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ORIGINAL PAPER

Quantifying the role of PSA screening in the US prostate cancer mortality decline

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Abstract
Objective To quantify the plausible contribution of prostate-specific antigen (PSA) screening to the nearly 30% decline in the US prostate cancer mortality rate observed during the 1990s.
Methods Two mathematical modeling teams of the US National Cancer Institute's Cancer Intervention and Surveillance Modeling Network independently projected disease mortality in the absence and presence of PSA screening. Both teams relied on Surveillance, Epidemiology, and End Results (SEER) registry data for disease incidence, used common estimates of PSA screening rates, and assumed that screening, by shifting disease from distant to local-regional clinical stage, confers a corresponding improvement in disease-specific survival.
Results The teams projected similar mortality increases in the absence of screening and decreases in the presence of screening after 1985. By 2000, the models projected that 45% (Fred Hutchinson Cancer Research Center) to 70% (University of Michigan) of the observed decline in prostate cancer mortality could be plausibly attributed to the stage shift induced by screening.
Conclusions PSA screening may account for much, but not all, of the observed drop in prostate cancer mortality. Other factors, such as changing treatment practices, may also have played a role in improving prostate cancer outcomes.

Keywords Prostate-specific antigen · Prostate cancer · Public health · Computer simulation

Detailed supplemental descriptions of the FHCRC and UMICH models are available at http://cisnet.cancer.gov/profiles/.

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Introduction

The past few years have not been kind to the PSA test. Its accuracy in detecting prostate cancer, a concern that dates back to its introduction, was again questioned by results from the Prostate Cancer Prevention Trial, a large controlled study involving over seven years of screening [1]. Continuing skepticism about the balance of risk and benefits associated with PSA screening has led to three recent editorials by prominent investigators, all of whom conclude that existing evidence is insufficient to justify its use for population screening [2–4]. Compounding the injury, a recent case–control study of PSA screening yielded a null association between use of the test and the likelihood of prostate cancer death [5].

The prevailing negative sentiment about the value of PSA screening coincides with a sustained decline in prostate cancer death rates in the US, where use of the test became widespread beginning in the early 1990s. Since 1992, prostate cancer mortality in the US has plummeted by 35% [6], accompanied by a 75% reduction in the incidence of late-stage disease. However, while there is a general consensus that PSA screening explains much of the distant-stage decline [7], 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 [8, 9]. 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 [10]. While concerns have been raised about the validity and interpretation of negative ecologic studies of PSA screening [11], 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 [12], and studies have shown that the use of hormone therapy in conjunction with primary radiation therapy in the US increased substantially during the 1990s [13, 14]. Both of these treatment approaches have shown benefit in randomized studies [15, 16]. 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 [17–20]. As results from two screening trials in the US and Europe are not expected for several years [21], important insights at present must rely on careful examination of the growing knowledge base concerning disease natural history, progression, and mortality. In this study, 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.

Materials and methods

Overview of models

The Cancer Intervention and Surveillance Modeling Network (CISNET)[12] is a consortium of investigators using mathematical modeling to quantify the association between cancer interventions and trends in cancer incidence and mortality. As part of the CISNET effort, two modeling teams were selected through a competitive National Institutes of Health peer-review process to model the impact of PSA screening on prostate cancer incidence and mortality. These teams—investigators at the Fred Hutchinson Cancer Research Center (FHCRC) and at the University of Michigan at Ann Arbor (UMICH)—worked independently but convened semi-annually for scientific meetings from September 2002 to July 2006. There we discussed methods, developed a common set of inputs pertaining to PSA use and historical disease trends, and studied discrepancies between model results.

Both models project prostate cancer mortality rates among men aged 50–84 in the absence and presence of PSA screening between 1980 and 2000. The models combine projections of age- and stage-specific disease incidence rates with corresponding survival frequencies. Both models assume that age- and stage-specific incidence would have remained constant at the 1987 level in the absence of PSA screening and that age- and stage-specific survival remained constant at the levels observed among cases diagnosed from 1983 to 1987. Both models capture the effect of screening by "stage shifting": assigning early stage survival to men screen detected with early stage disease but who would have been diagnosed with distant stage disease in the absence of screening. The percentage of the mortality decline attributable to PSA screening comes directly from this stage shifted survival improvement and is given by $100 \times (M_A - M_P)/(M_A - M_O)$,

where M_A and M_P denote mortality in the absence and presence of PSA and M_O is observed mortality.

The two models differ primarily in how they determine the stage shift under screening. This can be traced to fundamental differences in how the models conceptualize and estimate disease natural history—a description of how tumors arise and progress biologically (through disease stages) and clinically (from a latent to a clinically apparent state). These natural history descriptions ultimately determine how much earlier cancer is detected with screening, which, when linked with a corresponding improvement in survival, produces the model-projected mortality. Next we summarize key features of the two models, emphasizing their approaches to conceptualizing and estimating natural history.

The FHCRC model

The FHCRC model [7] builds directly on a previously developed model of prostate cancer progression and PSA screening [22]. The model simulates individual life histories for a hypothetical population of men with birth years corresponding to the cohort of interest. The natural history component of these life histories comprises tumor onset, progression through pathologic stages of disease, and clinical diagnosis, which is defined as detection of disease in the absence of screening. In addition to these events, a PSA growth trajectory is generated for each individual.

A key feature of the FHCRC model is that it combines external information on the various components of natural history to produce an integrated picture of the events leading up to clinical diagnosis. This approach, which methodically assembles the pieces of the disease process, is used in many policy models of disease [23, 24]. Here, the incidence of latent tumor onset is derived from an autopsy study of prostate cancer prevalence [25]. Tumor progression is based on estimated transition rates through the pathologic stages [26]. And PSA growth trajectories are taken from a retrospective stored serum study of men later diagnosed with prostate cancer and age-matched population controls [27]. The completed model is validated against the age-adjusted stage-specific incidence of disease both before and during the PSA era [7], and calibrated so that its projection of prostate cancer mortality prior to the PSA era matches that observed in the US.

Simulated individuals are assigned PSA screening tests by age and calendar year according to PSA testing frequencies in the US population. Hypothetical disease cases are assigned a recommendation for biopsy when PSA is greater than 4 ng/ml at a scheduled screening test. Biopsy compliance increases from 40% for PSA between 4 and 7 ng/ml to 53% for PSA between 7 and 10 ng/ml to 69% for PSA above 10 ng/ml [28]. Based on an extensive literature review of trends in number of biopsy cores, biopsy sensitivity improves from 50% in 1980 (four-core biopsies) to 80% in 1990 (six-core-biopsies; accuracy estimated by Babaian et al. [29] and others [30]) to 100% in 1995 and later years (extended-core biopsies [31]). Life histories in the absence of screening are also recorded. The model calculates survival gains due to screening at the individual level and then aggregates and age-adjusts these to obtain population estimates.

The UMICH model

The UMICH model of disease natural history consists of tumor onset, times from tumor onset to diagnosis (sojourn times), and sensitivity of PSA to detect latent disease [32]. The key distinguishing feature of the UMICH model is that it estimates natural history parameters based on population prostate cancer incidence rates, yielding population-level distributions of age at onset and sojourn time. The model then uses PSA screening trends to project prostate cancer incidence in the presence of PSA screening. As part of this computation, the model estimates the distribution of times by which screening advances diagnosis (lead times).

The estimated lead time distribution is used to project the decline in prostate cancer mortality associated with PSA screening. In practice, this is done at the aggregate or population level; however, the individual-level analog of this process is described as follows. To a case detected in the PSA era, assign a date and a stage at diagnosis based on the observed stage distribution (this is where stage shifting occurs), assign a lead time from the estimated lead time distribution, assign a disease-specific survival time given stage at diagnosis and lead time, and compute the date of prostate cancer death as the sum of the date of diagnosis, the lead time, and the survival time. The population-level estimates of mortality in the absence and presence of PSA screening represent age-adjusted measures comparable to those produced by the FHCRC model.

Data sources

Both models rely heavily on prostate cancer age- and stage-specific incidence reported by the Surveillance, Epidemiology, and End Results (SEER) Program [33] of the National Cancer Institute and age-, stage-, and disease-specific mortality rates reported by the National Center for Health Statistics (NCHS) [34]. We used data from the nine primary SEER catchment areas: Connecticut, Hawaii, Iowa, New Mexico, Utah and metropolitan Atlanta, Detroit, San Francisco-Oakland, and Seattle-Puget Sound. Both models were developed to reflect the disease experience of all races.

The SEER incidence data and the NCHS mortality data were used by both models for calibration. In these calibrations, model inputs were adjusted so that the model-projected outputs matched observed trends. The FHCRC model was calibrated to stage-specific incidence and prostate cancer mortality in the pre-PSA era. The UMICH model was calibrated to disease incidence both prior to and during the PSA era.

Both models also used information on the frequency of PSA screening by age and calendar year. The National Cancer Institute's PSA dissemination estimates [35] are based on National Health Interview Survey (NHIS) [36] data from the year 2000, which asked interviewees for the age interval in which they had first been tested, and on the linked SEER-Medicare database [37], which contains medical claims for PSA testing among men aged 65 and older. The link between the SEER registry (cancer diagnosis data) and Medicare (medical claims data) allowed tests performed after a cancer diagnosis to be eliminated. The NHIS data were used to estimate the probability of a first PSA test by age and calendar year. The SEER-Medicare data were used to estimate the typical interval between tests.

In addition to the data sources used by both models, the FHCRC model relies on results from several studies (cited above) of the natural history of the disease and the growth of PSA in men with and without prostate cancer. The UMICH model estimates its natural history parameters from disease incidence rates both prior to and during the PSA era. See Table 1 for a comparative list of data sources.

Results

Figure 1 presents age-adjusted mortality results from the two models. The UMICH results, which are based on population-level distributions of disease event times, are smoother than the FHCRC projections, which are aggregates over 50 million simulated individual disease histories.

In the absence of PSA screening, both models project a continuation of the historical trend in prostate cancer mortality. Model-projected increases in mortality result from historically increasing disease incidence trends. The UMICH model produces slightly lower projections than the FHCRC model, although the models show almost identical results in 1989, with both nearly matching observed age-adjusted mortality (114 cases per 100,000 men). By 2000, both models project that in the absence of PSA annual age-adjusted prostate cancer mortality rates would have risen: the FHCRC model projects 120 per 100,000 and the UMICH model projects 118 per 100,000.

In the presence of PSA, both models project an initial rise in mortality that continues the historical trend, but neither exactly matches the peak observed in 1991. Reasons for the observed rise and fall in mortality in the early years of the PSA era are unclear. Feuer et al. [38]

Table 1 Model inputs and outputs: Fred Hutchinson Cancer Research Center (FHCRC) model versus University of Michigan (UMICH) model

Parameter	FHCRC model	UMICH model
Age-specific incidence of occult disease	Input [43]	Output
Rate of progression from early to late stage of disease (FHCRC)	Input [26]	Not used
Cumulative risk of transition to distant stage by time since onset (UMICH)	Not used	Output
Annual PSA growth rate before and after prostate cancer onset (FHCRC)	Input [27]	Not used
PSA test sensitivity by time since onset (UMICH)	Not used	Output
Age-specific incidence of prostate cancer before introduction of PSA	Input* [6]	Input* [6]
Age-specific incidence of prostate cancer in the PSA-era in the absence of screening	Input	Input
Age-specific incidence of prostate cancer in the presence of screening	Output	Input* [6]
Mean sojourn time (duration of occult or pre-clinical stage of disease)	Output	Output
Mean lead time (time by which screening advances diagnosis)	Output	Output
The rate of overdiagnosis	Output	Output
Annual PSA testing frequencies	Input	Input
Likelihood of biopsy following a positive PSA test (i.e., PSA>4.0 ng/ml) (FHCRC)	Input [28]	Not used
Disease-specific survival by stage at diagnosis in the absence of screening	Input [6]	Input* [6]
Disease-specific survival by stage at diagnosis in the presence of screening	Output	Output
Prostate cancer mortality with no screening	Output*	Output
Prostate cancer mortality given screening	Output	Output

A * indicates that the parameter is used to calibrate the model: other model parameters are estimated or adjusted so that the model produces results for this parameter that match those observed. References provide sources

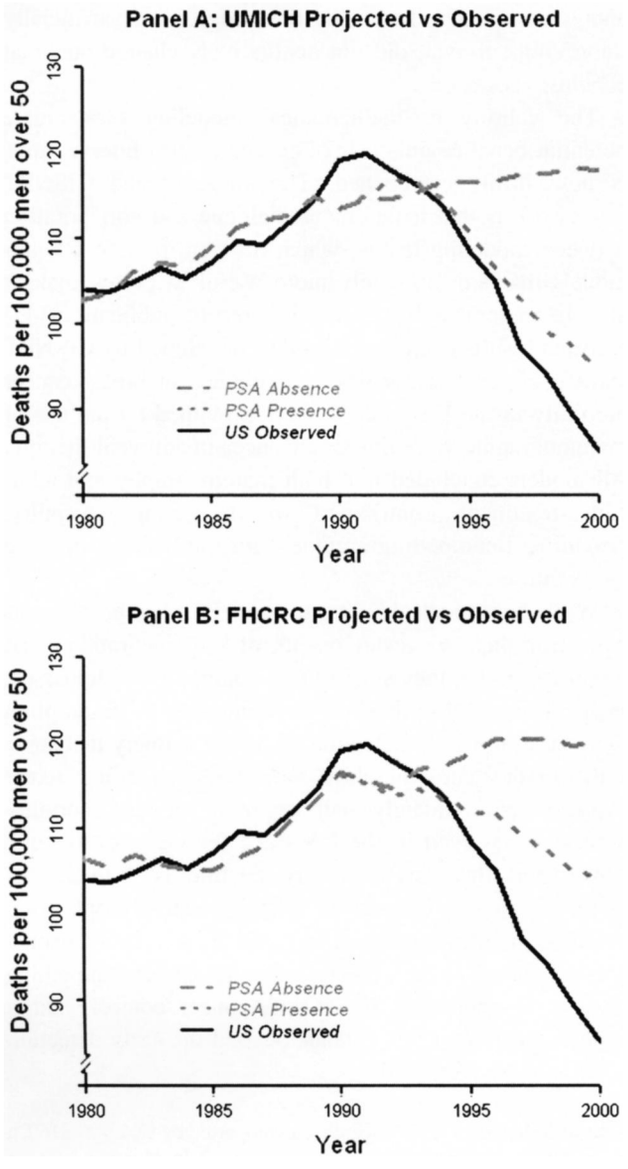

Fig. 1 Projected prostate cancer mortality for men aged 50 and older under the University of Michigan (UMICH) model (Panel A) and under the Fred Hutchinson Cancer Research Center (FHCRC) model (Panel B)

suggested that this may have been caused by a rise then a fall in misattribution of cause of death as due to prostate cancer, consistent with the increase and subsequent decline in the prevalence of newly diagnosed disease. Neither model attempts to capture this phenomenon.

By 1994, both models project mortality declines, and by 2000, projected mortality rates are 104 per 100,000 (FHCRC) and 95 per 100,000 (UMICH). The FHCRC model attributes 45% of the observed mortality decline to PSA screening while the UMICH model attributes 70% to screening. Mortality declines averaged across years from 1995 to 2000 were qualitatively similar. The failure of both models to ascribe the entire mortality decline to PSA testing implies that an improvement in cause-specific survival has occurred over and above that induced by stage shifting. Nonetheless, PSA screening is identified as contributing substantially to the mortality decline in both models.

Discussion

The widespread adoption of PSA screening represents one of the greatest uncontrolled experiments in modern medical history. While no study has conclusively proven that PSA screening is beneficial, it is now standard practice in the US, and screening rates are increasing in many countries around the globe.

This article describes two independently developed models of prostate cancer progression and PSA screening. Both models assume that a screening-induced stage shift from distant to local-regional disease carries with it a disease-specific survival improvement that corresponds to the survival difference between distant and local-regional prostate cancers diagnosed in the pre-PSA years. Although the models are quite different in their basic structure and approach, they use common values for critical inputs and all projected survival gains result from this stage shift.

The model projections indicate that stage shifting associated with PSA screening explains 45% (FHCRC) to 70% (UMICH) of the mortality decline observed by 2000. The model results differ, in part, because the FHCRC model does not produce as extreme a decline in distant-stage incidence as that observed in the population. The FHCRC model attains about 80% of the observed distant-stage decline and uses this to project mortality trends while the UMICH model uses observed trends in distant stage incidence to produce its projections. The distant stage decline projected by the FHCRC model is not substantively altered by changes in the model's input assumptions. Specifically, varying the mean length of stage A1, the mean annual change in PSA after disease onset, and the minimum time from onset to acceleration of PSA growth all produced similar distant stage incidence projections under screening.

Both models predict that prostate cancer mortality with PSA screening diverges from the mortality projected in the absence of screening before 1995. Thus, the models indicate a fairly early impact of PSA screening on population mortality trends, although even in these early years screening does not explain all of the mortality reduction observed. In fact, the models project that in 1995, screening accounts for 64% (FHCRC) and 72% (UMICH) of the mortality decline.

It is important to note that both models only allow survival improvements associated with stage shifting from

distant to local-regional stage at diagnosis. These broad stage groupings were used because SEER combines data on local and regional diagnoses. Since both models conclude that PSA accounts for only a fraction of the observed mortality decline, our results are consistent with an additional material improvement in local-regional survival relative to the pre-PSA era. This may have been partly due to shifts from regional to local or shifts within local stage; however, TNM stage data in SEER beginning in 1988 indicates that differences in 10-year relative survival (e.g., between T2 and below versus T3 and above) were negligible. More likely, additional improvements were due to treatment changes, such as increasing use of radical prostatectomy or more recent increases in the use of adjuvant hormone therapy among men with localized disease [13].

The fundamental assumption of both models, and of nearly all models of cancer screening, is that cases shifted by screening from a late stage diagnosis to early stage disease enjoy survival rates similar to those of early stage cases. We know that screening leads to length bias, so that the selected subset of tumors detected early by screening will tend to be more indolent and progress more slowly than the general population of tumors. Length bias is not a problem in our models because we model the same individuals (FHCRC) or populations (UMICH) in the absence and presence of screening. However, whether late stage cases that would be fatal in the absence of screening can have their "prognostic clock" reset by early detection is a fundamental question that ultimately determines the value of early detection as an effective approach for cancer control. The validity of this assumption is difficult to prove or disprove empirically, but Pollack and Foulkes argue that this is probably overly optimistic in practice [39].

A second assumption made by both models is that disease incidence would have been constant after 1987 in the absence of PSA. This constant secular trend assumption is based on developments in the control of benign prostatic hyperplasia (BPH) in the late 1980s and early 1990s. During this time, medical therapy gradually replaced transurethral resection of the prostate (TURP) as first-line treatment for the majority of BPH cases [40, 41]. Much of the increase in prostate cancer incidence in the 1980s was attributed to incidental prostate cancers detected by TURPs during these years. Declining TURP rates would eliminate many of these incidental diagnoses. Thus, in the absence of PSA screening, we consider it unlikely that prostate cancer incidence would have continued to increase. It is also possible that prostate cancer incidence might have fallen. Our use of a constant secular trend balances historical increases in prostate cancer incidence with this diminishing use of TURP. This assumption gains support from a recent study that estimated incidence in the absence of PSA screening [20]. It is also worth noting that a sensitivity analysis, which examined the impact of artificially improving survival, did not qualitatively change our final conclusions.

The validity of mathematical modeling to evaluate potential benefits and costs of cancer control interventions is now firmly established. The value of the CISNET framework is that it facilitates dialogue and collaboration between modeling teams, which, in turn, produces better models that are ultimately more useful to policy makers and the general public. Indeed, a recent publication [42] reported results from seven models developed by CISNET investigators to assess whether declines in breast cancer mortality in the US could be best explained by the use of mammographic screening or advances in adjuvant therapy. All models concluded that both mammography and adjuvant treatment contributed to decreasing mortality, providing a compelling argument for the benefits of these interventions.

While our models do not prove that PSA screening saves lives (for this, we await results of ongoing randomized screening trials), they suggest two compelling conclusions. First, if one subscribes to the fundamental assumption motivating the early detection of cancer, namely that stage shift implies survival shift, then PSA screening likely explains approximately half or more of the mortality reduction observed in the US since the early 1990s and, conversely, that this mortality decline is evidence of screening benefit. Second, under this relatively optimistic assumption, the stage shift induced by screening cannot account for all of the observed decline. Clearly something positive is happening in prostate cancer control, and it appears likely that this extends beyond the early detection of disease by PSA testing.

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