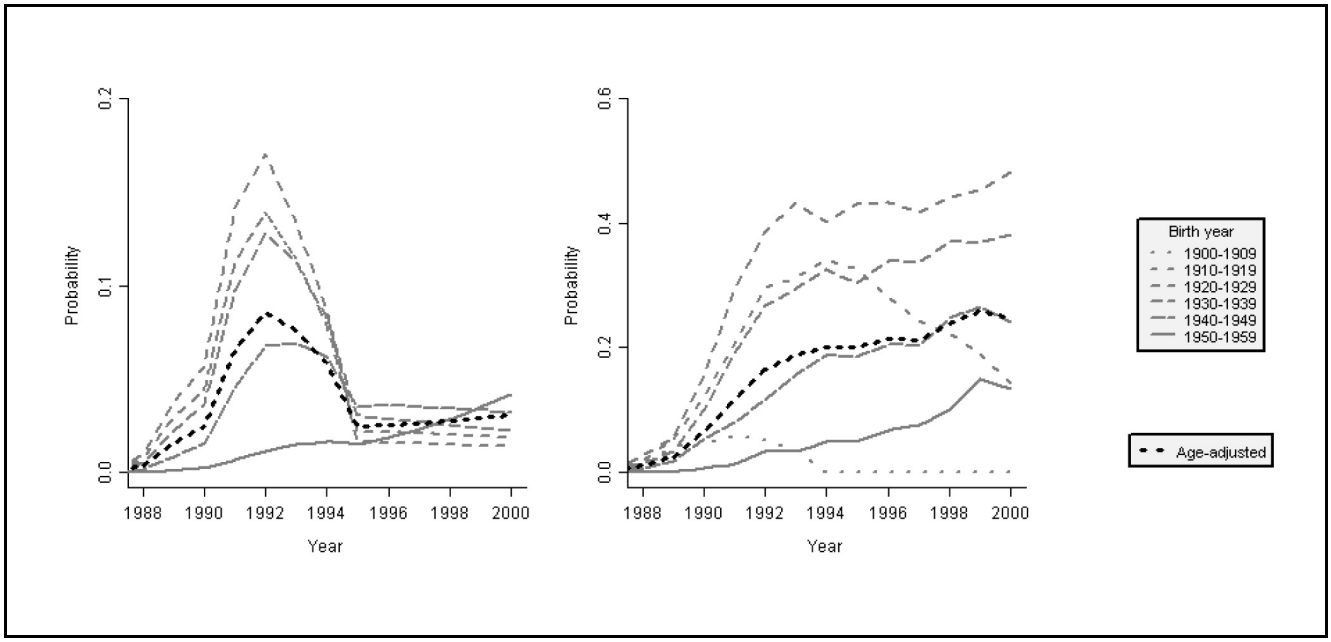

Figure 2 Annual probabilities of first (left) and overall (right) prostate-specific antigen (PSA) tests for 10-year birth cohorts together with age-adjusted curves. The series shown are derived from a combination of survey data from the 2000 National Health Interview Survey and claims data from the SEER-Medicare database.[20] Note that the scales on the vertical axes are different. In the figure on the left, the series for birth cohorts 1900–1909 and 1910–1919 are on top of each other and are the second highest curve in the figure.

with longer natural histories have slower PSA growth than cases with highly progressive disease.

Screening Module

The screening module superimposes PSA screening according to age-specific annual testing frequencies observed in the population. Screening histories are generated on a per-individual basis from a simulator[19] developed at the National Cancer Institute. The simulator combines information on first screens from the 2000 National Health Interview Survey with information on interscreening intervals from the SEER-Medicare linked database[20] to generate a series of testing times for each individual by birth cohort. Probabilities of first PSA tests and of first and subsequent PSA tests are presented in Figure 2. Screening histories within birth cohorts are randomly assigned to modeled subjects.

Men who test positive (PSA $>$ 4.0 ng/mL) undergo biopsy with specified probabilities that vary with PSA level based on biopsy frequencies[21] from the prostate cancer portion of the Prostate, Lung, Colon, and Ovarian (PLCO) Cancer Screening Trial (40% for PSA between 4 and 7, 53% for PSA between 7 and 10, and 69% for PSA greater than 10). Each biopsy is associated with a sensitivity that increases over time following trends in the United States toward more extensive biopsy protocols. Quadrant biopsies were standard until the late 1980s, but these were replaced by sextant biopsies in the late 1980s and early 1990s. When a series of studies[22,23] showed that sextant (6-core) biopsies missed 20% to 30% of cancers, this protocol was gradually replaced by extended schemes sampling 10 or even 12 cores. We assume that the extended scheme is perfectly sensitive, so that if an individual has had disease onset, the biopsy result will be positive. Sensitivity of the quadrant biopsy is assumed to be two-thirds the sensitivity of the sextant biopsy.

Modeled incidence projections are calibrated to match observed pre-PSA incidence. Calibration involves informal fitting to smoothed pre-PSA incidence trends over a set of input parameters. We conduct a range of calibrations and sensitivity analyses focusing on the mean stage A1 duration, the minimum local-regional stage duration (i.e., the threshold for a left truncated exponential distribution), the stage distribution at clinical diagnosis, and the PSA growth rates for latents and for cases clinically diagnosed in distant stage.

The calibrated model generates 5 million disease and screening histories and aggregates the resulting age- and stage-specific incidence rates over birth

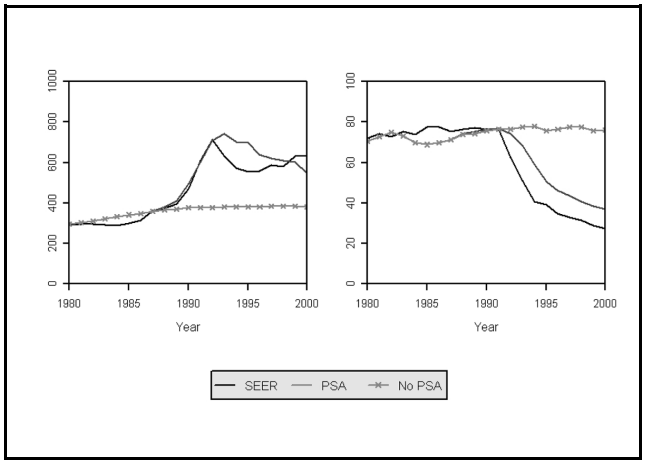

Figure 3 Observed and model-projected age-adjusted local-regional (left) and distant (right) stage incidence in the absence and presence of prostate-specific antigen (PSA) screening. Model-projected results are averaged over 10 runs of 5 million subjects. The increase in local-regional incidence in the late 1980s and early 1990s coincides with the widespread adoption of PSA screening as shown in Figure 2. Standard errors for the observed series range from 10 to 14 per 100,000 for local-regional stage and from 3 to 5 per 100,000 for distant stage.

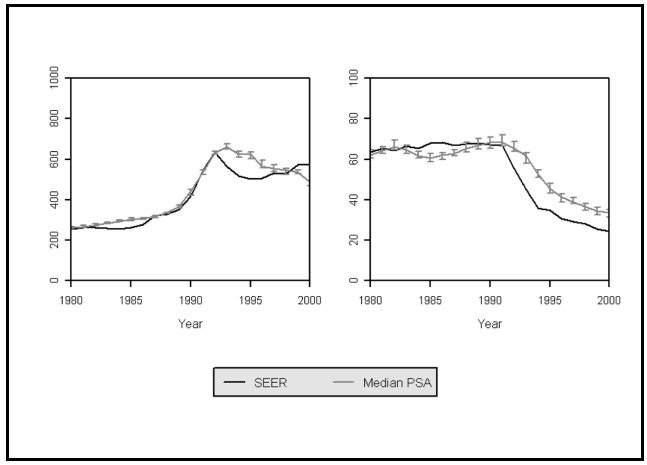

Figure 4 Median and range of local-regional (left) and distant (right) stage model projections for randomly varying values of the simulation model random seed. Results are based on 10 runs of 5 million subjects each.

cohorts using the US standard million for 2000 to produce results comparable to SEER rates, which are age-adjusted for the same age groups. As part of the model validation, we compute the model-projected sojourn and lead times and compare these with published estimates. Sojourn time is the time from disease onset to clinical diagnosis and is computed for cases by age group at onset. Thus, we only compute the sojourn time for individuals in whom it is well defined, that is, those who would progress to clinical disease within their lifetimes. 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.

RESULTS

Observed and model-projected age-adjusted local-regional and distant stage incidence series are presented in Figure 3. Calibration to pre-PSA incidence is generally satisfactory, but we find that the model-projected distant-stage incidence is slightly lower and the local-regional incidence slightly higher than what was observed during the mid-1980s. We attribute these slight anomalies to the smoothing of the age- and calendar-year-specific incidence rates input to the model; changing the specific calendar years for which data on incidence is provided does little to improve the calibration.

In the absence of screening, model-projected stage-specific incidence remains constant at the 1987 level. Under screening, the model-projected distant stage incidence declines from 77 per 100,000 in 1990 to 37 per 100,000 in 2000; observed distant stage incidence declines from 76 to 27 per 100,000. Thus, PSA screening appears to account for approximately 80% of the observed drop in the incidence of advanced disease. Figure 4 illustrates the variation in distant stage incidence projections due to the seed choice for the model random number generator.

The distributions of age at onset and stage A1 durations for cases and latents are shown in Figure 5. The case-latent matching algorithm yields cases with earlier onset of disease (16 years) and shorter stage A1 duration (9 years) on average than latents. Within cases, the stage A1 duration is generally shorter among subjects destined to be clinically distant stage than among those destined to be clinically local or regional stage (7 years). This is intuitively reasonable since cases diagnosed in distant stage must progress through earlier stages relatively quickly before the competing risk of other-cause death intervenes.

Although the projected local-regional incidence generally follows the rising-then-falling pattern observed during the PSA era, the modeled incidence peaks later and takes longer than the observed

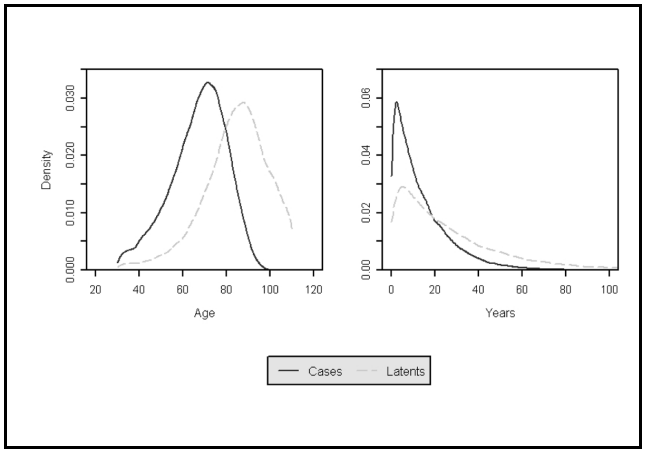

Figure 5 Age at onset (left) and stage A1 duration (right) distributions are different for cases and latents due to the matching algorithm. Results are based on 5 million subjects.

incidence to stabilize. The wider incidence peak produced by the model suggests that either the latent natural histories produced by the model are too lengthy or the opportunity for detection among latent cases is greater than would be expected. Figure 6 shows the impact on local-regional incidence of reducing the mean stage A1 length, which is the dominant component of latent natural history, and of altering the mean post-onset PSA growth rate among latents. Neither adjustment significantly alters the modeled patterns of local-regional incidence.

That the modeled peak in incidence is asynchronous with the observed incidence suggests that the likelihood of PSA-associated detection of disease in the early years of the PSA era may be higher than is implied than by the screening and biopsy patterns provided as inputs. We note that since the biopsy frequency figures obtained from the PLCO study are based on data beginning in 1993, it is possible that the likelihood of a biopsy following an abnormal test might have been higher in the early years of the PSA era. A model run (not reported) that assumed a biopsy frequency of 90% given a PSA level above 4.0 ng/mL prior to 1993 improved the fit slightly but did not shift the incidence peak. Another possibility is that the screening frequencies input to the model might have underestimated the rate of PSA screening in the early part of the PSA era. Unfortunately, during the early years of PSA, patterns of PSA use were not recorded and so we were forced to reconstruct these from retrospective survey and medical claims data.

Sojourn and lead times are summarized in Table 1. Our overall, model-projected sojourn time is close to

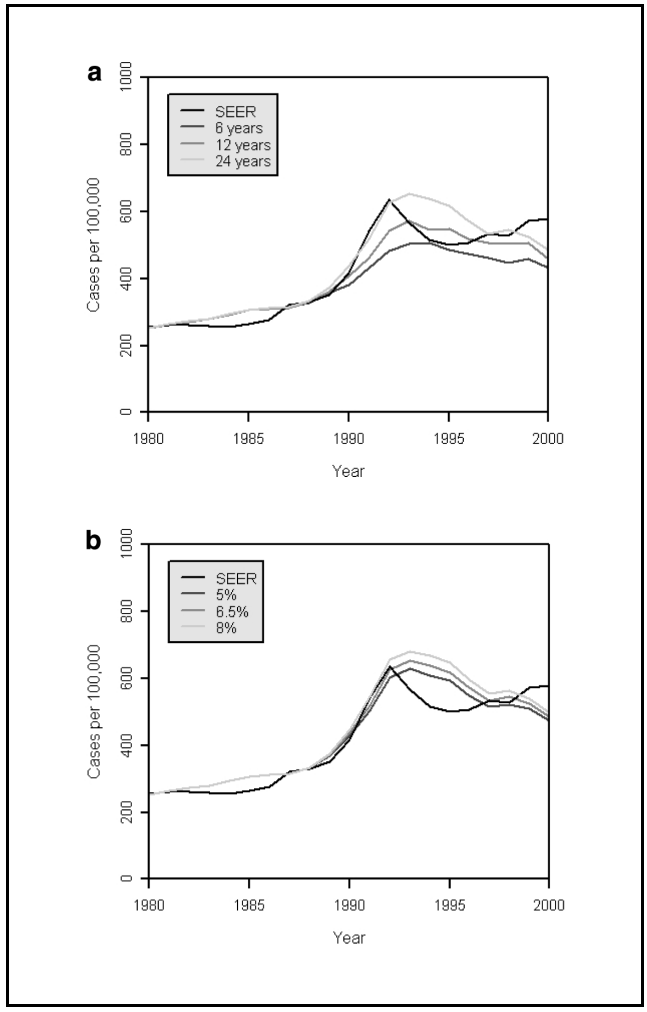

Figure 6 (a) Local-regional stage model projections for selected mean stage A1 durations. Mean post-onset prostate-specific antigen (PSA) growth rate for latent cases fixed at 6.5%. Each series is based on 5 million subjects. (b) Local-regional stage model projections for selected mean post-onset PSA growth rates among latent cases. Mean stage A1 duration fixed at 24.5 years. Each series is based on 5 million subjects.

the estimate of 10 to 12 years obtained by Etzioni and others[12] and slightly lower than the estimate of 12.7 years obtained by Draisma and others.[24] The estimated lead time among clinical cases is between the 5 years obtained by Gann and others[25] and the 7 years implied by Tsodikov and others.[26]

Since our focus is on distant stage incidence, our sensitivity analyses focus on those parameters that are likely to be most influential in the projection of distant stage incidence—namely, the mean post-onset PSA growth rate and the minimum duration of the local-regional phase of the disease for cases

Table 1 Sojourn and Lead Times (Years) Based on Random Samples of 1000 Cases across 10 Simulations

	Sojourn Times				Lead Times			
Age	**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
80–85	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	—

Note: 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.

diagnosed in distant stage. Even though this effectively increases the mean local-stage duration to above the 24.5 years implied by the model of Cowen and others[13] we conducted this analysis as an exercise to extend the opportunity for early detection of late-stage cases. For PSA growth, we considered annual percent changes of 40%, 60% (the default), and 80%. For the minimum local-regional stage duration, we used 3 (the default), 5, and 10 years. Similar to a longer preclinical interval, faster PSA growth also raises the chances of screen detection. Results are presented in Figure 7. We find that even with an 80% post-onset PSA growth rate, model-projected distant stage incidence is well above that observed. Similarly, even with a minimum of at least 10 years, model-projected distant-stage incidence is higher than the observed incidence trend.

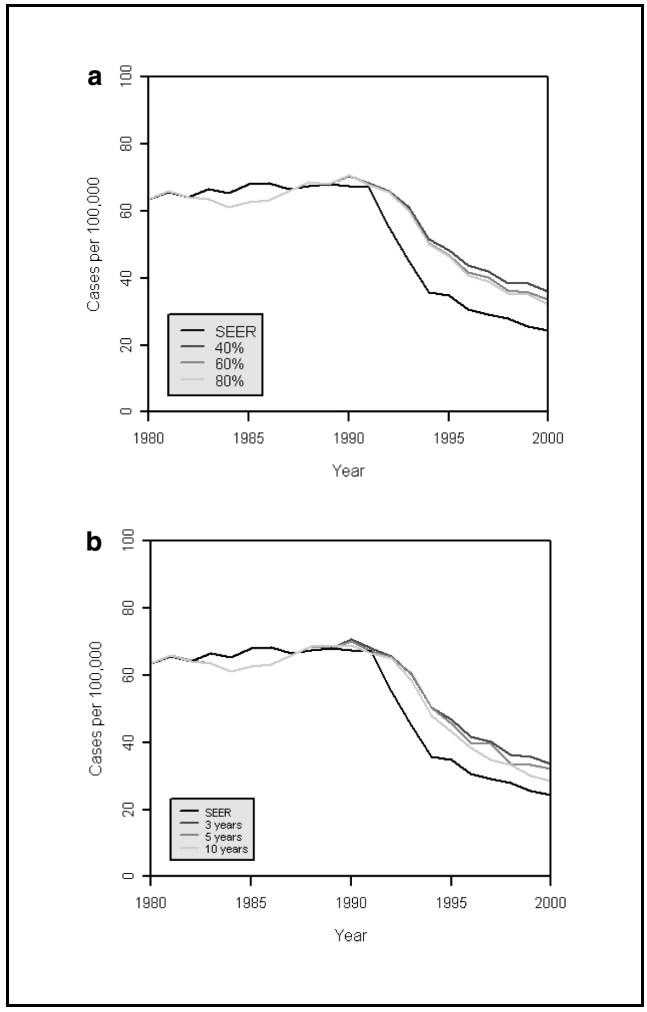

Figure 7 (a) Distant stage model projections for selected mean post-onset PSA growth rates among cases destined to be clinically diagnosed with distant stage disease. Minimum local-regional stage length is fixed at 3 years. Each series is based on 5 million subjects. (b) Distant stage model projections for selected minimum local-regional stage length. Mean post-onset PSA growth rate for cases destined to be clinically diagnosed in distant stage is fixed at 60%. Each series is based on 5 million subjects.

DISCUSSION

Population declines in distant stage prostate cancer incidence in the United States are assumed to be due to PSA screening. In this article we present a model explicitly designed to assess whether this is the case by quantifying the proportion of the decline in distant stage incidence attributable to PSA.

Our approach details how models that are developed to test specific intervention strategies in a defined cohort may be adapted to reflect and evaluate interventions as they are implemented in a multicohort population. The result is a case study of the tasks, information, and assumptions required when moving from a hypothetical cost-benefit analysis to a population surveillance model.

Adaptation of an intervention model to the population setting is a challenging task. Multiple birth cohorts must be generated and structured to form the population. Historical life table and disease incidence data may be required. Intervention patterns in

the population must be studied and applied to the simulated population. In the case of PSA screening, it is necessary to take into account not only patterns of testing but also frequencies of prostate biopsy and even the biopsy protocol itself. Variations in these practices carry important implications for disease incidence. Finally, results from different cohorts must be aggregated in a way that permits comparison with observed surveillance data.

Our model results indicate that PSA screening accounts much of the observed decline in distant stage incidence but that it does not explain all of the decline, except under extreme assumptions about natural history. There are several possible explanations for this finding. First, public awareness of prostate cancer increased in the early 1990s with the widespread introduction of the PSA test. This may have induced more frequent detections of prostate cancer outside of the screening framework. Second, there may have been some self-selection in the screening of men with positive family histories or other risk factors. Neither of these phenomena is modeled.

The model results also indicate that PSA screening likely explains less than the 18% decline in prostate cancer mortality from 1990 to 1999 estimated by Feuer and others[10] in their stage-shift model. In fact, our results suggest that PSA screening might only account for a decline of 14%, or approximately two-thirds of the 21% decline observed since 1990. Given the model assumptions and inputs, this suggests that other factors, such as changes in treatment, are also playing a role in the prostate cancer success story.

All models are built on assumptions. The key assumptions made by our model are: 1) disease natural history is adequately captured by the Markov model of Cowen and others[13]; 2) PSA growth rates are adequately estimated by the model of Inoue and others[17], and in addition, latent cases have a PSA growth rate that is roughly half that of the local-regional cases; 3) age- and stage-specific incidence of disease would have remained at 1987 levels in the absence of the introduction of PSA; and 4) PSA screening and biopsy rates are adequately reflected by the estimates input to the model. Even when we use the best retrospective information available on PSA testing rates, we underestimate the true rates in older men.[21] Higher testing rates would presumably yield a greater projected decline in distant stage incidence; however, doing so directly would require extensive reprogramming of the screening simulator provided to us by the National Cancer Institute. The same effect could be achieved by increasing biopsy frequencies, which we have done (data not shown). We found that even with biopsy frequencies of 90% for PSA levels greater than 4.0 ng/mL, model-projected distant stage incidence still did not match that observed during the PSA era.

Our local-regional stage projections also suggest that our natural history assumptions may be erring on the side of indolence, leading to local-regional durations that are longer on average than those occurring in practice. This tendency toward longer natural histories should increase the chance that a distant-stage case will be shifted to a local-regional stage by screening. However, we still find that our model-projected incidence of distant stage disease does not drop sufficiently to match that observed. This increases our confidence in our conclusion that other factors must also be acting to produce the observed distant stage decline.

Our sensitivity analyses explore the impacts of 2 assumptions about key input parameter values—namely, the PSA growth rate and the minimum local-regional stage duration for individuals clinically diagnosed with distant stage disease—but there still remains a great deal of uncertainty in both the input parameters and the structure of the model. For example, we created a link between stage A1 duration and the individual-specific rate of PSA growth by assuming that, for a given individual, the PSA growth rate percentile is the inverse of the stage A1 percentile. Similarly, we linked clinical incidence with latent natural histories via a disease-matching algorithm that is designed to achieve the correct age- and stage-specific incidence over time. We recognize that these intuitive connections may not be entirely correct from a quantitative perspective, but at the time the model was developed, the links between PSA growth, disease progression, and clinical diagnosis had not been quantified. We have recently developed a model that formalizes the connection between PSA growth, disease progression, and clinical incidence.[27] In current work we are calibrating this model to US prostate cancer trends and plan to use it to further validate the results presented in this article.

REFERENCES

1. National Cancer Institute. Surveillance, Epidemiology, and End Results registry. Available from: http://seer.cancer.gov/.

2. Barry MJ. Revisiting my personal decision about prostate-specific antigen testing in 2005. BJU Int. 2005;96(7):954–6.

3. Martin RM, Smith GD, Donovan J. Does current evidence justify prostate cancer screening in Europe? Nat Clin Pract Oncol. 2005;2(11):538–9.

4. Albertsen PC. What is the value of screening for prostate cancer in the US? Nat Clin Pract Oncol. 2005;2(11):536–7.

5. 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. J Natl Cancer Inst. 1999;91(12):1033–9.

6. Lu-Yao G, Albertsen PC, Stanford JL, Stukel TA, Walker-Corkery ES, Barry MJ. Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. BMJ. 2002;325(7367):740.

7. Shaw PA, Etzioni R, Zeliadt SB, Mariotto A, Karnofski K, Penson DF, et al. An ecologic study of prostate-specific antigen screening and prostate cancer mortality in nine geographic areas of the United States. Am J Epidemiol. 2004;160(11):1059–69.

8. Bill-Axelson A, Holmberg L, Ruutu M, Haggman M, Andersson S-O, Bratell S, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med. 2005;352(19):1977–84.

9. Bolla M, Collette L, Blank L, Warde P, Dubois JB, Mirimanoff RO, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet. 2002;360(9327):103–6.

10. Feuer EJ, Mariotto A, Merrill R. Modeling the impact of the decline in distant stage disease on prostate carcinoma mortality rates. Cancer. 2002;95(4):870–80.

11. Etzioni R, Cha R, Cowen ME. Serial prostate specific antigen screening for prostate cancer: a computer model evaluates competing strategies. J Urol. 1999;162:741–8.

12. Etzioni R, Cha R, Feuer EJ, Davidov O. Asymptomatic incidence and duration of prostate cancer. Am J Epidemiol. 1998;148 (8):775–85.

13. Cowen ME, Chartrand M, Weitzel WF. A Markov model of the natural history of prostate cancer. J Clin Epidemiol. 1994;47(1):3–21.

14. Telesca D, Etzioni R, Gulati R. Estimating lead time and overdiagnosis associated with PSA screening from prostate cancer incidence trends. Biometrics (OnlineEarly Articles): doi:10.1111/j.1541-0420.2007.00825.x.

15. Statistical Research and Applications Branch, Division of Cancer Control and Population Sciences, National Cancer Institute. DevCan—probability of developing or dying of cancer. Available from: http://srab.cancer.gov/devcan/.

16. Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, et al. Serum prostate-specific antigen in a community-based population of healthy men. JAMA. 1993;270(7): 860–64.

17. Inoue L, Etzioni R, Slate E, Morrell C. Combining longitudinal studies of PSA. Biostatistics. 2004;5(3):484–500.

18. Etzioni RD, Howlader N, Shaw PA, Ankerst DP, Penson DF, Goodman PJ, et al. Long-term effects of finasteride on prostate specific antigen levels: results from the Prostate Cancer Prevention Trial. J Urol. 2005;174(3):877–81.

19. 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. Cancer. 2007;109(9):1877–86.

20. SEER-Medicare Linked Database. Applied Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute. Available from: http://healthservices.cancer.gov/seermedicare/.

21. 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. J Urol. 2005;173(3):746–50; discussion 750–1.

22. Babaian RJ, Toi A, Kamoi K, Troncoso P, Sweet J, Evans R, et al. A comparative analysis of sextant and an extended 11-core multisite directed biopsy strategy. J Urol. 2000;163(1):152–7.

23. 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. J Urol. 2000;163 (1):163–6; discussion 166–7.

24. Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RA, Schröder FH, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst. 2003;95(12):868–78.

25. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. JAMA. 1995;273(4):289–94.

26. Tsodikov A, Szabo A, Wegelin J. A population model of prostate cancer incidence. Stat Med. 2006;25(16):2846–66.

27. Inoue L, Etzioni R, Morrell C, Muller P. Modeling disease progression with longitudinal markers. J Am Stat Assoc. In press.