



An Ecologic Study of Prostate-specific Antigen Screening and Prostate Cancer Mortality in Nine Geographic Areas of the United States

Pamela A. Shaw^{1,2}, Ruth Etzioni¹, Steven B. Zeliadt¹, Angela Mariotto³, Kent Karnofski¹, David F. Penson⁴, Noel S. Weiss^{1,5}, and Eric J. Feuer³

¹ Fred Hutchinson Cancer Research Center, Seattle, WA.

² Department of Biostatistics, School of Public Health and Community Medicine, University of Washington, Seattle, WA.

³ Statistical Research and Applications Branch, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD.

⁴ Keck School of Medicine, University of Southern California/Norris Cancer Center, Los Angeles, CA.

⁵ Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA.

Received for publication February 26, 2004; accepted for publication June 24, 2004.

Ecologic studies of cancer screening examine cancer mortality rates in relation to use of population screening. These studies can be confounded by treatment patterns or influenced by choice of outcome and time horizon. Interpretation can be complicated by uncertainty about when mortality differences might be expected. The authors examined these issues in an ecologic analysis of prostate-specific antigen (PSA) screening and prostate cancer mortality across nine cancer registries in the United States. Results suggested a weak trend for areas with greater PSA screening rates to have greater declines in prostate cancer mortality; however, the magnitude of this trend varied considerably with the time horizon and outcome measure. A computer model was used to determine whether divergence of mortality declines would be expected under an assumption of a clinically significant survival benefit due to screening. Given a mean lead time of 5 years, the model projected that differences in mortality between high- and low-use areas should be apparent by 1999 in the absence of other factors affecting mortality. The authors concluded that modest differences in PSA screening rates across areas, together with additional sources of variation, could have produced a negative ecologic result. Ecologic analyses of the effectiveness of PSA testing should be interpreted with caution.

computer simulation; confounding factors (epidemiology); mass screening; mortality; prostate-specific antigen; prostatic neoplasms

Abbreviations: APC, annual percentage change; HT, hormone ablation therapy; PSA, prostate-specific antigen; SEER, Surveillance, Epidemiology, and End Results.

Prostate-specific antigen (PSA) screening for prostate cancer has become common practice among older men in the United States. The test was introduced in 1986 to monitor patients after diagnosis, but it was adopted for screening beginning in the late 1980s. By 1998, almost 40 percent of White men and 35 percent of Black men over age 65 years in the United States were being tested each year (1).

The rapid adoption of this test in the United States has occurred against a backdrop of controversy about its benefits and costs. Two large-scale clinical trials of PSA screening in Europe and the United States are ongoing, but results are not

expected before 2008 (2, 3). In the absence of direct evidence about test efficacy, attention has focused on population trends in prostate cancer incidence and mortality. Declines in distant-stage incidence and prostate cancer mortality in the United States (4–6) have fueled speculation that the test may be saving lives (7, 8).

Ecologic studies of cancer screening examine trends in cancer mortality rates in relation to the use of population screening. International studies of PSA screening have generally yielded negative findings. One noted that mortality rates were declining in the United States but not

Correspondence to Dr. Ruth Etzioni, Program in Biostatistics, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, M2-B230, Seattle, WA 98109-1024 (e-mail: retzioni@fhcrc.org).

in Australia, whereas the use of PSA screening had been high in both places (9). A second study observed that although PSA screening rates (as measured by prostate cancer incidence) in the United States and the United Kingdom were dramatically different, mortality rates in 1993–1995 were similar (10).

Ecologic analyses within countries have yielded conflicting results. An Austrian study found significantly lower prostate cancer mortality rates in the Tyrol region, where a mass screening program was introduced in 1993, than in the rest of the country (11). However, an Italian study found that while prostate cancer incidence differed dramatically between two regions in Tuscany, prostate cancer mortality rates did not (12). Similarly, a US study comparing Seattle-Puget Sound, Washington, and Connecticut found that although PSA testing, biopsy, and treatment rates in Seattle through 1993 were higher than those in Connecticut, mortality rates through 1997 in the two areas were virtually the same (13). A recent Canadian study also found no association between changes in prostate cancer incidence and mortality in 88 small health areas within the British Columbia Cancer Registry (14).

One common concern of ecologic studies is that results may be biased by the omission of important confounders. In screening studies, it is particularly important to consider changes in treatment patterns that may have occurred concurrently with dissemination of the screening test. For example, the increased use of PSA screening over time has been accompanied by a trend toward earlier and more frequent use of hormone ablation therapy (HT) after diagnosis (15). Thus, HT use could be a confounding variable in ecologic analyses of PSA screening and prostate cancer mortality.

In ecologic studies of screening, the principal outcome of interest is the change in disease-specific mortality following introduction of the screening test. However, there are different ways to express mortality changes over time. These include the percentage change in mortality from an earlier to a later calendar period or the annual percentage change (APC) in mortality over a specified interval. Different measures may yield different outcomes; moreover, results may be affected by the calendar period over which the study has been conducted. Studies conducted too soon after the test has been introduced may fail to show any association with mortality, even if screening is efficacious. In fact, updates of two studies (9, 10) comparing mortality rates in the United States with those in the United Kingdom and Australia have found growing mortality reductions in the United States and Australia with additional years of data (16, 17). The timing of mortality declines depends on the lead time, which is the time by which the test advances diagnosis. Therefore, knowledge of lead time is critical for study interpretation. With PSA screening, the mean lead time has been estimated to be 5 years (18) or more (19).

This article addresses these issues of bias and interpretation through an ecologic analysis within nine registries of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (Bethesda, Maryland). We directly measured the frequency of PSA screening use among men without a prostate cancer diagnosis in each

registry by using data from a linked SEER-Medicare database (20). To assess sensitivity of our results to the choice of outcome, we considered three different measures of mortality change over time as well as different time horizons for estimating mortality declines. To illustrate how results might change when information on treatment trends is included, we conducted analyses with and without adjustment for the use of HT. To determine whether mortality differences across areas reflect those expected under different efficacy and lead-time assumptions, we used a computer model that simulates PSA testing and prostate cancer mortality in the US population.

MATERIALS AND METHODS

Our analysis covers nine SEER registries: those in the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah; the metropolitan areas of Atlanta, Georgia, Detroit, Michigan, and San Francisco-Oakland, California; and the 13-county Seattle-Puget Sound area. To avoid confounding by race, we analyzed data for Whites only. In this paper, all rates are presented for men aged 65–84 years at diagnosis and were age adjusted to the 2000 US Census population.

PSA screening use

Information on PSA testing among men aged 65 years or older was obtained for each SEER registry from linkage between the SEER database and Medicare claims (1, 21, 22). Medicare claims are the most complete record of PSA screening use over the study period because nationally representative surveys (23, 24) began including questions on PSA screening use in only the late 1990s. The SEER-Medicare files provide information on cancer cases as well as a 5 percent sample of controls without a history of a cancer diagnosis. We used data from both cases and controls, weighting controls by a factor of 20 to 1. The linkage data for this analysis contained claims from 1991 to 1998 and diagnosis information through 1996.

For each year, PSA screening use was defined as the percentage of men without a prostate cancer diagnosis who had at least one PSA test that year. Linkage with the SEER database allowed us to exclude all tests conducted after a prostate cancer diagnosis. For tests conducted prior to diagnosis, it was not possible to distinguish true screening tests from diagnostic tests because the reason for testing was not available. If a test was followed by another test within 3 months, only the first test was counted. We considered use up to age 84 years because men in this age group are generally considered eligible for prostate cancer screening.

To summarize the use of PSA screening over time within each registry, we computed the average proportion of men aged 65–84 years tested each year from 1991 to 1996.

Mortality outcomes

Prostate cancer mortality rates through 1999 were obtained from the National Center for Health Statistics (Hyattsville, Maryland) by using SEER data. We considered

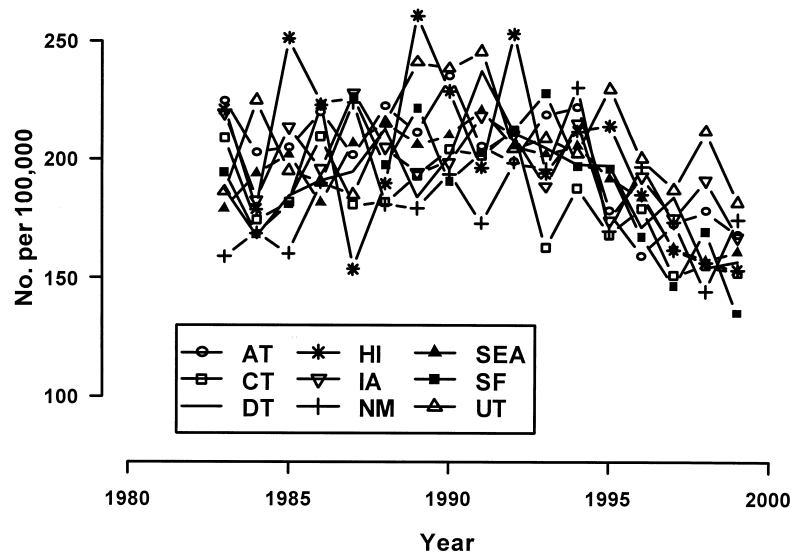


FIGURE 1. Annual prostate cancer mortality rates for White men aged 65–84 years, age adjusted to the 2000 US Census population. AT, Atlanta, Georgia; CT, Connecticut; DT, Detroit, Michigan; HI, Hawaii; IA, Iowa; NM, New Mexico; SEA, Seattle, Washington; SF, San Francisco, California; UT, Utah.

three different outcomes to describe prostate cancer mortality trends.

The first outcome was the percentage change in prostate cancer mortality between two intervals I_1 and I_2 . For I_1 , we used three different baseline intervals: 1985–1987, 1988–1990, and 1991–1993. The interval 1985–1987 represents the period before PSA screening was introduced, 1988–1990 was just prior to widespread adoption of PSA screening, and 1991–1993 spans the peak in prostate cancer mortality in the vast majority of registries. For I_2 , we used the interval 1997–1999. Three-year averages were calculated to reduce the effect of year-to-year variability in the observed rates within each registry.

Our second outcome was the APC in prostate cancer mortality between the years Y_1 and Y_2 . A negative APC describes a decreasing trend. The APC is estimated by a least-squares regression line fit to the logarithm of the observed mortality rates between Y_1 and Y_2 . For Y_1 , we used 1991; for Y_2 , we used 1999. In contrast to the percentage decline, which uses the mortality rates for just I_1 and I_2 , the APC utilizes all data between Y_1 and Y_2 inclusive. However, the APC measure imposes a linear assumption on the temporal changes in the log of the prostate cancer mortality rate. Because most registries showed that mortality rates were level or increased slightly until about 1991 and then declined steadily afterward (figure 1), Y_1 was chosen as 1991 to satisfy the linearity condition.

Our third outcome was the annual, age-adjusted prostate cancer mortality rates in the population. For stability and ease of analysis, we grouped registries by their levels of PSA screening use and computed annual, age-adjusted mortality rates for high- and low-use areas.

Practice patterns

In analyzing practice patterns, we focused on trends in HT use within 2 years following diagnosis. Use of HT among men with early stage disease has increased dramatically over the past decade (15), and this change has been proposed as a possible explanation for observed declines in disease-specific mortality (6, 25). Using the SEER-Medicare linked

TABLE 1. Average population size by SEER* Program cancer registry for 1991–1993 and 1997–1999, United States

Registry	Average population	
	1991–1993	1997–1999
San Francisco-Oakland, California	129,849	136,650
Connecticut	160,621	163,553
Detroit, Michigan	145,506	152,343
Hawaii	12,620	13,708
Iowa	155,374	155,518
New Mexico	65,448	74,876
Seattle (Puget Sound), Washington	146,541	158,149
Utah	62,885	71,803
Atlanta, Georgia	50,583	58,146
Combined SEER Program registries		
CT/HI/IA/NM/UT*	456,949	479,457
DT/AT*	276,391	294,799

* SEER, Surveillance, Epidemiology, and End Results; CT/HI/IA/NM/UT, Connecticut, Hawaii, Iowa, New Mexico, Utah; DT/AT, Detroit, Michigan; Atlanta, Georgia.

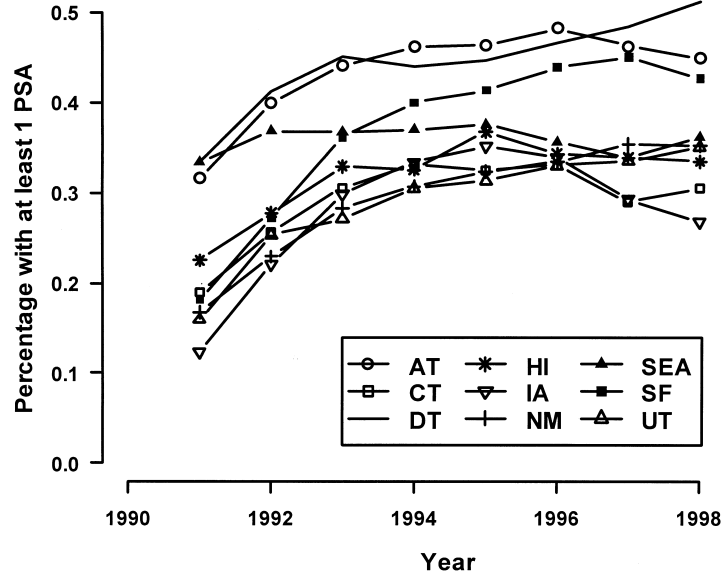


FIGURE 2. Annual percentage of men without a prostate cancer diagnosis who received at least one prostate-specific antigen (PSA) test. Rates are for White men aged 65–84 years and were age adjusted to the 2000 US Census population. AT, Atlanta, Georgia; CT, Connecticut; DT, Detroit, Michigan; HI, Hawaii; IA, Iowa; NM, New Mexico; SEA, Seattle, Washington; SF, San Francisco, California; UT, Utah.

database, we assessed the frequency of treatment with luteinizing hormone-releasing hormone agonists among localized/regional cases diagnosed from 1991 to 1996 who were treated initially with prostatectomy or radiation therapy. We used the Kaplan-Meier estimator to calculate the proportion of men who received any Medicare-covered HT up to 24

months after diagnosis (Health Care Common Procedure Coding System (HCPCS) codes J9202, J9217, J9218 for leuprolide/goserlin), with censoring due to death or loss to follow-up. Men were also censored if they received an orchiectomy within 24 months of diagnosis (*International Classification of Diseases*, Ninth Revision, procedure code

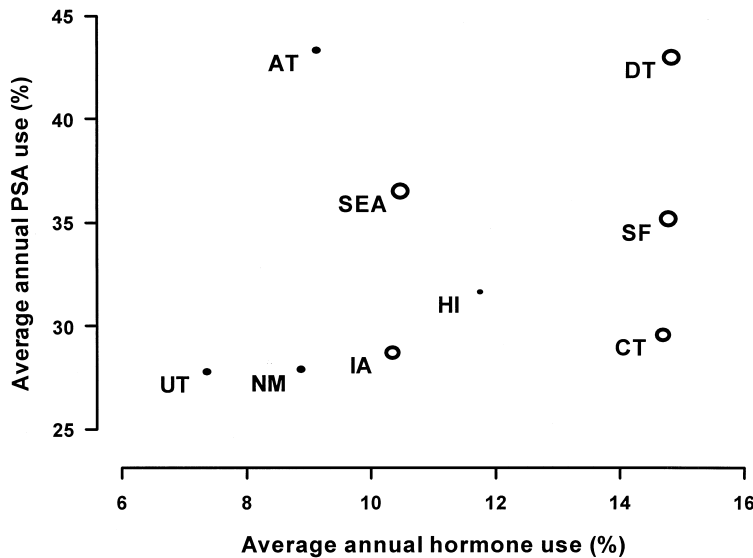


FIGURE 3. Average annual prostate-specific antigen (PSA) screening vs. hormone ablation therapy use (%), averaged over 1991–1996. The size of the plotting character is proportional to the size of the registry of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. AT, Atlanta, Georgia; CT, Connecticut; DT, Detroit, Michigan; HI, Hawaii; IA, Iowa; NM, New Mexico; SEA, Seattle, Washington; SF, San Francisco, California; UT, Utah.

TABLE 2. Estimated unadjusted regression coefficients for the use of PSA* screening from regression analysis of the percentage decline† and the annual percentage decline‡ in prostate cancer mortality, United States

Outcome measure	Baseline interval	Regression coefficient	<i>p</i> value	Correlation coefficient
Percentage decline	1985–1987	0.12	0.80	0.10
	1988–1990	0.36	0.33	0.37
	1991–1993	0.55	0.14	0.53
Annual percentage decline	1991	0.11	0.06	0.64

* PSA, prostate-specific antigen.

† The percentage decline is between a baseline rate I_1 , set to one of 1985–1987, 1988–1990, and 1991–1993, and $I_2 = 1997$ –1999.

‡ The annual percentage decline is for 1991–1999.

624x/HCPSC codes 54520, 54521, 54530). HT rates were averaged similarly to PSA screening rates, from 1991 to 1996.

Ecologic analysis

We conducted three statistical analyses to examine the association between PSA screening rates and prostate cancer mortality. First, we performed a weighted linear regression across registries to determine the association between percentage decline in mortality and PSA screening rates. Second, we conducted a weighted regression of the APC measure by registry and PSA screening rates. Third, we used Poisson regression to analyze the prostate cancer mortality rates at different points on the mortality curve for registries in which PSA screening rates were consistently high versus consistently low.

Weighted linear regression requires an assessment of variability in the outcome. For percentage decline, we used a Monte Carlo approach. First, we assumed that the observed number of prostate cancer deaths within a given 5-year age group followed a Poisson distribution. For the two time periods of interest, we independently simulated numbers of

prostate cancer deaths within each age group by using observed counts as mean parameters. Corresponding age-adjusted mortality rates were then calculated to yield a percentage decline from the earlier to the later calendar period. This procedure was repeated 10,000 times to produce an empirical estimate for the variance of the percentage-decline measure within each registry. The inverse of this variance was used as the weight in the regression analysis. For APC, we used the standard variance estimate from least-squares regression.

To compare the age-adjusted mortality curves for high-versus low-use areas, we used Poisson regression. The Poisson models compared mortality rates over specified 3-year intervals (1985–1987, 1988–1990, 1991–1993, 1994–1996, and 1997–1999). In a supporting analysis, we calculated the percentage decline and APC summary measures for the high- and low-use groups and compared them by using a *t* test.

Interpretation of results

To determine whether divergence of mortality declines across areas would be expected within the time horizon of

TABLE 3. Estimated regression coefficients for the use of PSA* screening and hormone ablation therapy from multivariate regression analysis of the percentage decline† and the annual percentage decline‡ in prostate cancer mortality, United States

Outcome measure	Baseline interval	PSA screening use			Hormone ablation therapy use		
		Slope	<i>p</i> value	Partial correlation coefficient	Slope	<i>p</i> value	Partial correlation coefficient
Percentage decline	1985–1987	−0.098	0.82	−0.10	1.52	0.13	0.60
	1988–1990	0.28	0.49	0.29	0.59	0.48	0.26
	1991–1993	0.33	0.28	0.43	1.38	0.06	0.69
Annual percentage decline	1991	0.066	0.17	0.57	0.21	0.07	0.67

* PSA, prostate-specific antigen.

† The percentage decline is between a baseline rate I_1 , set to one of 1985–1987, 1988–1990, and 1991–1993, and $I_2 = 1997$ –1999.

‡ The annual percentage decline is for 1991–1999.

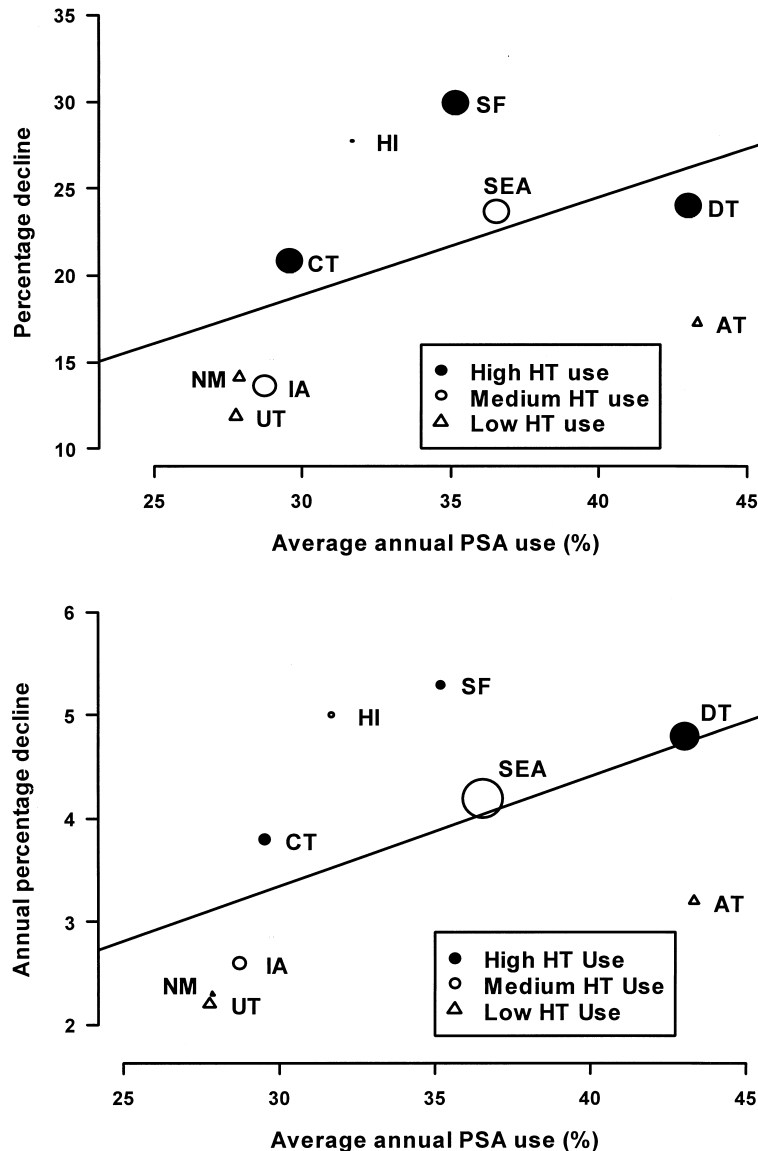


FIGURE 4. Decline in age-adjusted prostate cancer mortality rates vs. average prostate-specific antigen (PSA) screening use. Rates were age adjusted to the 2000 US Census population. Top: Percentage decline in prostate cancer mortality from 1991–1993 to 1997–1999. Bottom: Annual percentage decline estimated for 1991–1999. The size of the plotting character is inversely related to the variance within a particular registry of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute for percentage decline (top) and average percentage decline (bottom). HT, hormone ablation therapy; AT, Atlanta, Georgia; CT, Connecticut; DT, Detroit, Michigan; HI, Hawaii; IA, Iowa; NM, New Mexico; SEA, Seattle, Washington; SF, San Francisco, California; UT, Utah.

the present study, we used a computer model developed previously by Etzioni et al. (26). This model translates assumptions about mean lead time in the population and screening efficacy into declines in age-adjusted prostate cancer mortality relative to pre-PSA-era levels. Screening efficacy is expressed as the reduction in annual risk of prostate cancer death (relative risk) following the projected date of diagnosis in the absence of screening. Thus, for a screen-detected case, the model assumes that the hazard of prostate cancer death is zero until the original date of diagnosis, after

which it is equal to the relative risk times the hazard of death in the absence of screening.

Input data for the model include registry-specific population sizes (table 1) and PSA screening use trends (figure 2). We used the model to project expected mortality declines within each registry, beginning in 1988 and assuming a mean lead time of 5 years and a 50 percent relative risk. The 50 percent relative risk assumption corresponds to the efficacy assumed in the design of the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (3, 27). We ran the model

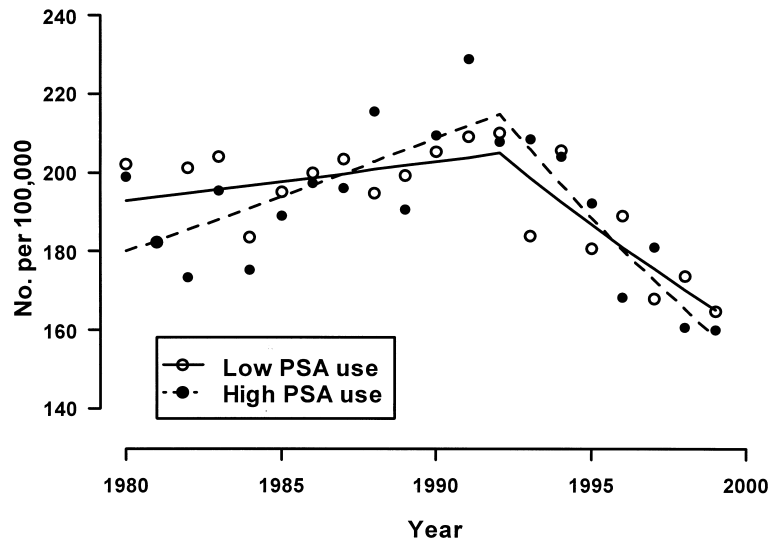


FIGURE 5. Age-adjusted prostate cancer mortality rates by registry of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute for White men aged 65–84 years, grouped by high vs. low use of prostate-specific antigen (PSA) screening. Rates were age adjusted to the 2000 US Census population. Joinpoint regression (35) was used to summarize the trends within each group. Low PSA screening use: Connecticut, Hawaii, Iowa, New Mexico, and Utah; high PSA screening use: Detroit, Michigan, and Atlanta, Georgia.

1,000 times for each site to obtain an empirical distribution for the site-specific annual declines in prostate cancer mortality. We then compared the model results with the observed percentage decline estimates for $I_1 = 1985\text{--}1987$, which represents the most recent calendar interval prior to the era of PSA testing. For an analysis of sensitivity, we repeated this procedure by assuming a mean lead time of 10 years (19) and a 50 percent relative risk, as well as a mean lead time of 5 years and a 70 percent relative risk.

RESULTS

Screening use and mortality across SEER sites

Figure 1 illustrates the age-adjusted mortality rates of prostate cancer by registry for 1983–1999. Shown is considerable variability in the observed mortality, particularly for the smallest registry, Hawaii (table 1). Despite the large degree of variability, a declining trend in prostate cancer mortality after 1991 was apparent within all registries.

Figure 2 shows annual frequencies of PSA screening use. Seven registries exhibited either a consistently high-use or a consistently low-use trend. Atlanta and Detroit had generally high levels of PSA screening, whereas the frequencies in Connecticut, Hawaii, Iowa, New Mexico, and Utah were consistently about 10–15 percent lower. Use in San Francisco and Seattle could not be categorized as consistently high or low.

HT use

The proportion of local-regional cases receiving HT ranged from 7 percent to 15 percent across registries. From 1991 to 1996, overall use of HT within 24 months increased

from 8 percent to 22 percent. Intensity of HT was not strongly correlated with the use of PSA screening (figure 3). For example, Detroit had both a high PSA screening rate and one of the highest intensities of HT, but Atlanta, which also had a high rate of PSA screening, had one of the lowest frequencies of HT use. Similarly, both Utah and Connecticut had low-PSA-use profiles but very different intensities of HT.

Ecologic analysis

Results of the weighted regression analyses are summarized in tables 2 and 3. Table 2 presents unadjusted estimates, and table 3 gives estimates adjusted for HT use.

The size of the ecologic association between PSA screening rates and prostate cancer mortality depended on both the measure of outcome and the baseline period assumed for the analysis. For the percentage decline measure, associations were strongest when a baseline period of 1991–1993 was assumed. The fitted slope, unadjusted for treatment, was 0.55 ($p = 0.14$; figure 4 (top)). In other words, for two registries with a 10 percent difference in PSA screening rates, the expected difference in the percentage decline in prostate cancer mortality was 5.5 percent. However, using the baseline period 1985–1987 produced a slope of 0.12 ($p = 0.80$). Adjusting for HT lowered the regression slope associated with PSA screening use to 0.33 ($p = 0.28$) for 1991–1993 and 0 ($p = 0.82$) for 1985–1997. HT use was positively correlated with percentage decline in mortality, although the strength of this association also varied by baseline period.

The negative APC, the annual percentage decline, is shown for each registry in figure 4 (bottom). The unadjusted

TABLE 4. Percentage decline in prostate cancer mortality rates between a baseline rate I_1 , set to 1985–1987, 1988–1990, or 1991–1993, and $I_2 = 1997–1999$ for White men aged 65–84 years, United States

Combined SEER* Program registries	Percentage decline						Annual percentage decline, 1991–1999	95% CI*	Average PSA* screening use (%), 1991–1996
	$I_1 = 1985–1987$	95% CI	$I_1 = 1988–1990$	95% CI	$I_1 = 1991–1993$	95% CI			
Low PSA screening use: CT/HI/IA/NM/UT*	14.4	10.9, 20.6	16.0	11.1, 20.7	16.3	11.5, 20.9	3.0	1.5, 4.4	29
High PSA screening use: DT/AT*	15.8	6.1, 22.1	18.8	11.2, 26.0	22.2	15.2, 28.9	4.4	3.2, 5.5	43

* SEER, Surveillance, Epidemiology, and End Results; CI, confidence interval; PSA, prostate-specific antigen; CT/HI/IA/NM/UT, Connecticut, Hawaii, Iowa, New Mexico, Utah; DT/AT, Detroit, Michigan; Atlanta, Georgia.

slope for PSA screening use was 0.11 ($p = 0.06$). For two registries with a 10 percent difference in PSA screening rates, the expected difference in prostate cancer mortality (based on the APC) over the 9-year period from 1991 to 1999 was approximately 7 percent. The slope adjusted for HT was 0.066 ($p = 0.17$). The analysis showed an association between HT and mortality declines, with an unadjusted slope of 0.28 ($p = 0.02$) and an adjusted slope of 0.21 ($p = 0.07$).

Figure 5 presents the annual prostate cancer mortality rates for sites associated with high versus low PSA screening rates. Mortality in the early 1990s was greater in the high-use group ($p = 0.08$ for Poisson regression applied to 1991–1993 rates), but this difference had disappeared by the end of the study period ($p > 0.5$). Table 4 presents the percentage decline in prostate cancer mortality in each group for the different baseline periods, together with the APC estimates for 1991–1999. For a baseline interval of 1991–1993, the high-use registries showed a decline of 22.2 percent (95 percent confidence interval: 15.2, 28.9) and the low-use registries a decline of 16.3 percent (95 percent confidence interval: 11.5, 20.9; $p = 0.17$). Differences between high- and low-use registries were considerably smaller when earlier baseline intervals were used. Greater declines were estimated based on the APC: 24 percent for low-use areas and 33 percent for high-use areas from 1991 to 1999.

Model results

With a 50 percent relative risk and a 5-year mean lead time, the model projected a weighted regression slope of 0.5 (95 percent confidence interval: 0.12, 0.89), which was

greater than the slope of 0.12 from the ecologic regression analysis with a baseline interval of 1985–1987 (table 2). Under these assumptions, the model projected an average 23.6 percent decline in prostate cancer mortality for the high-use group and an average 14.0 percent decline for the low-use group, implying a difference of 9.6 percent between the two groups (table 5). A relative risk of 70 percent and a 5-year mean lead time yielded lower percentage declines, a weighted regression slope of 0.29, and an average difference of 5.6 percent between the high- and low-use groups. Increasing the mean lead time to 10 years with a relative risk of 50 percent yielded still lower declines, a slope of 0.22, and a projected difference of 4.4 percent on average between the two groups. The 5-year mean lead time and 50 percent relative risk yielded overall declines in prostate cancer mortality that were closest in magnitude to those observed in the population.

DISCUSSION

For this article, we used data on PSA screening and prostate cancer mortality from nine geographic areas of the United States to study issues of bias and interpretation that arise in ecologic studies of cancer screening. We observed declines in mortality from prostate cancer across registries but only slightly greater declines in registries where PSA screening use was highest. Moreover, under the specified efficacy assumptions, our model predicted greater divergence of mortality rates across these groups than was observed.

Do these findings indicate lack of test efficacy? We urge caution in making such an inference. First, disease-specific

TABLE 5. Model-projected percentage decline in prostate cancer mortality between 1985–1987 and 1997–1999, United States*

Combined SEER† Program registries	Model-projected value					
	MLT† = 5, RR† = 50%	95% CI†	MLT = 5, RR = 70%	95% CI	MLT = 10, RR = 50%	95% CI
Low PSA† screening use: CT/HI/IA/NM/UT†	14.0	11.6, 16.5	8.1	5.9, 10.2	5.3	4.0, 6.7
High PSA screening use: DT/AT†	23.6	18.0, 29.3	13.7	9.2, 18.3	9.7	6.7, 12.8

* The average percentage decline and empirical 95% confidence intervals were computed across 1,000 simulations.

† SEER, Surveillance, Epidemiology, and End Results; MLT, mean lead time; RR, relative risk; CI, confidence interval; PSA, prostate-specific antigen; CT/HI/IA/NM/UT, Connecticut, Hawaii, Iowa, New Mexico, Utah; DT/AT, Detroit, Michigan; Atlanta, Georgia.

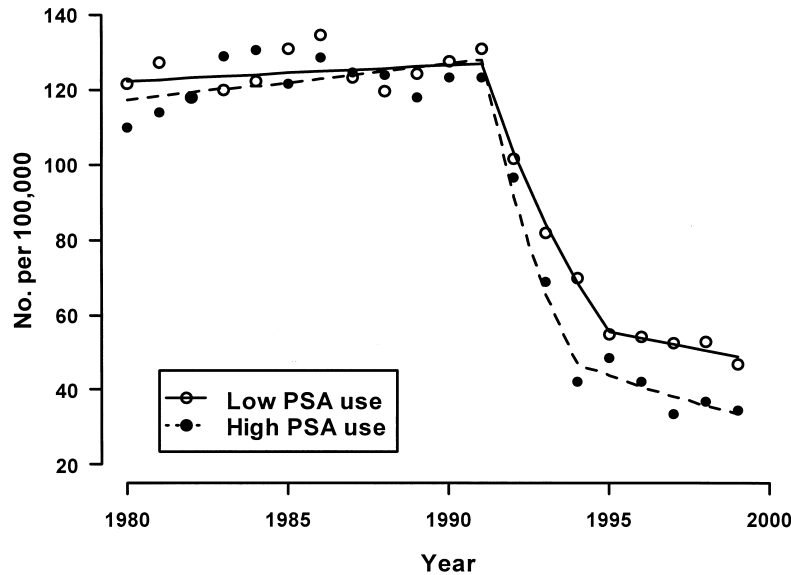


FIGURE 6. Age-adjusted distant-stage incidence rates of prostate cancer by registry of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute for White men aged 65–84 years, grouped by high vs. low use of prostate-specific antigen (PSA) screening. Rates were age adjusted to the 2000 US Census population. Joinpoint regression (35) was used to summarize the trends within each group. Low PSA screening use: Connecticut, Hawaii, Iowa, New Mexico, and Utah; high PSA screening use: Detroit, Michigan, and Atlanta, Georgia.

mortality in the late 1980s and early 1990s was greater in the high-use areas. If this early difference in mortality rates is real, then later convergence of the mortality curves is not inconsistent with some degree of test efficacy. However, it is possible that misattributing other causes of death to prostate cancer could be more pronounced in high-use areas, which would explain the early inflation in mortality (26). Continuing misattribution, even at a constant level, would then act against mortality declines attributable to PSA screening because of increased disease prevalence in these areas. Understanding trends in cause-of-death misattribution is key to reconciling the different analyses and interpreting study results. Studies among prostate cancer patients have yielded conflicting estimates of the extent of misattribution (28–30).

Knowledge of mortality declines that would be expected under screening efficacy is also critical to understanding study results. When a clinically significant level of screening efficacy (relative risk = 0.5) and a mean lead time of 5 years were assumed, the model-projected mortality declines matched those observed through 1999. These results are consistent with an overall impact of PSA screening on population mortality. However, the model predicted greater mortality differences across areas than we observed in our ecologic analysis. This discrepancy could mean that additional sources of variation are making it difficult to detect mortality differences across areas using an ecologic approach. Note that the model projects mortality changes in the absence of other factors such as HT, socioeconomic status, and access to care. These factors could induce sufficient variability to obscure any ecologic association—

except, perhaps, by assuming extreme differences in screening use between areas. In the present study, differences in PSA screening rates between the high- and low-use areas were far smaller than those observed in the positive Tyrol study of Bartsch et al. (11). The modest differences in PSA screening rates, together with additional sources of variation, could have produced a negative ecologic result.

Other models have been used to project the impact of PSA screening based on declines in the incidence of distant-stage disease that began in 1990. Feuer et al. (31) demonstrated that overall declines in distant-stage disease would be expected to induce a decline in mortality of approximately 18 percent by 1999. Figure 6 shows that there was a modest difference in declines of the incidence of distant-stage disease between high- and low-use registries (approximately 20–25 percent of the overall decline by 1999). On the basis of the Feuer et al. model, we estimate that this would translate into a difference of approximately 4 percent between the declines in mortality in the two groups. This difference is lower than projected by our baseline model, which assumed that survival benefits apply to all screen-detected cancers rather than being restricted to cancers shifted out of the distant stage by screening.

In our analysis, we focused on the impact of different calendar intervals on ascertainment of study outcomes. However, the choice of the interval for the exposure may also affect results, which may explain differences between the findings of different studies. For example, a study comparing Seattle and Connecticut (13) found large differences in PSA testing frequencies from 1988 to 1990, when the use of PSA screening was generally low. These differ-

ences diminished considerably after 1990, during the period covered by our analysis. To analyze sensitivity, we repeated our ecologic regressions by using average PSA screening frequencies for 1991–1993 as the exposure measure. The overall trend across areas remained the same, but San Francisco, which had lower use of PSA screening in the earlier period, became more of an outlier, weakening the regression result.

One of our incidental findings was that an ecologic association appears to exist between intensity of HT within the first 2 years after diagnosis and declines in mortality. If early HT is associated with improved survival, as has been suggested by some studies (6, 32–34), such use could explain, for example, why prostate cancer mortality declined less in Atlanta and more in San Francisco than was predicted on the basis of PSA screening use alone.

It is possible that changes in other treatment modalities may also be affecting mortality. However, PSA screening and HT use were novel changes in clinical care that began during the 1990s. Changes in the use of other treatments, such as radical prostatectomy and radiation, occurred over longer periods of time. In general, use of these therapies increased according to all registries during the 1980s and stabilized during the 1990s, but differences between the registries were not always consistent throughout this time period. Quantifying the impact of these changes would require in-depth modeling, which is beyond the scope of this analysis.

Since we conducted the analyses presented in this article, the SEER data have been updated to provide cancer mortality rates through 2001. Between 1999 and 2001, prostate cancer mortality declined from 152 to 138.3 per 100,000 among White men aged 65–84 years. We reran the regression analyses on the updated data, which showed greater mortality declines in the low-use areas but similar declines in the high-use areas relative to the earlier data. The updated regression results showed a weaker association between PSA screening rates and mortality declines than in the earlier data. Regression slopes for all analyses decreased, and the corresponding *p* values increased.

In conclusion, ecologic analyses of PSA screening and prostate cancer mortality should take into account the range of screening use across areas, the simultaneous dissemination of other cancer control methods, and the expected timing of any mortality declines that could plausibly arise as a result of the screening intervention. It is important to recognize that results of these analyses do not provide quantitative information about any individual survival benefit that may be associated with PSA screening. For better evidence regarding test efficacy, we therefore await the results of the ongoing randomized PSA screening trials.

ACKNOWLEDGMENTS

Research for this study was supported by grants CA88160 and CA92408 from the National Institutes of Health, Bethesda, Maryland.

The authors thank Kristin Berry for supplying the PSA screening rates and biopsy frequencies from the SEER-Medicare data and Seth Falcon for assisting with output generation for the simulation model runs.

REFERENCES

1. Etzioni R, Berry KM, Legler JM, et al. Prostate-specific antigen testing in black and white men: an analysis of Medicare claims from 1991–1998. *Urology* 2002;59:251–5.
2. Beemsterboer PM, de Koning HJ, Kranse R, et al. Prostate specific antigen testing and digital rectal examination before and during a randomized trial of screening for prostate cancer: European randomized study of screening for prostate cancer, Rotterdam. *J Urol* 2000;164:1216–20.
3. Gohagan JK, Prorok PC, Hayes RB, et al. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. *Control Clin Trials* 2000;21:251S–272S.
4. Hankey BF, Feuer EJ, Clegg LX, et al. Cancer surveillance series: interpreting trends in prostate cancer—part I: evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. *J Natl Cancer Inst* 1999;91:1017–24.
5. Chu KC, Tarone RE, Freeman HP. Trends in prostate cancer mortality among black men and white men in the United States. *Cancer* 2003;97:1507–16.
6. Demers RY, Tiwari A, Wei J, et al. Trends in the utilization of androgen-deprivation therapy for patients with prostate carcinoma suggest an effect on mortality. *Cancer* 2001;92:2309–17.
7. Farkas A, Schneider D, Perrotti M, et al. National trends in the epidemiology of prostate cancer, 1973 to 1994: evidence for the effectiveness of prostate-specific antigen screening. *Urology* 1998;52:444–8; 448–9 (discussion).
8. Magee C, Thompson I. Evidence of the effectiveness of prostate cancer screening. In: Thompson I, Resnick M, Klein E, eds. *Prostate cancer screening*. Totowa, NJ: Humana Press, 2001.
9. Oliver SE, May MT, Gunnell D. International trends in prostate-cancer mortality in the “PSA ERA.” *Int J Cancer* 2001;92: 893–8.
10. Shibata A, Ma J, Whittemore AS. Prostate cancer incidence and mortality in the United States and the United Kingdom. *J Natl Cancer Inst* 1998;90:1230–1.
11. Bartsch G, Horninger W, Klocker H, et al. Prostate cancer mortality after introduction of prostate-specific antigen mass screening in the Federal State of Tyrol, Austria. *Urology* 2001; 58:417–24.
12. Crocetti E, Ciatto S, Zappa M. Prostate cancer: different incidence but not mortality trends within two areas of Tuscany, Italy. *J Natl Cancer Inst* 2001;93:876–7.
13. Lu-Yao G, Albertsen PC, Stanford JL, et al. Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut. *BMJ* 2002;325:740.
14. Coldman AJ, Phillips N, Pickles TA. Trends in prostate cancer incidence and mortality: an analysis of mortality change by screening intensity. *CMAJ* 2003;168:31–5.
15. Cooperberg MR, Grossfeld GD, Lubeck DP, et al. National practice patterns and time trends in androgen ablation for localized prostate cancer. *J Natl Cancer Inst* 2003;95:981–9.
16. Shibata A, Whittemore AS. Re: Prostate cancer incidence and mortality in the United States and the United Kingdom. (Letter). *J Natl Cancer Inst* 2001;93:1109–10.

17. Coory M, Baade P. Mortality from prostate cancer is decreasing. (Letter). *Med J Aust* 2002;176:354–5; 355 (author reply).
18. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA* 1995;273:289–94.
19. Draisma G, Boer R, Otto SJ, et al. Lead times and overdiagnosis due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst* 2003;95:868–78.
20. Cancer Control & Population Sciences, National Cancer Institute, Bethesda, MD, 2004. SEER-Medicare Linked Database home page. (<http://healthservices.cancer.gov/seermedicare/>).
21. Legler JM, Feuer EJ, Potosky AL, et al. The role of prostate-specific antigen (PSA) testing patterns in the recent prostate cancer incidence decline in the United States. *Cancer Causes Control* 1998;9:519–27.
22. Surveillance, Epidemiology, and End Results. National Cancer Institute, Bethesda, MD, 2004. (<http://seer.cancer.gov/>).
23. Breen N, Wagener DK, Brown ML, et al. Progress in cancer screening over a decade: results of cancer screening from the 1987, 1992, and 1998 National Health Interview Surveys. *J Natl Cancer Inst* 2001;93:1704–13.
24. Weir HK, Thun MJ, Hankey BF, et al. Annual report to the nation on the status of cancer, 1975–2000, featuring the uses of surveillance data for cancer prevention and control. *J Natl Cancer Inst* 2003;95:1276–99.
25. Albertsen PC. The prostate cancer conundrum. *J Natl Cancer Inst* 2003;95:930–1.
26. Etzioni R, Legler JM, Feuer EJ, et al. 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;91:1033–9.
27. 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.
28. Albertsen PC, Walters S, Hanley JA. A comparison of cause of death determination in men previously diagnosed with prostate cancer who died in 1985 or 1995. *J Urol* 2000;163:519–23.
29. Penson DF, Albertsen PC, Nelson PS, et al. Determining cause of death in prostate cancer: are death certificates valid? *J Natl Cancer Inst* 2001;93:1822–3.
30. Newschaffer CJ, Otani K, McDonald MK, et al. Causes of death in elderly prostate cancer patients and in a comparison nonprostate cancer cohort. *J Natl Cancer Inst* 2000;92:613–21.
31. Feuer EJ, Mariotto A, Merrill R. Modeling the impact of the decline in distant stage disease on prostate carcinoma mortality rates. *Cancer* 2002;95:870–80.
32. Seidenfeld J, Samson DJ, Aronson N, et al. Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostate cancer. *Evid Rep Technol Assess (Summ)* 1999;i-x, 1–246, I1–36, passim.
33. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337:295–300.
34. Messing EM, Manola J, Sarosdy M, et al. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. *N Engl J Med* 1999;341:1781–8.
35. Joinpoint Regression Program. Statistical Research and Applications Branch, Cancer Control and Population Sciences, National Cancer Institute, Bethesda, MD, 2004. (<http://srab.cancer.gov/joinpoint/>).