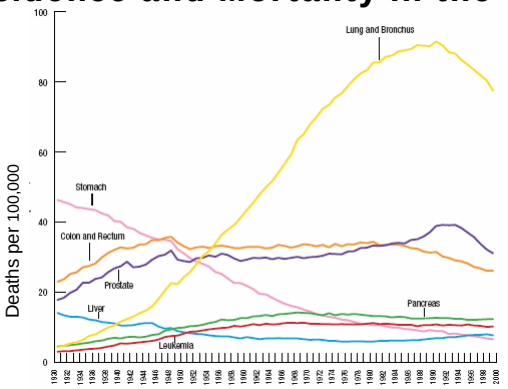
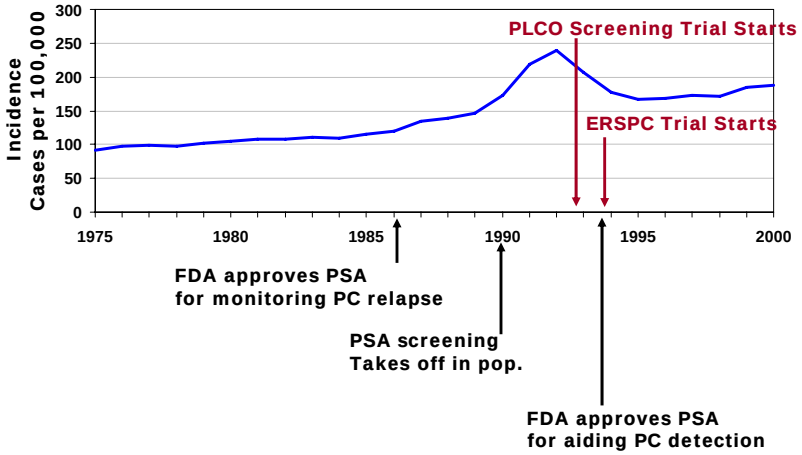
Impact of PSA Screening on Prostate Cancer Incidence and Mortality in the US



Ruth Etzioni
Fred Hutchinson Cancer Research Center
JASP Symposium, Montreal 2006

Prostate Cancer Incidence & PSA History

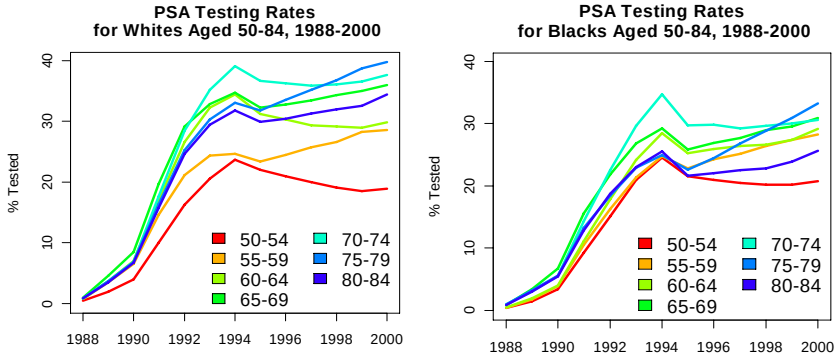


Source: SEER Whites (Delay Adjusted)

Cette présentation a été effectuée le 26 octobre 2006, au cours du Symposium "La santé publique et le dépistage du cancer : espoirs et réalités" dans le cadre des Journées annuelles de santé publique (JASP) 2006. L'ensemble des présentations est disponible sur le site Web des JASP, à l'adresse http://www.inspq.qc.ca/jasp.

PSA Screening Frequencies in the US

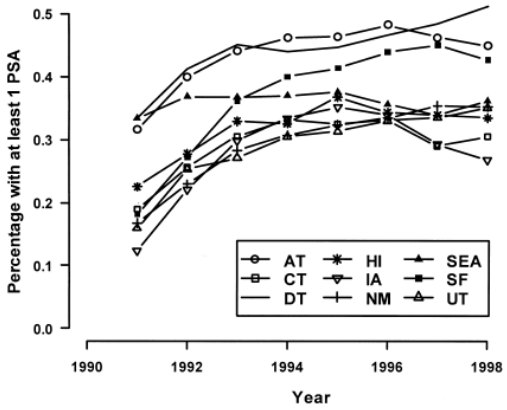
Proportion of eligible men (alive, without prostate cancer) receiving at least one test in a given year



Source: Mariotto A. et al, submitted. Data from 2000 NHIS and SEER-Medicare

Variation across 9 Geographic Areas of the US

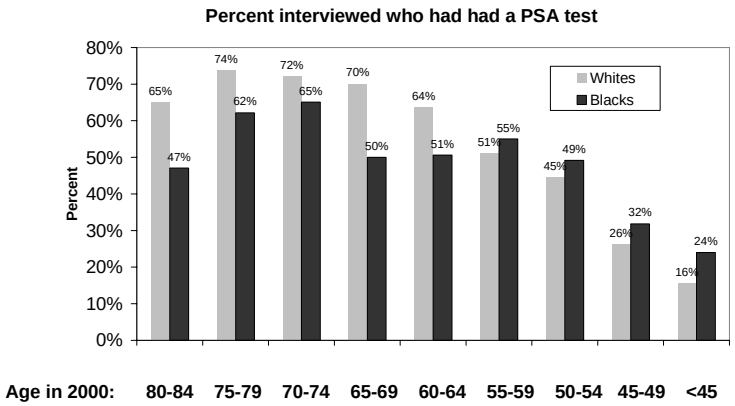
Shaw et al; AJE 2004



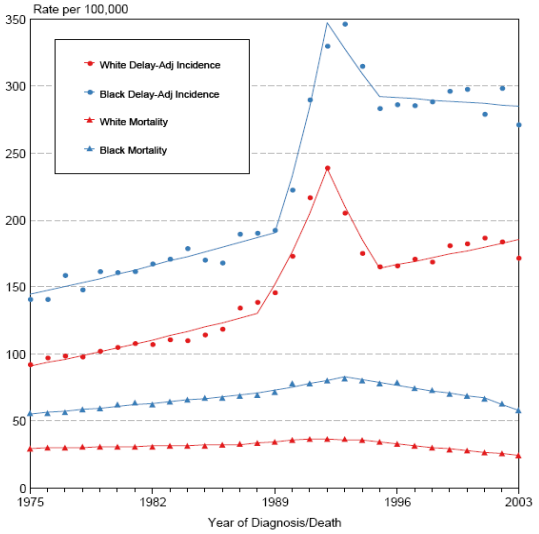
Low-utilization:
- Connecticut
- Hawaii
- Iowa
- New Mexico
- Utah

High-utilization:
- Atlanta
- Detroit

PSA Utilization From 2000 NHIS



Prostate Cancer
Delay-Adjusted SEER Incidence & US Mortality
1975-2003



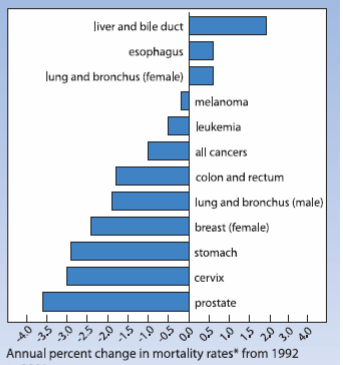
Prostate Cancer Mortality has declined by 33%since 1992

Cancer Mortality in the US: Status Report

STAT BITE

Trends in Cancer Mortality by Primary Cancer Site, 1992–2001

According to this year's Annual Report to the Nation on the Status of Cancer, incidence rates for all cancers combined decreased by 0.5% per year from 1991 through 2001. Death rates decreased by 1.1% per year from 1993 to 2001 for all cancers combined and for 11 of the top 15 cancers in men and for 8 of the top 15 cancers in women.



Sources: *Annual Report to the Nation on the Status of Cancer, 1975–2001, with a Special Feature Regarding Survival*, Cancer 2004; DOI 10.1002/cncr.20288; *Cancer Statistics Review 1975–2001*, (NCI 2004), access at http://seer.cancer.gov.

Has Mortality Declined Because of PSA Screening?

Is PSA Screening Beneficial?

The Positive Perspective

Annals of Internal Medicine | In the Balance

Viewpoint: Expanding Prostate Cancer Screening

William J. Catalona, MD; Stacy Loeb, MD; and Misop Han, MD

Prostate cancer screening is controversial, and major professional associations offer differing screening guidelines. The authors address 3 key issues about prostate cancer screening: 1) the prostate-specific antigen (PSA) criteria to recommend a prostate biopsy, 2) the appropriate age to start screening, and 3) the appropriate age to stop screening. The authors argue, on the basis of evidence published since 2000, that data supporting the efficacy of PSA screening are convincing. They recommend screening for risk assessment for average-risk men beginning at age 40 years, screening selected healthy men older than age 70 years, and lowering the PSA threshold for considering biopsy to 2.5 ng/mL for all men.

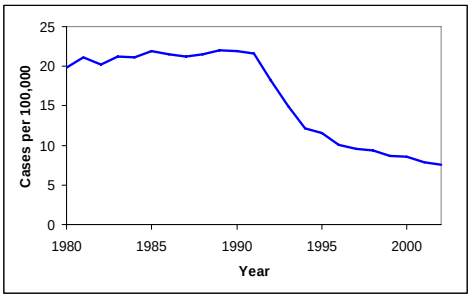
Ann Intern Med. 2006;144:441-443. www.annals.org
For author affiliations, see end of text.

"The authors argue, on the basis of evidence published since 2000, that data supporting the efficacy of PSA screening are convincing."

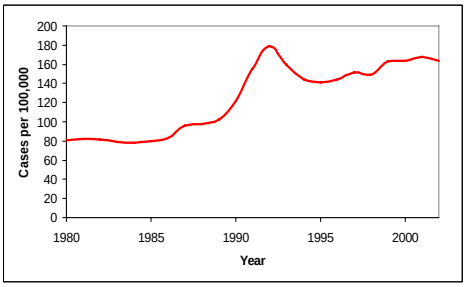
The Case For

The Most Compelling Data: Stage-Specific Incidence In SEER

Distant Stage



Local/Regional Stage



The Negative Perspective

Annals of Internal Medicine | In the Balance

Viewpoint: Limiting Prostate Cancer Screening

Richard M. Hoffman, MD, MPH

Prostate cancer screening is controversial, and major professional associations offer differing screening guidelines. The author addresses 3 key issues about prostate cancer screening: 1) the prostate-specific antigen (PSA) criteria to recommend a prostate biopsy, 2) the appropriate age to start screening, and 3) the appropriate age to stop screening. The author argues, on the basis of evidence published since 2000, that data supporting the efficacy of PSA screening remain unconvincing. The author recommends that screening should not be expanded to include average-risk men younger than age 50 years or older than age 75 years and that a PSA threshold below 4.0 ng/mL should not be used to trigger biopsy referral.

Ann Intern Med. 2006;144:438-440. www.annals.org
For author affiliation, see end of text.

" Without convincing data to support the efficacy of PSA screening, efforts to begin screening average-risk men at an earlier age and lowering the PSA threshold for biopsy are inappropriate."

Albertsen 2005

VIEWPOINT
www.nature.com/clinicalpractice/onc

What is the value of screening for prostate cancer in the US?

Peter C Albertsen

PC Albertsen is Professor and Chief of Urology at the Univers of Connecticu Center, Farm CT, USA.

"The associated morbidity and cost of a public-health policy favoring widespread screening are unacceptable. Until better data become available from the large randomized trials currently underway, the true balance of benefits and risks remains a matter of opinion…"

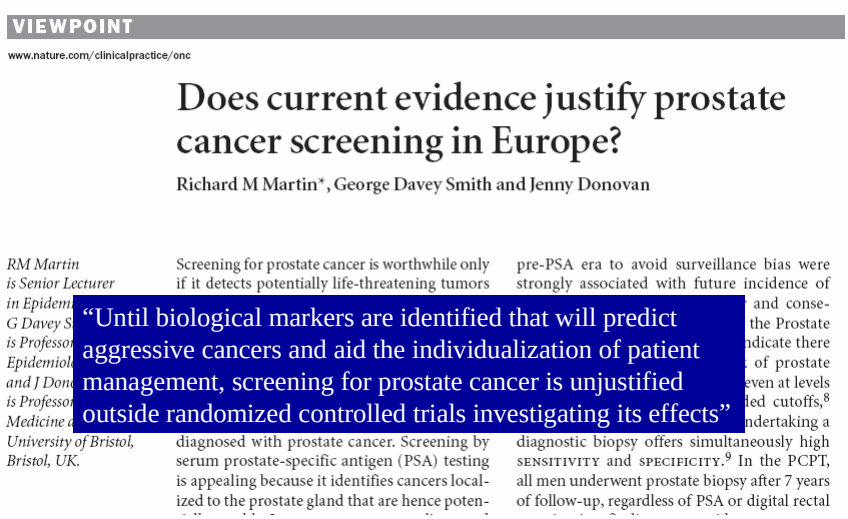
Although practiced by clinicians in the US for over a decade, screening for prostate cancer using prostate-specific antigen (PSA) remains

the high prevalence of prostate cancer among men with PSA levels of less than 4.0 ng/ml has heightened the debate concerning the value of PSA testing.[1] As part of a large chemo-

or 7 (3+4). Many pathologists are reluctant to report Gleason scores of less than 6 because of the high probability that patients are harboring

in a mean lead time in diagnosis of 12.5 years (range 11.6–14.1 years).[4] They suggest that annual screening from age 55 to age 67 results in an overdetection rate of 50% and increases

Martin, Smith, Donovan 2005



VIEWPOINT

www.nature.com/clinicalpractice/onc

Does current evidence justify prostate cancer screening in Europe?

Richard M Martin*, George Davey Smith and Jenny Donovan

RM Martin
is Senior Lecturer
in Epidem
G Davey S
is Professor
Epidemiol
and J Don
is Professor
Medicine a
University of Bristol,
Bristol, UK.

Screening for prostate cancer is worthwhile only if it detects potentially life-threatening tumors

pre-PSA era to avoid surveillance bias were strongly associated with future incidence of

and conse-

the Prostate

ndicate there

of prostate

even at levels

ied cutoffs,[8]

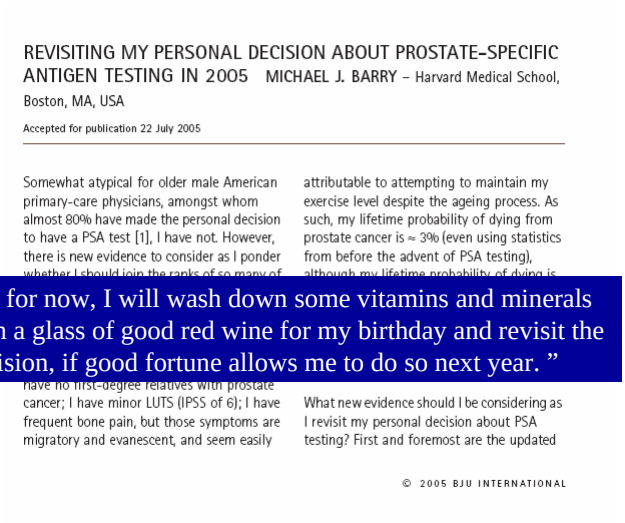
ndertaking a

diagnosed with prostate cancer. Screening by serum prostate-specific antigen (PSA) testing is appealing because it identifies cancers localized to the prostate gland that are hence poten-

diagnostic biopsy offers simultaneously high SENSITIVITY and SPECIFICITY.[9] In the PCPT, all men underwent prostate biopsy after 7 years of follow-up, regardless of PSA or digital rectal

"Until biological markers are identified that will predict aggressive cancers and aid the individualization of patient management, screening for prostate cancer is unjustified outside randomized controlled trials investigating its effects"

Barry, 2005



REVISITING MY PERSONAL DECISION ABOUT PROSTATE-SPECIFIC ANTIGEN TESTING IN 2005 MICHAEL J. BARRY – Harvard Medical School, Boston, MA, USA

Accepted for publication 22 July 2005

Somewhat atypical for older male American primary-care physicians, amongst whom almost 80% have made the personal decision to have a PSA test [1], I have not. However, there is new evidence to consider as I ponder

attributable to attempting to maintain my exercise level despite the ageing process. As such, my lifetime probability of dying from prostate cancer is ≈ 3% (even using statistics from before the advent of PSA testing),

have no first-degree relatives with prostate cancer; I have minor LUTS (IPSS of 6); I have frequent bone pain, but those symptoms are migratory and evanescent, and seem easily

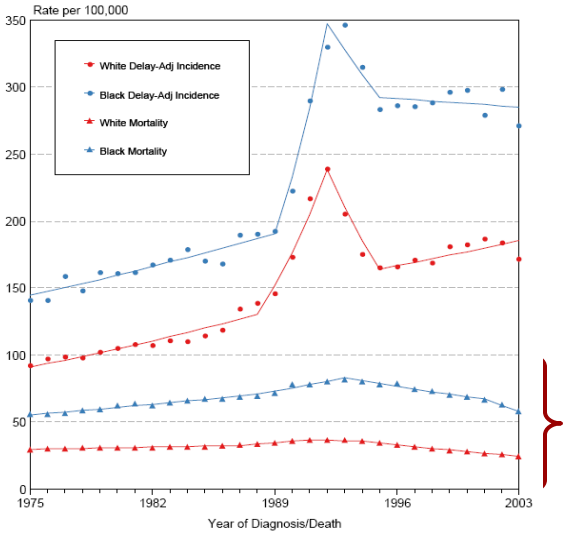
What new evidence should I be considering as I revisit my personal decision about PSA testing? First and foremost are the updated

"So for now, I will wash down some vitamins and minerals with a glass of good red wine for my birthday and revisit the decision, if good fortune allows me to do so next year. "

The Case Against

- Mortality began declining very soon after screening became widespread
- Population studies have been mostly negative
  - Ecologic studies
  - Case-control studies
- Other factors have changed
  - Radical prostatectomy, hormone therapy
- Concern about costs of screening, particularly overdiagnosis

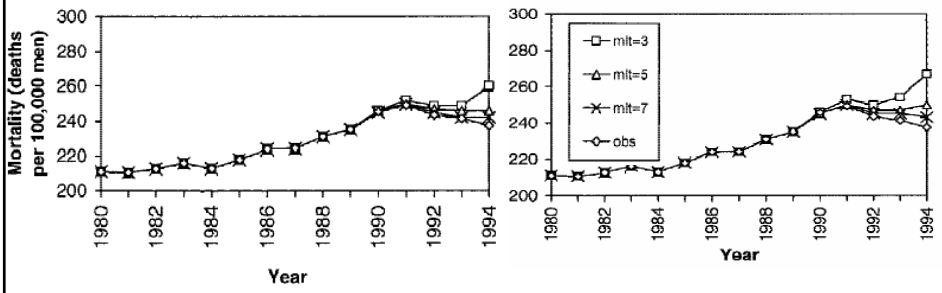
Prostate Cancer
Delay-Adjusted SEER Incidence & US Mortality
1975-2003



Prostate Cancer Mortality has declined by 33%since 1992

Can PSA Screening Explain Early Declines in Prostate Cancer Mortality?

- Only if:
  - Mean Lead Time (MLT) extremely short (3 years or less)
  - Survival benefit associated with screening is very great, i.e., hazard ratio for post-lead time survival < 0.3. Note: value assumed in PLCO trial is approximately 0.5



Hazard ratio: 0.5

Hazard ratio 0.3

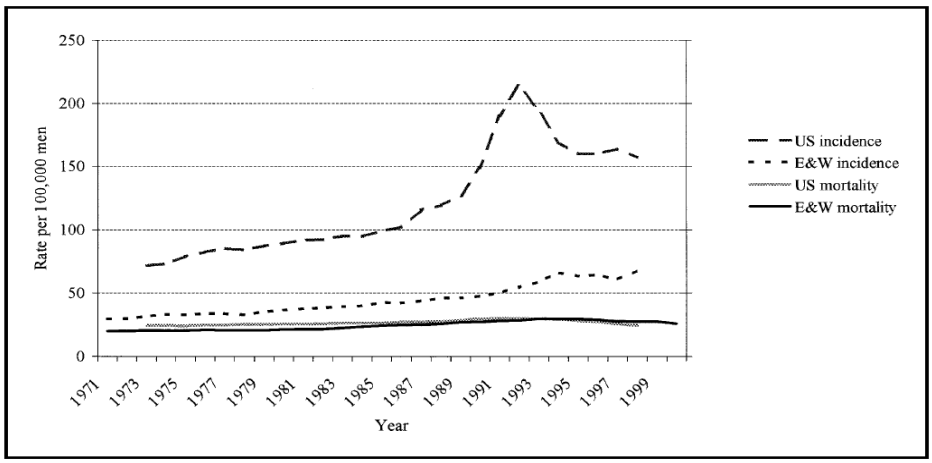
Etzioni et al, JNCI 1999

The Case Against

- Mortality began declining very soon after screening became widespread
- Population studies have been mostly negative
  - Ecologic studies
  - Case-control studies
- Other factors have changed
  - Radical prostatectomy, hormone therapy
- Concern about costs of screening, particularly overdiagnosis

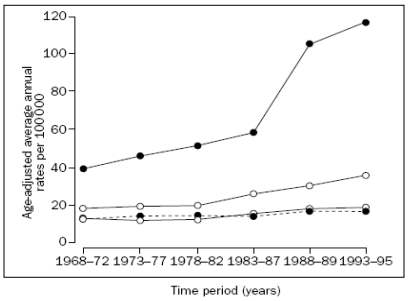
1. Ecologic Studies of PSA Screening

Trends in Britain vs US



Source: Quinn 2003

UK vs US Continued



Incidence and mortality rates of prostate cancer in white men from the US and UK (all ages)
The last data point on all curves (except for UK incidence) represents data for a 3-year period instead of a 5-year period. Redrawn from Shibata and colleagues[44] by permission of Oxford University Press.

Tannock 2002; Shibata et al 1998

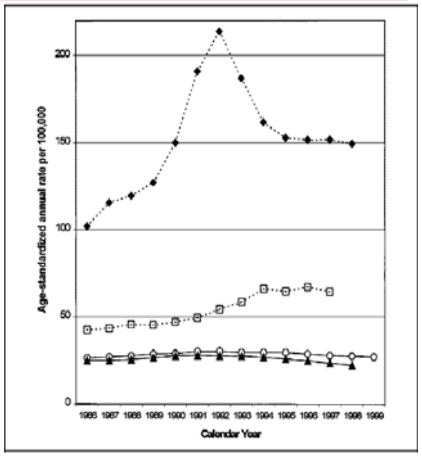
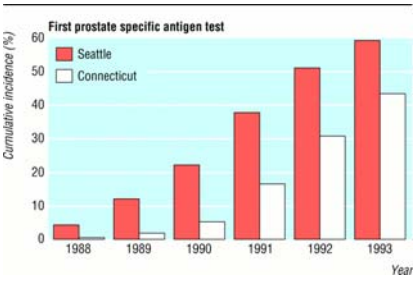


Fig. 1. Prostate cancer incidence and mortality rates in U.S. men (white) and in U.K. men (all races). Both rates from each country were age-standardized to the European standard population. ♦ = incidence, U.S. white men (nine Surveillance, Epidemiology, and End Results [SEER] registries); □ = incidence, U.K. men (all races) (England); ▲ = mortality, U.S. white men (entire U.S.); ● = mortality, U.K. men (all races) (England and Wales).

Shibata et al, JNCI 2001

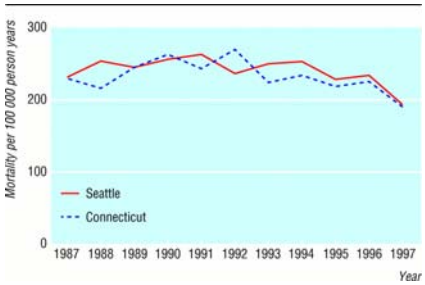
Trends in Seattle and Connecticut



PSA Utilization

	Mortality Rate Ratio	95% C.I.
1987-1997	1.03	(0.95, 1.11)
1987-1992	0.97	(0.81,1.16)
1993-1997	1.08	(0.98,1.20)

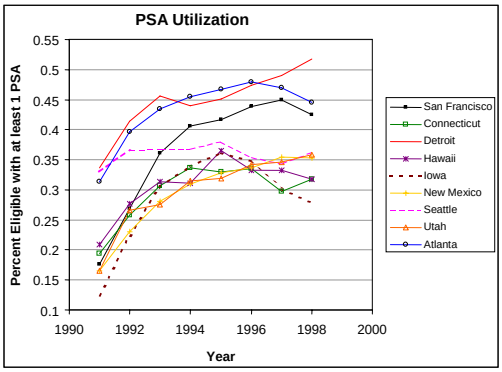
Prostate Cancer Mortality



Lu-Yao, G. Albertsen, P. Stanford, J. et al. BMJ, 2002

A Study Across 9 Areas of the US…

Shaw et al; AJE 2004

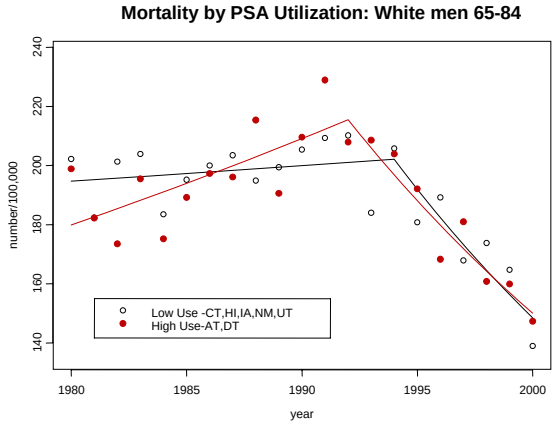


Low-utilization:
- Connecticut
- Hawaii
- Iowa
- New Mexico
- Utah

High-utilization:
- Atlanta
- Detroit

Shaw et al, AJE 2004

…Shows Similar Mortality Trends in High and Low Use Areas



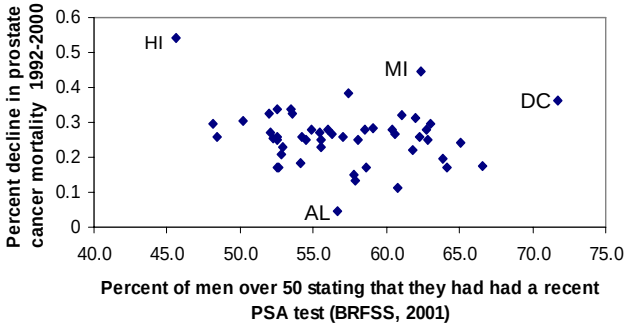
Shaw et al, AJE 2004

Ecologic Studies of PSA Screening: Limitations

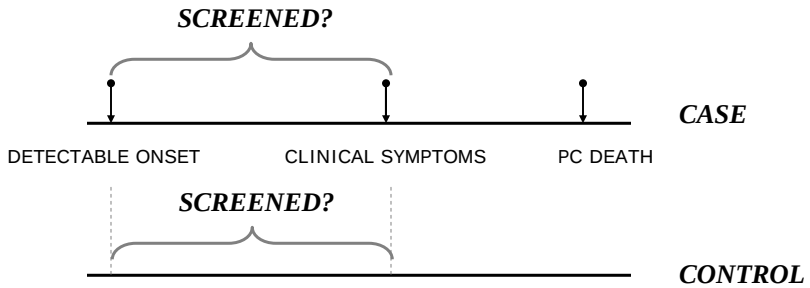
- **Timing:**
  - Ascertainment of exposure
  - Measurement of outcome
- **Confounding (positive or negative)**
  - Need treatment information
- **Omission of factors that may be affecting cancer control**
- **Many sources of variation**
  - Need extreme differences in exposure

Some Recent Data….

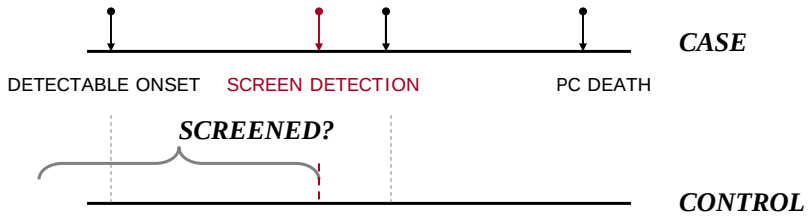
- Annual Report to the Nation on the Status of Cancer (2003)
- Prostate cancer mortality by state – APC's 1992-2000
- Also: Data from 2001 BRFSS; included a question on PSA use



2. Case-Control Studies of PSA Screening



2. Case-Control Studies of PSA Screening



Epidemiology 2005

Screening by Prostate-Specific Antigen and Digital Rectal Examination in Relation to Prostate Cancer Mortality

A Case–Control Study

Sheila Weinmann,[*] Kathryn E. Richert-Boe,[*] Stephen K. Van Den Eeden,[†] Shelley M. Enger,[‡] Benjamin A. Rybicki,[§] Jean A. Shapiro,[¶] and Noel S. Weiss[‖]

TABLE 4. Receipt of at Least 1 Prostate-specific Antigen Screening Test in Cases and Controls During 10 Yrs Up to and Including Reference Date, by Race, Among Men With No History of "Definitely or Probably" Screening Digital Rectal Examination During the Same 10 Yrs

History of 1 or More PSA Tests							
Yes							
Yes							
Yes	screening						
No	No PSA	58	105	Reference‡	24	88	Reference‡

*Unconditional logistic regression adjusted for age, health plan, reference date, and number of months in health plan in 10 yrs before reference date.
†Odds ratio for first and second categories combined.
‡Reference group is both reference categories combined.

Digital rectal screening was associated with a reduced risk of death due to prostate cancer in our population. Because of several data limitations, this study could not accurately estimate the effect of PSA screening separate from digital rectal examination

Arch Internal Med 2006

ORIGINAL INVESTIGATION

The Effectiveness of Screening for Prostate Cancer

A Nested Case-Control Study

John Concato, MD, MPH; Carolyn K. Wells, MPH; Ralph I. Horwitz, MD; David Penson, MD; Graeme Fincke, MD; Dan R. Berlowitz, MD, MPH; Gregory Froehlich, MD; Dawna Blake, MD; Martyn A. Vickers, MD; Gerald A. Gehr, MD; Nabil H. Raheb, MD; Gail Sullivan, MD, MPH; Peter Peduzzi, PhD

Background: Screening for prostate cancer is done commonly in clinical practice, using prostate-specific antigen (PSA) tests or digital rectal examination (DRE). Evidence is lacking, however, to confirm a survival benefit among screened patients. We evaluated the effectiveness of PSA, with or without DRE, in reducing

were men who were alive at the time the corresponding case patient had died, matched (1:1 ratio) for age and Veterans Affairs facility. The exposure variable (determined blind to case-control status) was whether PSA testing or

DRE was performed for screening prior to the diagnosis of prostate cancer among case patients, with the same time interval for control patients. The association of screening and overall or cause-specific (prostate cancer) mortality was adjusted for race and comorbidity.

ommendations for obtaining "verbal informed consent" from men regarding such screening should continue.

Arch Intern Med. 2006;166:38-43

A benefit of screening was not found in our primary analysis assessing PSA screening and all-cause mortality (adjusted OR 1.08, 95% CI 0.71-1.64), nor in a secondary analysis of PSA and/or DRE screening and cause-specific mortality (adjusted OR 1.13, 95% CI 0.63-2.06)

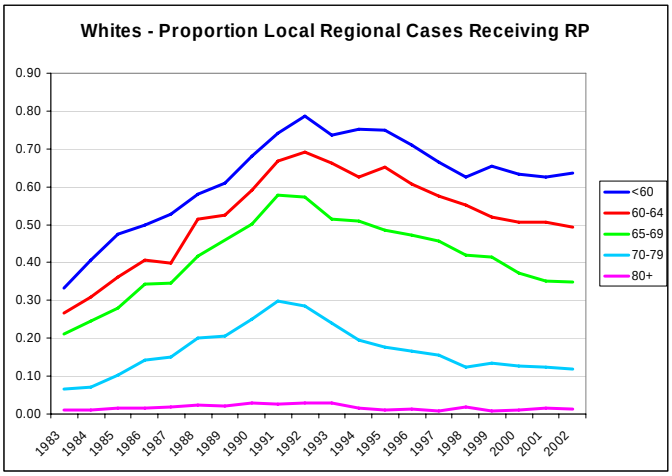
Case-Control Studies of PSA Screening: Limitations

1. **Requires sufficient followup** to identify all deaths from prostate cancer among individuals diagnosed during the study period
2. Requires ascertaining **exposure to screening during the detectable preclinical period**: misspecification or missing data will lead to an inflated OR
3. Requires **knowing the reason for the test**; incorrectly classifying diagnostic tests as screening tests will raise the OR
4. **Challenging to separately estimate effects of PSA and DRE** when both are conducted as part of a screening examination
5. Increasing use of the screening modality over time can attenuate the estimated OR

The Case Against

- Mortality began declining very soon after screening became widespread
- Population studies have been mostly negative
  - Ecologic studies
  - Case-control studies
- Other factors have changed
  - Radical prostatectomy, hormone therapy
- Concern about costs of screening, particularly overdiagnosis

Radical Prostatectomy Trends in the US



Source: SEERSTAT

Efficacy of Radical Prostatectomy

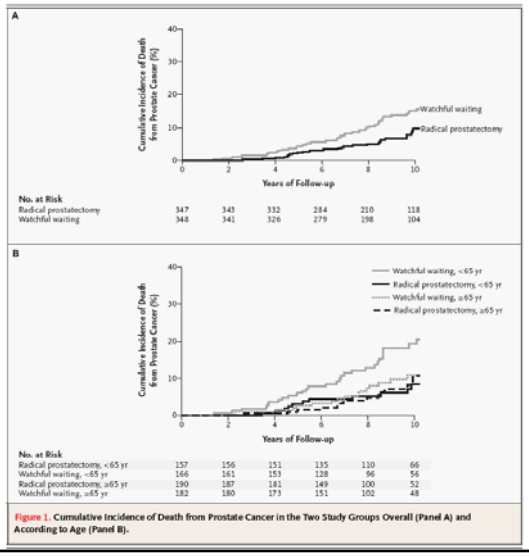
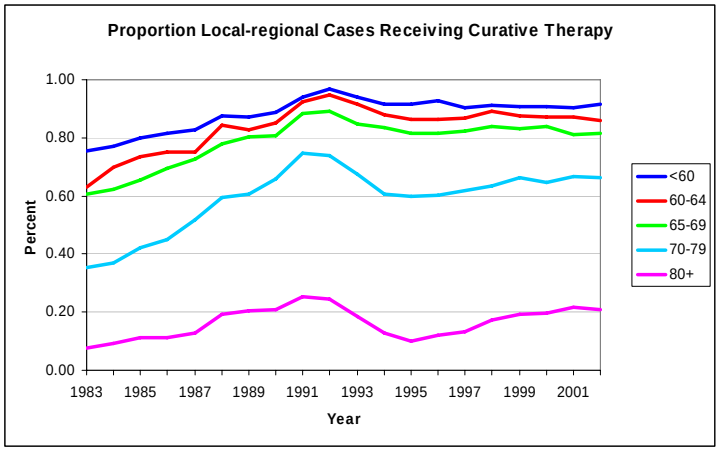


Figure 1. Cumulative Incidence of Death from Prostate Cancer in the Two Study Groups Overall (Panel A) and According to Age (Panel B).

Hazard Ratio: 0.56

Bill-Axelson et al, NEJM 2005

Curative Therapy Trends in the US



Source: SEERSTAT

Use of Hormone Ablation Therapy Increased Dramatically During the PSA era

Park et al, J Urol 2005

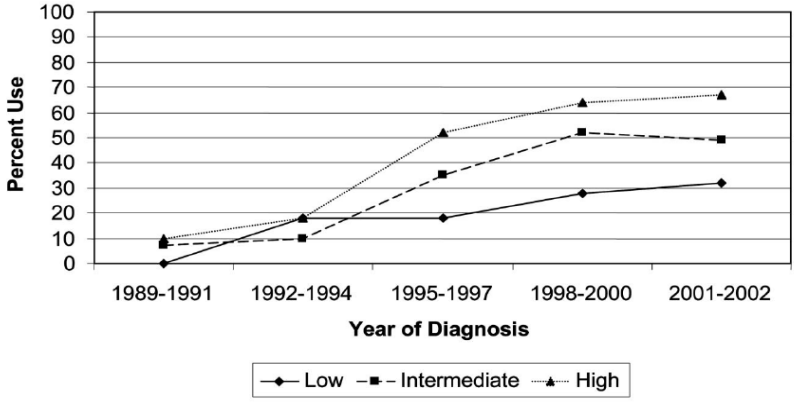


FIG. 2. Time trend of adjuvant hormone use in CaPSURE™

Use of Hormone Ablation Therapy Increased Dramatically During the PSA era

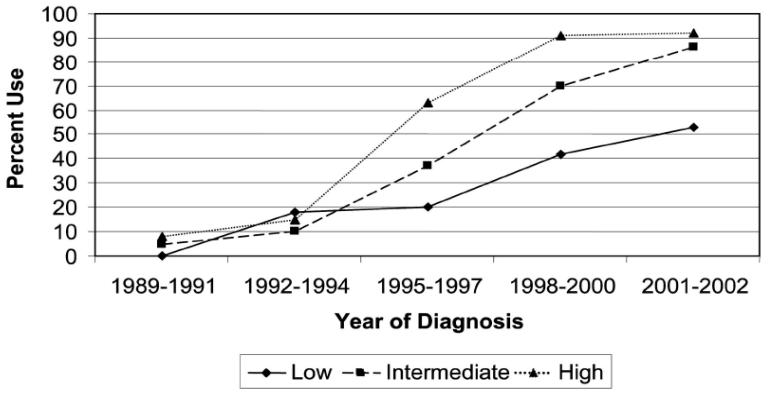


FIG. 1. Time trend of neoadjuvant hormone use in CaPSURE™

Efficacy of Hormone Ablation Therapy Used With External Bean Radiation Therapy

Bolla et al, 2002

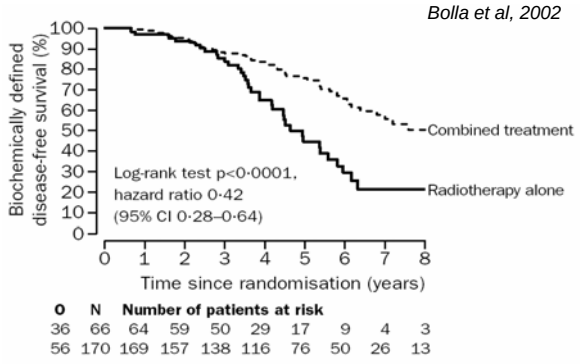


Figure 3: **Kaplan-Meier estimates of the biochemically defined disease-free survival**
O=number of failures; N=number of patients.

Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer (Review)

Kumar S, Shelley M, Harrison C, Coles B, Wilt TJ, Mason MD

"Hormone therapy combined with either prostatectomy or radiotherapy is associated with significant clinical benefits in patients with local or locally advanced prostate cancer. When given adjuvant to these primary therapies, hormone therapy, not only provides a method for local control, but there is also evidence for a significant survival advantage"

Kumar et al, Cochrane reviews, Oct 2006

THE COCHRANE COLLABORATION®

JNCI July 2003

The Prostate Cancer Conundrum

Peter C. Albertsen

In 2003, the American Cancer Society estimates that 220 900 men will be diagnosed with prostate cancer and that 28 900 will die from this disease *(1)*. Since the introduction of testing for prostate-specific antigen (PSA), the incidence of prostate cancer has increased, whereas the mortality from this disease has decreased. During the early 1990s, mortality from prostate cancer peaked in the United States at a rate of 26.4 prostate cancer deaths per 100 000 men at risk. By 1998, this rate had fallen to 21.5 per 100 000 men at risk, a decline of 2.6% per year *(2)*. The drop in prostate cancer mortality has continued, and the rate in 2003 is now similar to levels seen during the 1950s, 1960s, and early 1970s, the years preceding the widespread use of transurethral prostate surgery *(1,3)*.

What is happening? Many researchers attribute these dramatic changes to the pervasive use of PSA testing. Most epidemiologists would agree that the sharp rise and subsequent fall in incidenc… direct re… for the … Some ha… lowed b… primary… U.K., C… concern… port a d… and a s… What might be another plausible explanation?

The article by Cooperberg et al. *(8)* appearing in this issue of the Journal suggests one intriguing possibility. The authors

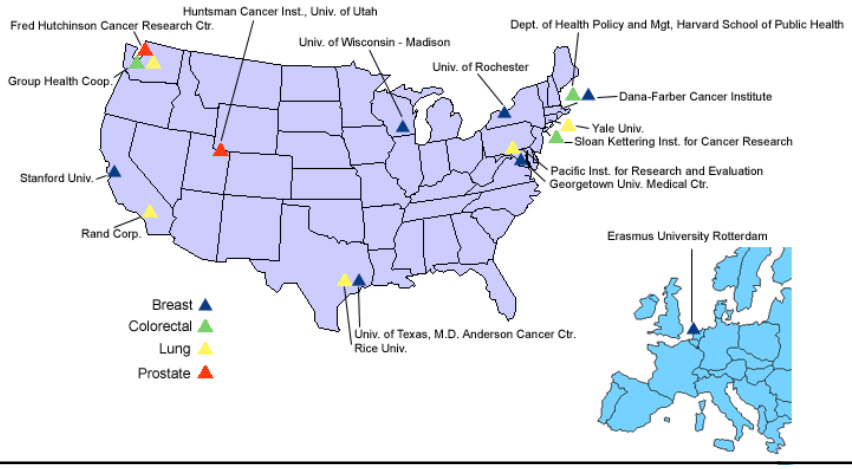
gists frequently cite declines in disease-specific mortality rates as proof of the efficacy of screening; however, two conditions must be satisfied. First, the screening test must identify disease sufficiently early in its natural history when it can be treated effectively. PSA testing appears to achieve this goal. Second, effective treatments must be available that can alter the natural outcome of the disease. The decline in prostate cancer mortality appears to support this condition, but which treatment is producing the effect?

The recently published data *(12)* from a randomized trial in Sweden comparing radical prostatectomy with watchful waiting suggests that radical surgery in the treatment of prostate cancer can have a modest impact on disease-specific survival. The treatment effect in relative terms is substantial: a decrease in disease-specific mortality of approximately 50%. In absolute terms, however, the impact is more modest: a decrease in disease-specific mortality rates from 13.6% to 7.1%. For younger men, …lder …may …ow- …rent …were …dy, …ing. …tan- …un- …10 years. For these men, observation followed by the early initiation of androgen withdrawal therapy may be the preferred approach.

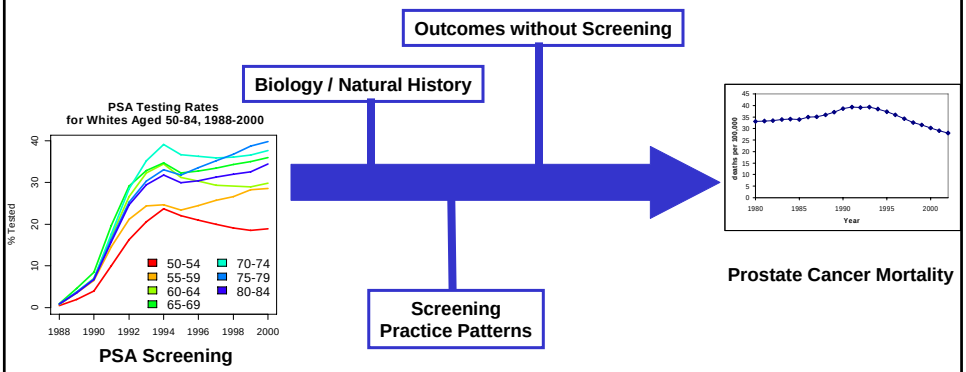
"The recent decline in prostate cancer mortality rates suggests that some treatment is having an impact. Whether this is the result of the early use of androgen withdrawal therapy or whether this is the result of widespread use of surgery or radiation remains to be determined…"

Cancer Intervention and Surveillance Modeling Network (CISNET)

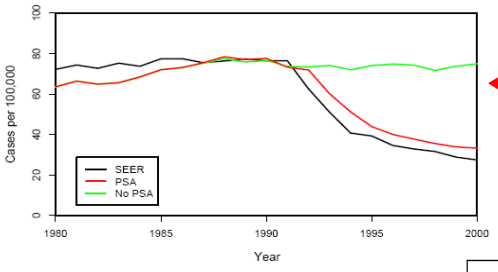
NCI-Funded consortium of modelers focused on modeling the impact of cancer control interventions (screening, treatment, prevention) on population cancer trends



Modeling the Proportion of the Mortality Decline Explained by PSA Screening

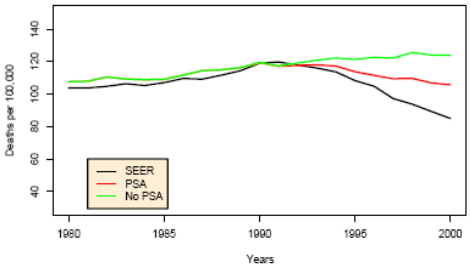


Mortality Decline from A Model of Prostate Cancer Natural History and Screening



Distant stage incidence

Prostate cancer mortality

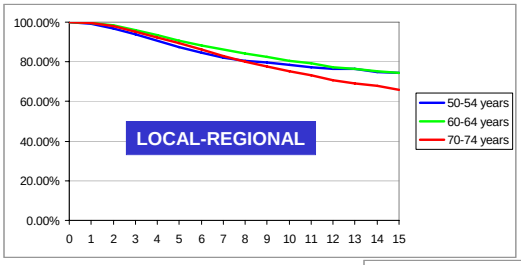


The model suggests that PSA screening can account for 50% of the mortality decline due to screening under the stage shift assumption

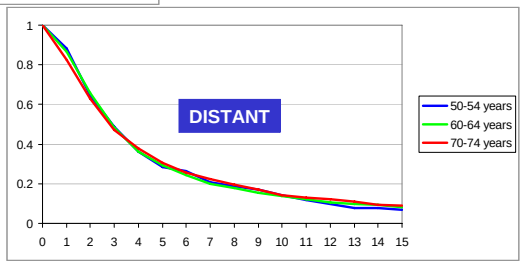
Etzioni et al, 2006 in preparation. Supported by CISNET, the Cancer Intervention & Surveillance Modeling Network

The Stage Shift Assumption

Relative Survival for SEER Cases Diagnosed 1980-1987



SCREENING



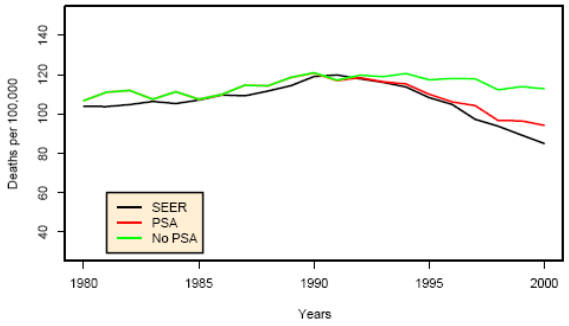
Our models show:

(1) Distant stage cases have shorter natural histories

(2) These cases also tend to have greater PSA growth from onset

Inoue et al, Biostatistics 2003

Model Results Imply a Real Improvement in Life Expectancy Over and Above Stage Shift



In this plot we have improved post-lead-time survival for local-regional stage cases beginning in 1990

Relative hazard in 2000 is 0.65 compared with the pre-PSA era

PSA and Prostate Cancer Mortality in the US: The Promise

- **My opinion**: We are seeing some evidence of PSA benefit in US prostate cancer mortality trends
  - It is probable that these benefits are not as great as what one would expect from the stage shift assumption
  - The benefits from the stage shift do not account for all the declines in mortality
- US Mortality declines in the early 1990s:
  - Consistent with increases in curative therapy in the early 1980s
- US Mortality declines in the late 1990s:
  - Consistent with increased use of hormonal therapies for locally advanced/high risk disease
  - May be synergistic with early detection

4 THE NEW YORK TIMES, WEDNESDAY, FEBRUARY 17, 1999

MEN'S HEALTH

Can the Prostate Test Be Hazardous to Your Health?

By LARRY KATZENSTEIN

FOR millions of American men over age 50, the Prostate Specific Antigen blood test for detecting prostate cancer has become a routine part of their annual checkup. If they don't ask for it, their doctors often recommend it. But there are serious concerns about the test's usefulness and whether the treatment for prostate cancer may be harming more lives than it saves.

Despite a recent barrage of high-profile endorsements for the test by Arnold Palmer and H. Norman Schwarzkopf, among others, not one major medical or public-health group endorses the screening. And in recent years, most of the groups that have evaluated the test either oppose its use for routine screening, or do not recommend it. These include the National Cancer Institute, the American College of Physicians, the American College of Preventive Medicine and the United States Preventive Services Task Force.

The American Cancer Society, which once endorsed the screening, changed its stance in 1997 and now recommends that the Prostate Specific Antigen test, also known as P.S.A., be offered annually to men 50 and older, who should be given information about the risks and benefits of treatment should cancer be found.

Even the American Urological Association, whose members are among the most enthusiastic advocates of P.S.A. testing, now endorses the new American Cancer Society policy.

Dr. Gabriel Feldman, the society's national director of prostate and colorectal cancer control, calls the P.S.A. "the most controversial medical test in the country right now."

Some objections to the screening involve errors. The test fails to detect prostate cancer in 1 in 4 men who have the disease (false-negative results), and as many as two-thirds of the men tested receive false-positive results, meaning that biopsies and other follow-ups fail to confirm the cancer finding. A P.S.A. score above four nanograms of antigen per milliliter of serum usually prompts follow-up tests.

But the main reason so many groups oppose P.S.A. screening is the lack of evidence that early detection actually improves a man's chances of surviving prostate cancer. "That's the big secret that nobody likes to talk about," Dr. Feldman said.

A discovery of cancer through P.S.A. testing usually leads to treatment, Dr. Feldman said. "But we don't have any conclusive evidence that surgery or other aggressive treatment make any difference in the long term in helping men live longer or better," he said. "Instead, we are going completely on intuition." Dr. Feldman contrasts prostate cancer with breast cancer, where clinical studies have proven that regular mammograms result in early detection and treatment that can save lives.

Dr. Feldman added that radical prostatectomy, the principal treatment for prostate cancer, causes 50 percent to 70 percent of all patients to become impotent for at least some period of time. Radiation, the other form of aggressive treatment, can cause similar side effects as well as other complications, he added. There is also some risk: approximately 1 percent of patients who undergo a radical prostatectomy die from it.

The P.S.A. detects prostate cancers 10 to 15 years earlier than was possible with the digital rectal exam. But because of the nature of prostate cancer — it is overwhelmingly a disease that afflicts elderly men and is usually very slow-growing — the early warning is often meaningless.

The prostate gland, the size of a walnut, is located in front of the rectum and beneath the bladder. The gland produces the fluid portion of semen and secretes prostate specific antigen, a protein that is pumped into the bloodstream in higher-than-normal amounts by cancerous cells.

While it is not uncommon for a few cancer cells to develop when men are in their 20's or 30's, these cells typically divide so slowly that tumors are rare in men younger than 50. After that, prostate cancer becomes increasingly common: men in their 60's and 70's have a 1-in-6 chance of being diagnosed with prostate cancer; a man living to 100 is almost certain to develop it.

But again, given prostate cancer's languid growth, most older men will die of other causes, like heart disease or stroke. Hence the adage that most prostate cancer patients die with their disease rather than from it. Moreover, the P.S.A. test cannot pinpoint those faster growing tumors for which early treatment might make a difference.

Still, the P.S.A. continues to have strong advocates, not the least of whom are patients who have had surgery and never experienced a recurrence. They are usually convinced that P.S.A. testing has prolonged their lives, if not saved them. Indeed, in some cases the test may have done just that.

And urologists, who in general treatment doesn't work, why are we using the P.S.A. to look for tumors?"

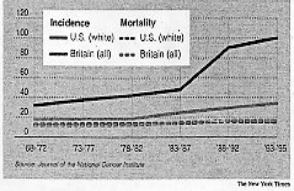
To underscore their argument, critics of the P.S.A. point to studies showing that prostate cancer screening has little effect on the mortality rates. In a 1997 study in the journal Cancer, Dr. Otis Brawley, a medical oncologist and epidemiologist at the National Cancer Institute, calculated new prostate cancer cases per 100,000 men and prostate cancer deaths per 100,000 men in nine regions of the United States from 1974 through 1994. Not surprisingly, regions screened most intensely for prostate cancer (the Seattle-Puget Sound area, for example) had a much higher incidence of the cancer than regions screening the least (Connecticut, for one).

MORTALITY rates, however, were basically identical for all nine regions — and actually slightly higher in the Seattle-Puget Sound area. Dr. Brawley cites similar findings from a recent study comparing the United States with Britain. "I believe prostate cancer screening probably does save some lives," Dr. Brawley said, "but I can prove through studies like these that it ruins some lives."

A recent study of men living near the Mayo Clinic has added more fire to the debate. The Journal of Urology this month published a report by researchers who analyzed prostate cancer deaths in Olmsted County, Minn., from 1960 to 1997. They found

Finding More Cases, Not More Deaths

Incidence and mortality rates of prostate cancer in the United States (white men) and Britain (all men) for all ages. Age-adjusted average annual rates per 100,000.



Source: Journal of the National Cancer Institute

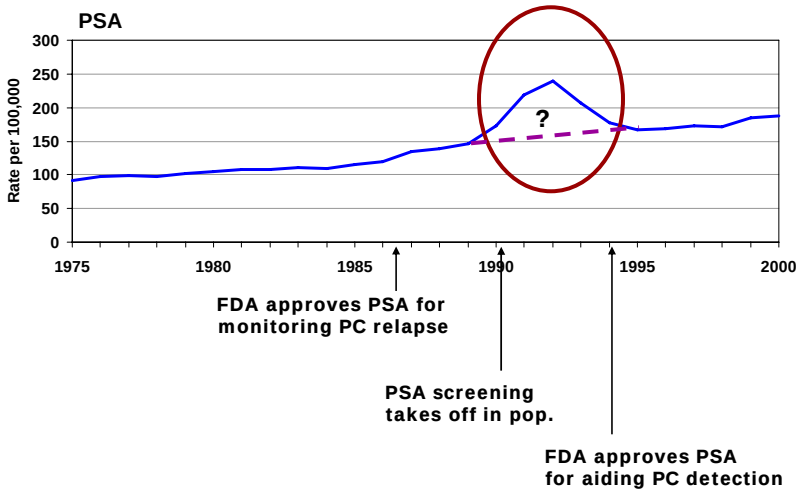
The New York Times

PSA and Prostate Cancer Incidence in the US: The Peril

- Approximately 75% or more of prostate cancers are silent!

- Main cost associated with PSA screening: **overdiagnosis**
- **Longer lead times imply more overdiagnosis**
- US incidence trends under screening inform about the lead time

Prostate Cancer Incidence Under Screening Informs About the Lead Time

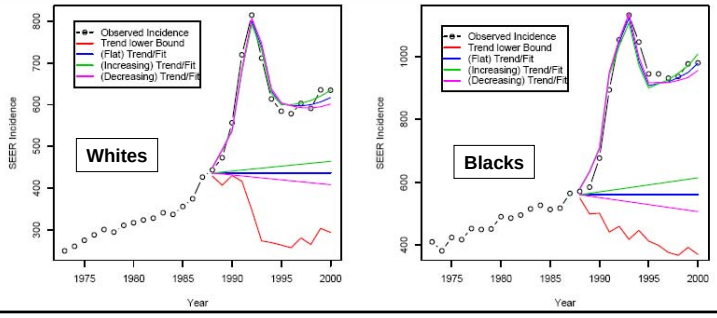


Source: SEER Whites (Delay Adjusted)

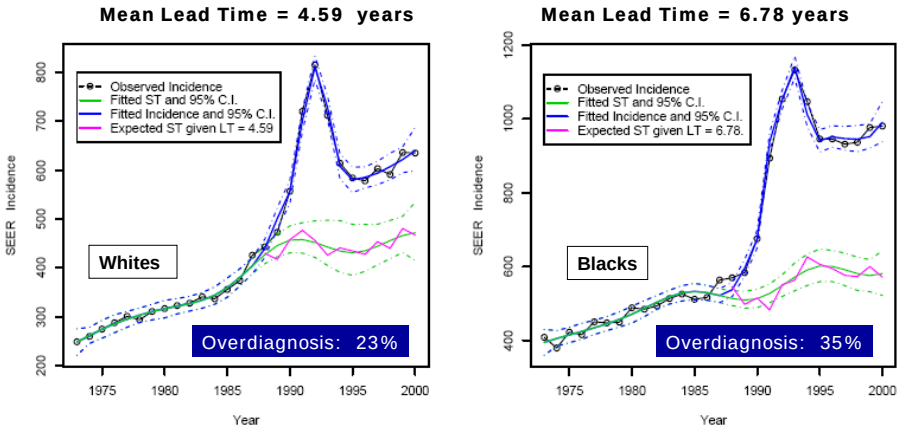
Estimated Mean Lead Times Conditional on Background Trend

Table 1: Lead time estimation given linear secular incidence trends

Trend	Blacks (SE) [95% C.I.]	Whites (SE) [95% C.I.]
Increasing	5.76 (0.21) [5.36, 6.18]	5.22 (0.24) [4.78, 5.71]
Constant	7.69 (0.28) [7.18, 8.26]	6.28 (0.27) [5.79, 6.82]
Decreasing	10.71 (0.40) [9.98, 11.51]	7.69 (0.33) [7.06, 8.37]



Simultaneous Estimation of Mean Lead Time and Smooth Background Trend



Draisma et al (2003): 57% overdiagnosis in European Trial (Rotterdam) – JNCI 2003

Telesca, Etzioni, Gulati, 2006, Biometrics, to appear

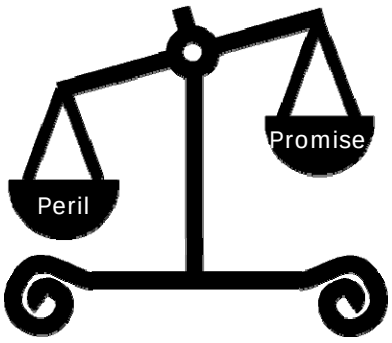
Reasons for Differences between Estimates of Overdiagnosis due to PSA Screening

- **Population differences**
  - Age, race, **baseline frequency of prostate cancer diagnosis without screening**
- Frequency of screening
- **Criteria for and compliance with biopsy recommendations**
- Biopsy protocol
- Statistical model
- Definition of lead time
- Study design: prospective screening or stored-serum study?

The Peril Is Increasing

- Recent publications from the PCPT (Thompson et al, NEJM 2003, 2004) showing that cancer can be present at low PSA levels have increased calls for lowering the PSA threshold
- Another PCPT publication (Thompson et al, JAMA 2005) showing that PSA had only 20% sensitivity at the end-of-study biopsy has created a sense that it is inadequate as a screening test
  - Many biomarker studies aimed at improving the sensitivity of PSA, biopsy
- Extended biopsy protocols (10-12 cores) are now routine
- The potential for unacceptable levels of overdiagnosis with little or no improvement in outcomes is very great (Welch et al, 2005)
  - Focus on sensitivity within the population of non-overdiagnosed cases

The Weight of Evidence Based on US Population Data



Collaborators

FHCRC

Lurdes Inoue

Seth Falcon

Kent Karnofski

Steve Zeliadt

Pam Shaw

Dave Penson, MD

Noel Weiss

Preet Dhillon

NCI

Eric Feuer

Angela Mariotto

CISNET Collaborators

Elizabeth Slate

Christopher Morrell

Alex Tsodikov

Funding Source: CISNET U01, NCI