

## 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

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**Background:** The prostate-specific antigen test was approved by the U.S. Food and Drug Administration in 1986 to monitor the disease status in patients with prostate cancer and, in 1994, to aid in prostate cancer detection. However, after 1986, the test was performed on many men who had not been previously diagnosed with prostate cancer, apparently resulting in the diagnosis of a substantial number of early tumors. Our purpose is to provide insight into the effect of screening on prostate cancer rates. Detailed data are presented for whites because the size of the population allows for calculating statistically reliable rates; however, similar overall trends are seen for African-Americans and other races. **Methods:** Prostate cancer incidence data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program and mortality data from the National Center for Health Statistics were analyzed. **Results/Conclusions:** The following findings are consistent with a screening effect: 1) the recent decrease since 1991 in the incidence of distant stage disease, after not having been perturbed by screening; 2) the decline in the incidence of earlier stage disease beginning the following year (i.e., 1992); 3) the recent increases and decreases in prostate cancer incidence and mortality by age that appear to indicate a calendar period effect; and 4) trends in the incidence of distant stage disease by tumor grade and trends in the survival of patients with distant stage disease by calendar year that provide suggestive evidence of the tendency of screening to detect slower growing tumors. **Implications:** The decline in the incidence of distant stage disease holds the promise that testing for prostate-specific antigen may lead to a sustained decline in prostate cancer mortality. However, population data are complex, and it is difficult to confidently attribute relatively small changes in mortality to any one cause. [J Natl Cancer Inst 1999;91:1017-24]

Prostate cancer incidence has undergone some of the most dramatic swings that we have ever observed in cancer statistics. Prostate cancer incidence had been increasing for some time; however, from 1989 to 1992, it increased, on average, 20% per year and then swung dramatically downward at a rate of 10.8% per year. Age-adjusted prostate cancer mortality increased over the last several decades, with an acceleration in the increase beginning in the mid-1980s, but it started to decline in 1991. In relation to the dramatic swings in incidence, the magnitude of the mortality decline has been small, from 26.7 deaths per 100 000 men in 1991 to 24.9 deaths per 100 000 men in 1995, a decrease of 6.7% (1).

Although there have been several advances in prostate cancer control over the past decade, the development that has generated the most publicity and controversy is undoubtedly the prostate-specific antigen (PSA) test. The U.S. Food and Drug Administration (FDA) approved the PSA test for the purpose of monitoring disease status in prostate cancer patients in 1986 and for aiding in the detection of prostate cancer in men 50 years and older in 1994 (FDA Press Release P94-16 dated 8/29/94). However, the use of the PSA test for the diagnosis of prostate cancer, either in response to symptoms or for screening, increased dramatically beginning in 1988 (2,3). The use of the PSA test was associated with a substantial increase in the reported incidence of prostate cancer in men 65 years and older during the late 1980s and early 1990s for geographic areas covered by the Surveillance, Epidemiology, and End Results (SEER) Program<sup>1</sup> (2). Speculation is rife that PSA screening may be responsible for the recent mortality decline, even though the ability of the PSA test to reduce prostate cancer mortality has not as yet been established by ongoing randomized controlled trials (4,5). In the absence of confirmatory data on efficacy, some medical organizations have questioned the value of using the PSA test for screening, whereas others have endorsed it (6).

There have been a number of studies (7-17) that have attempted to provide insight into the causality of recent trends in prostate cancer rates, particularly with regard to the possible effects of PSA testing on mortality. In general, these studies have focused on trends in prostate cancer incidence by stage and grade, mortality, patient survival, and age at diagnosis in a variety of attempts to provide evidence for or against the benefits of PSA screening. This article is the first of a series of three papers [the second paper is (18) and the third is (19)] on recent trends in prostate cancer incidence and mortality, all of which address some aspect of their possible cause, and are, in general, complementary to previously published studies, although some of the same observations are made to provide an overall perspective.

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See "Notes" following "References."

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The goal of this article is to go beyond examining associations in prostate cancer data for the purpose of supporting statements about the possible benefits of PSA screening. This is done by analyzing selected incidence and survival rates to provide evidence that screening is responsible for some of the observed patterns based on the known effects of the introduction of a screening test. Other possible explanations for some of the observed patterns in prostate cancer rates are discussed. These include the possibility that changes in the prevalence of risk factors in the population are also affecting trends in recent prostate cancer rates and that changes in treatment patterns are affecting incidence trends by tumor grade.

We begin by using join point regression to describe the trends and to establish the statistical significance of the recent changes in incidence and mortality by racial group and age at diagnosis. Subsequent analyses focus on whites because of the considerable variability in the subgroup analyses for African-Americans and for other races because of their relatively small size and because of a desire to limit confounding. Also, rates calculated for the relatively large white population have less variability, which is illustrated by the decrease in prostate cancer mortality for whites since 1991. This pattern is similar to that for the other racial groups but was found to be statistically significant on the basis of the join point regression analysis. Incidence rates by stage and grade are also described by use of join point regression. The decline in the incidence of distant stage disease from 1991 to 1995 is analyzed to determine whether the cases removed from the distant stage pool exhibit characteristics of a screen-detected group, in particular, the tendency of screening to detect slower growing tumors. Finally, we enumerate several alternative explanations for the observed incidence and mortality trends, one of which is explored in detail in the second paper of the series (18). The third paper (19) considers data on the dissemination of the PSA test in the population from 1988 through 1994 and uses a computer model to address whether the recent declines in mortality plausibly associate with population use of the PSA test. Thus, the three papers represent a multifaceted approach to provide additional insight into the question of the extent to which PSA testing is affecting recent prostate cancer mortality trends.

## MATERIALS AND METHODS

Cancer incidence data from 1973 through 1995 are from the SEER Program, based at the National Cancer Institute. The coverage areas of SEER registries contributing data to this study include the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii and the metropolitan areas of Atlanta, GA; Detroit, MI; Seattle, WA; and San Francisco, CA. These areas include roughly 10% of the total U.S. population. Data are collected on all cancers diagnosed in residents of the coverage areas and include demographics, primary site, extent of disease (stage), morphology, diagnostic confirmation, first course of treatment, and vital status including cause of death.

The International Classification of Diseases for Oncology, Second Edition (20), is used by the SEER Program to code site, histology, and behavior for all cancers. The site code for prostate cancer cases used in this article is C61.9. Prostate cancers with histology codes 9590–9989 (lymphomas) were excluded. Only prostate cancer cases considered to be invasive (malignant; i.e., with a behavior code of 3) are included in this article. From 1975 to 1995 in SEER areas, there were a total of 229 556 prostate cancers diagnosed in patients whose race was known. These cancers are used to calculate incidence rates, and their distribution over race is 85.9% white, 10.3% African-American, and 3.8% other.

The following definitions of stage of disease are used in this article. Localized refers to an invasive cancer confined to the prostate with no penetration of the capsule. Regional indicates a cancer that has involved the regional lymph nodes and/or penetrated the prostatic capsule with or without direct extension

beyond the limits of the prostatic capsule into surrounding organs or tissues. Distant refers to a cancer that has spread to parts of the body remote from the primary tumor. Unstaged indicates that there was insufficient information in the medical record to stage the cancer. The staging is based on pathologic information from surgery if available; otherwise clinical findings are used.

The grade or degree of differentiation of a tumor was coded from the final pathologic diagnosis in the pathology report as obtained from the hospital medical record or, if not available from the final diagnosis, from the microscopic description. Gleason's score was converted to grade as follows: A Gleason's score of 2, 3, or 4 was converted to grade 1 (well differentiated); a Gleason's score of 5, 6, or 7 was converted to grade 2 (moderately differentiated); and a Gleason's score of 8, 9, or 10 was converted to grade 3 (poorly differentiated or undifferentiated). When only Gleason's pattern was given, a 1 or 2 was converted to grade 1, 3 was converted to grade 2, and 4 or 5 was converted to grade 3. Data on grade are presented from 1977 to 1995.

Cancer mortality data for the total United States from 1969 to 1995 are from public use files obtained from the National Center for Health Statistics. Deaths included in this article are those for which prostate cancer was coded as the underlying cause. The site code for prostate cancer as the underlying cause of death from the International Classification of Diseases, Ninth Revision (21), is 185. From 1969 to 1995, there were 678 396 prostate cancer deaths in the total United States. The distribution over race is 83.5% white, 15.8% African-American, and 0.7% other.

Age-adjusted and age-specific rates per 100 000 men are presented. The 1970 U.S. standard is used for age adjustment.

Join point regression techniques (joined linear segments on a logarithmic scale) were used to characterize incidence and mortality trends by use of at most three join points (22). The statistics derived from these models are the annual percent change (APC) in the rates associated with each line segment, confidence intervals (CIs) for the APCs, and the join points (calendar years) at which there is a change in the trends. The models were estimated by use of weighted least squares, with the weights proportional to the inverse of the variance of the age-adjusted rates. A series of permutation tests (23) are performed, first testing  $H_0$  (no join points) versus  $H_a$  (three join points). The testing then proceeds sequentially and increases the number of join points under  $H_0$  by one if the null hypothesis is rejected and decreases the number of join points under the alternative hypothesis by one otherwise. For each hypothesized model, the best fitting join points are found by use of a grid search algorithm (24). By performing each test at the  $\alpha/3$  level, we ensure that the probability of concluding that there are one or more join points, when there are in fact none, is at most  $\alpha$ , which in this case is 0.05. An overview of the application of these methods to analyzing trends in cancer rates is presented by Kim et al. (25).

Ninety-five percent CIs are given for estimates of the APCs. They are not adjusted for multiple comparisons because this is an observational study and the focus of the study is on analyzing data for whites. This was done to minimize confounding that could result from the inclusion of other racial groups. Analyses of prostate cancer trends will be done in the future for other racial groups when more data become available.

Relative survival rates provide an estimate of the likelihood that a prostate cancer patient will not die of his disease within a specific period after diagnosis. The relative survival rate is obtained by correcting the observed survival rate for expected mortality (26). In computing relative survival rates, we excluded patients with a prostate cancer diagnosed as a second or later cancer, patients whose cancer was identified only by a death certificate or autopsy report, and patients with unknown survival time.

## RESULTS

### Prostate Cancer Incidence and Mortality Trends

Incidence trends for African-Americans and whites increased at very similar rates (Fig. 1), with the APCs from 1975 to 1985 being 2.3 and 2.4, respectively. For whites, there was an acceleration in the trend beginning in 1985, with the APC increasing to 6.9. The APC for whites further increased to 18.4 in 1989. In African-Americans, an acceleration in incidence began in 1989, with the APC increasing to 17.0. Incidence has been decreasing since 1992 for whites (APC = -12.8) and since 1993 for African-Americans (APC = -14.0).

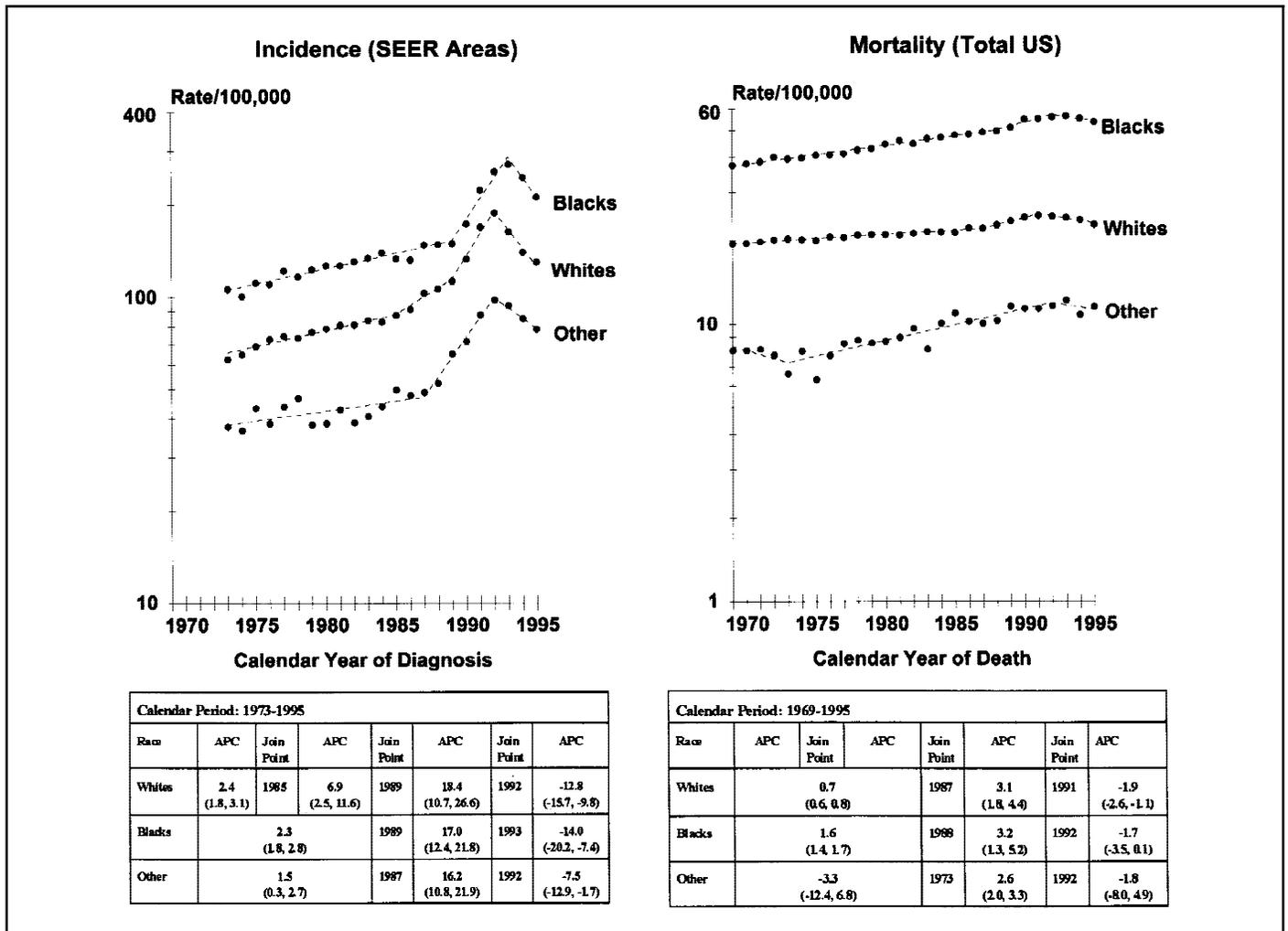


Fig. 1. Age-adjusted (1970 U.S. standard) prostate cancer incidence for Surveillance, Epidemiology, and End Results (SEER) areas and prostate cancer mortality for the total United States. The line segments from the fits of the join point regression models are graphed along with the observed rates (points). The join points and annual percent changes (APCs), with 95% confidence intervals in parentheses, are given in the tables below.

From 1969 until the late 1980s, the rate of increase in prostate cancer mortality in African-Americans (APC = 1.6) was roughly twice that for whites (APC = 0.7) (Fig. 1). There was an acceleration in the trend in mortality rates for whites and African-Americans during the 1980s, with the APC increasing to 3.1 for whites beginning in 1987 and to 3.2 for African-Americans beginning in 1988. In 1991, the trend for whites began to decrease with an APC of -1.9, which is statistically significantly different from zero. For African-Americans, the mortality trend began to decrease in 1992 with an APC of -1.7, which is not statistically significantly different from zero.

For the "other" group, both prostate cancer incidence and mortality rates are substantially lower than those for either whites or African-Americans (Fig. 1). An acceleration in the incidence trend for this group began in 1987, with the APC increasing to 16.2. In 1992, incidence began to decrease at an annual rate of 7.5%, which was half the rate of decrease for whites and African-Americans. Prostate cancer mortality for this group increased at an annual rate of 2.6% from 1973 through 1992. There is no evidence of an acceleration in the trend during this latter period as was observed for whites and African-Americans. There is evidence that the trend changed direction in 1992 to an APC of -1.8, which is not statistically significantly different from zero.

### Incidence and Mortality Trends by Age

Age-adjusted incidence and mortality rates for whites are given in Fig. 2 for selected age groups. The annual rates of increase in incidence by age that occurred after the introduction of the PSA test are inversely related to age, whereas the recent annual rates of decrease after 1992 are directly related to age. In the age group 50-59 years, the incidence rates have not decreased, although there is a clear break in the trend after 1992.

Prostate cancer mortality trends by age generally begin to decrease sometime around 1990. This pattern suggests that whatever affected the trends was associated with roughly the same calendar time for all age groups. Such an effect is generally referred to as a calendar period effect.

### Incidence Trends by Stage

Prostate cancer incidence trends for whites by stage are given in Fig. 3. The decrease and subsequent increase in unstaged incidence and compensating increase and subsequent decrease in localized and regional incidence before the mid-1980s are due to a coding artifact that resulted in unstaged cases being classified as localized or regional because of a misinterpretation of coding instructions that were in effect during this period. The problem was subsequently corrected. The cases added to the localized

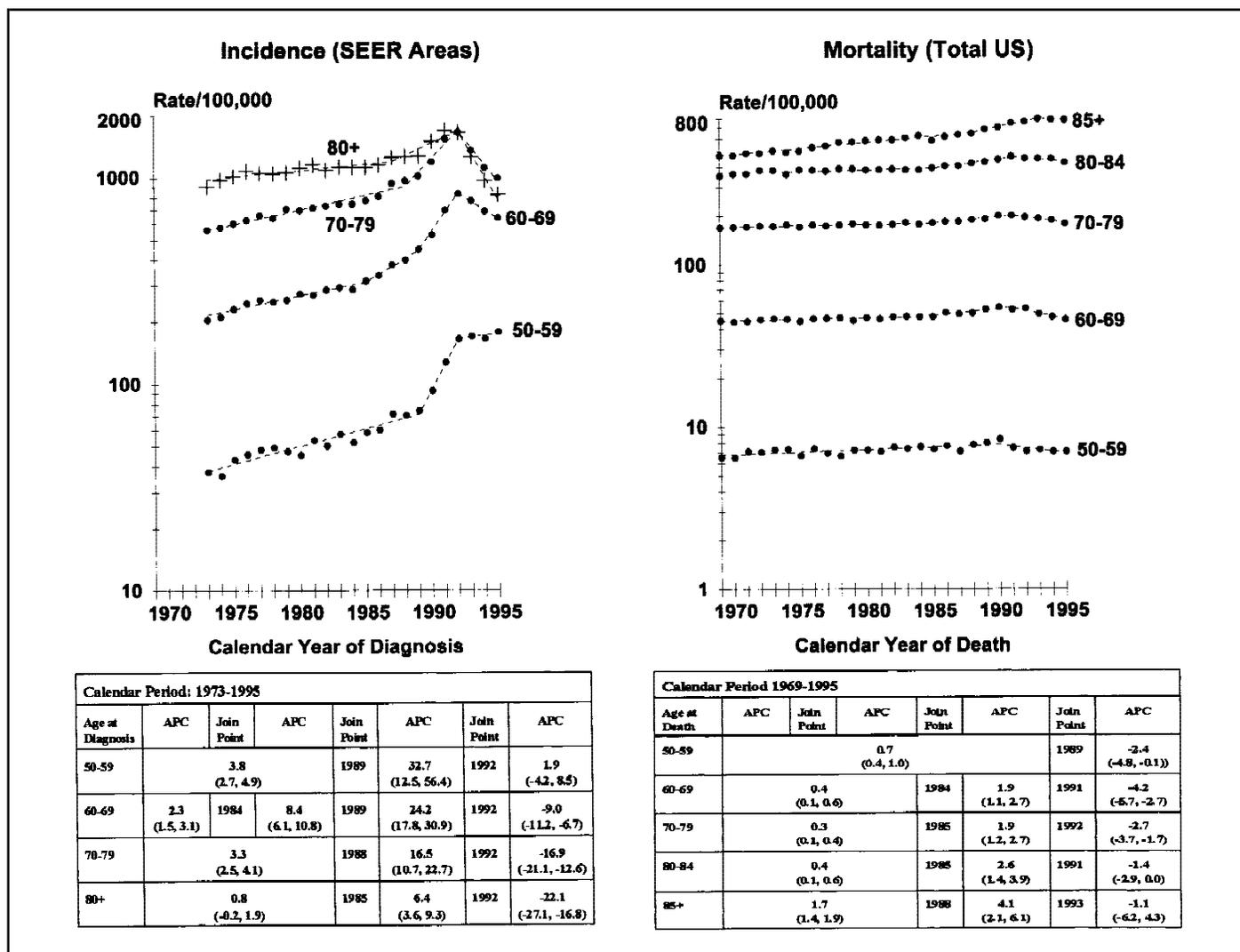


Fig. 2. Age-adjusted (1970 U.S. standard) prostate cancer incidence in whites for Surveillance, Epidemiology, and End Results (SEER) areas and prostate cancer mortality in whites for the total United States by selected age groups (for incidence, 50–59 years, 60–69 years, 70–79 years, and 80 years and older; for mortality, 50–59 years, 60–69 years, 70–79 years, 80–84 years, and 85 years and older). The line segments from the fits of the join point regression models are graphed along with the observed rates (points). The join points and annual percent changes (APCs), with 95% confidence intervals in parentheses, are given in tables below.

and regional categories are not relatively large enough to result in the identification of a join point during this period; however, the rates for this group do reflect the added cases (Fig. 3). In looking for the effects of screening with PSA, it is the trends after 1985 that are of interest.

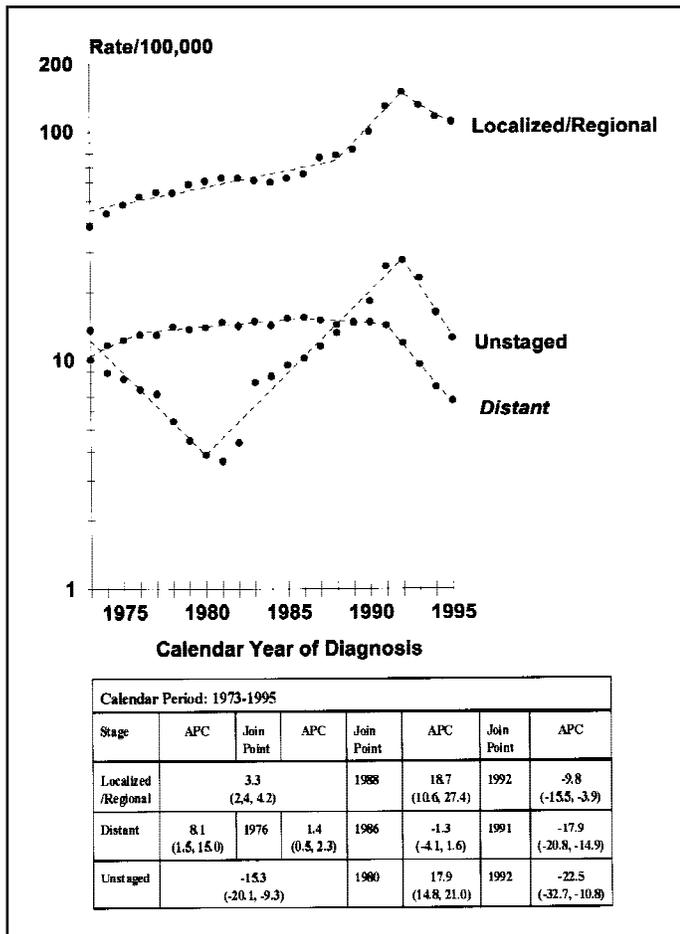
Because SEER uses either clinical or pathologic findings in assigning stage of disease at diagnosis with priority given to pathologic findings, the proportion of patients treated with a radical prostatectomy will influence the localized and regional stage trends. This is because surgery and pathologic findings lead to upstaging; i.e., clinically localized tumors were subsequently classified as regional. Consequently, the stage distribution of all patients in a given year will be related to the percentage of patients who were surgically treated. The percent of all prostate cancer patients treated with a radical prostatectomy increased from 7% in 1983 to 32% in 1992, when it leveled off. Because of the temporal confounding of surgery and stage, we have combined patients with localized disease and regional disease into one group.

Of particular note is the observation that the incidence of

distant stage disease is decreasing in whites at the dramatic annual rate of 17.9% since 1991. The incidence of distant stage disease is also decreasing in African-Americans and other racial groups (data not shown). Distant stage incidence for all races combined is currently decreasing in all age groups and in all SEER areas (data not shown).

#### Incidence Trends by Tumor Grade

Fig. 4 presents trends in incidence by tumor grade for whites. It appears that the increase in the incidence of moderately differentiated tumors is driving the overall incidence trend. Similar trends by grade are seen for African-Americans and the "other" group (data not shown). The incidence of moderately differentiated tumors increased from 1977 to 1988, with an APC of 9.1. Beginning in 1988, there was an acceleration in the trend, with the APC increasing to 26.9. In 1992, the trend began to decrease. For poorly differentiated and undifferentiated tumors, the pattern is somewhat similar to that for moderately differentiated tumors, but the rates of increase were smaller and the recent decreases were larger. In contrast, the incidence of well-differentiated tu-



**Fig. 3.** Age-adjusted (1970 U.S. standard) prostate cancer incidence in whites by stage. The line segments from the fits of the join point regression models are graphed along with the observed rates (points). The join points and annual percent changes (APCs), with 95% confidence intervals in parentheses, are given in the table below.

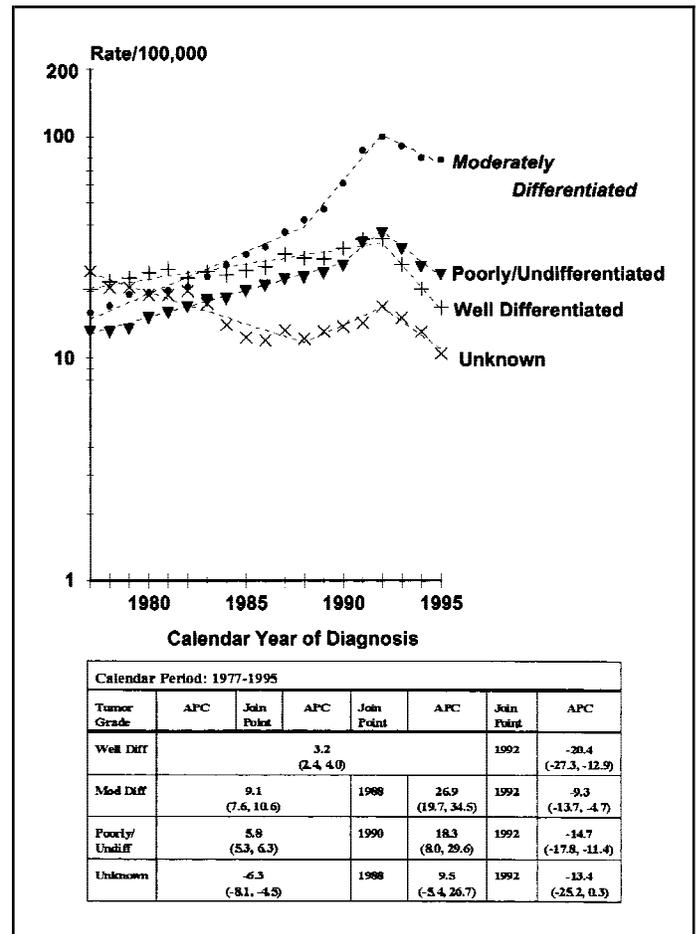
mors increased at an annual rate of 3.2% from 1975 to 1992, when the trend began to decrease at an annual rate of 20.4%.

### Evidence of the Effects of Screening

Cancers detected by a screening test tend to be relatively slow growing and, therefore, have a relatively good prognosis. Thus, if the decrease in distant stage incidence is due to screening, we would expect that many patients with a relatively good prognosis are being diagnosed at an earlier stage, whereas those with a poorer prognosis would tend to continue to be diagnosed with distant stage disease.

There were a total of 24,046 distant stage prostate cancers diagnosed in whites from 1975 through 1995, and these data are used to calculate incidence rates. Of these, survival could be calculated for 22,131 patients (92%) whose prostate cancer was diagnosed as the only cancer or the first of more than one cancer. This percent varied between 90% and 95% by calendar year and was not associated with calendar year. The number of patients available for survival analysis in each calendar year increased from 858 in 1975 to a maximum of 1,267 in 1990 and subsequently declined to 639 in 1995.

The magnitude of a screening effect in distant stage cases would be expected to be related to heterogeneity in patient survival. Because histologic grade is a prognostic factor, relative



**Fig. 4.** Age-adjusted (1970 U.S. standard) prostate cancer incidence in whites by tumor grade. The line segments from the fits of the join point regression models are graphed along with the observed rates (points). The join points and annual percent changes (APCs), with 95% confidence intervals in parentheses, are given in the table below.

survival rates were computed by histologic grade for distant stage cases diagnosed from 1987 through 1991. The 5-year relative survival rates for distant stage patients with well-differentiated tumors, moderately differentiated tumors, poorly differentiated and undifferentiated tumors combined, and tumors with unknown grade were 59%, 43%, 26%, and 24%, respectively. The poor prognosis of those patients whose tumor grade was unknown indicates that these cases tend to be in the poorly differentiated and undifferentiated group.

After 1991, the incidence of well-differentiated tumors is decreasing faster than tumors with higher grades (Fig. 5), which is consistent with a screening effect. However, the incidence of well-differentiated tumors and the relative frequency of such tumors were decreasing for distant stage cases in calendar years before 1991 (Fig. 5). This suggests that other factors, such as changes in criteria for grading tumors, are contributing to the trends.

One-, 2-, 3-, and 4-year relative survival rates were calculated by calendar year of diagnosis for white patients with distant stage disease (Fig. 6). The median age and the 25th and 75th percentiles of the age distribution for each calendar year are also shown in Fig. 6. The diagnosis at an earlier stage of some cases with a relatively good prognosis should result in the survival of the distant stage group getting progressively worse as the deficit

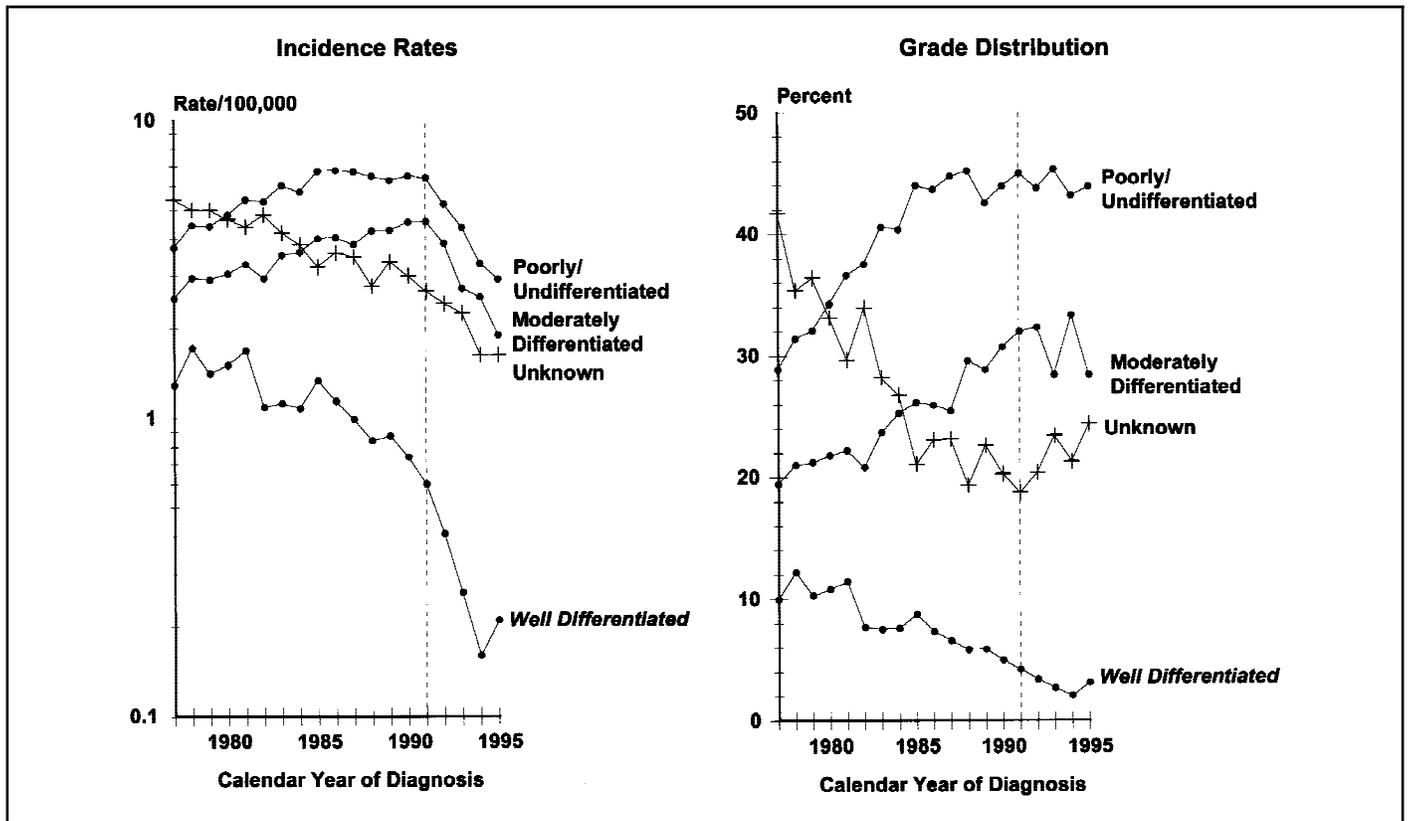


Fig. 5. Age-adjusted (1970 U.S. standard) distant stage prostate cancer incidence in whites by tumor grade. The tumor grade distribution by calendar year is also given.

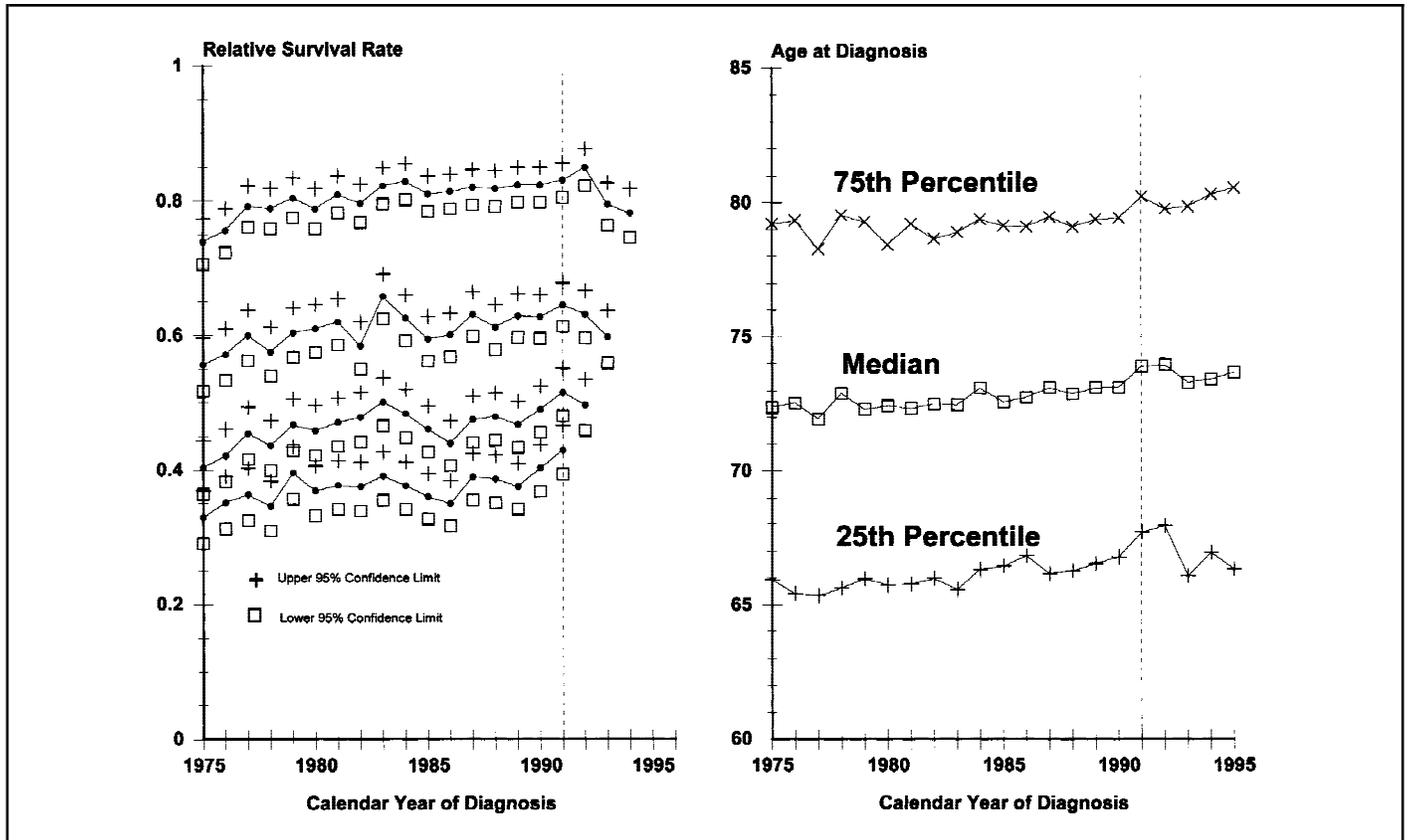


Fig. 6. One-, 2-, 3-, and 4-year relative survival rates by calendar year of diagnosis, with 95% confidence intervals (points), for white prostate cancer patients with distant stage disease.

associated with these cases becomes manifest. It can be seen that the effect on the age distribution of screening has been minimal. To further explore the possible confounding effects of age, we calculated by calendar year age-adjusted relative survival rates using four age groups (<60 years, 60–69 years, 70–79 years, and ≥80 years and older) and found them to be in very good agreement with the unadjusted rates shown in Fig. 6; therefore, only the unadjusted rates are shown. There appears to be a drop-off in the rates for calendar years of diagnosis since 1991. Thus, the survival data available to this point appear to be consistent with this expected effect of screening; however, data for additional calendar years will be necessary to more reliably demonstrate this effect.

## DISCUSSION

This analysis provides evidence of a role of PSA testing in recent prostate cancer incidence and mortality trends. The dramatic acceleration in prostate cancer incidence that occurred for whites beginning in 1989, the peaking of the rates in 1992 and subsequent decline, the dramatic decrease in distant stage disease that began in 1991 (which was consistent with the tendency of screening to detect slower growing tumors), the subsequent decrease in localized and regional stage disease that began in 1992, and the evidence of a period effect in regard to the recent decrease in the age-specific mortality rates for the total United States are consistent with a screening effect.

If screening is primarily responsible for the decline in incidence, then a certain stage-specific pattern should emerge. Lead time, the amount of time diagnosis is advanced because of screening, is probably shorter for patients who present clinically with distant disease than for patients who present clinically with localized or regional disease. This means that the incidence of distant disease should decline sooner than that for earlier stages. In fact, localized and regional stage incidence did begin to decline roughly 1 year after the decrease in distant stage incidence occurred (Fig. 3). Thus, lead-time effects are apparent in the incidence data since 1990, supporting the impression that PSA screening is playing some role in the observed trends.

However, there are other possible explanations for the observed trends. For example, incidence in recent years could be going down because of a decrease in exposure to a risk factor, and this, in turn, could be driving down mortality. This seems unlikely because risk factors usually affect incidence data by birth cohort, and the declines in both incidence and mortality appear to be period effects. Another possibility is that changes in treatment practices may be confounding our view of mortality. In the late 1980s and early 1990s, new pharmaceutical agents (the gonadotropin-releasing hormone analogues and antiandrogenic agents) made the treatment of recurrent or advanced disease more attractive to patients and clinicians (27,28). The androgen blockade approach to hormonal therapy rapidly superceded the use of surgical castration or estrogen therapy: Hormonal therapy for patients with advanced disease has become essentially universal. Although it is unlikely that androgen blockade in such settings has much genuine biologic curative potential, the greater utilization of this treatment for patients with minimal metastatic disease, or only biochemical (PSA) evidence of disease, could be expected to delay disease progression or postpone recognition of progression for several years or until some patients die of unrelated illnesses. Thus, the widespread

adoption of this therapeutic approach could have contributed to the recent decline in mortality rates for prostate cancer.

Changes in the use of established therapies may have had an impact on prostate cancer incidence by tumor grades. The surgical removal of the prostate gland (i.e., radical prostatectomy generally with dissection of regional lymph nodes) was modified in the early 1980s to preserve regional innervation and potency. The resulting increase in radical prostatectomy rates through the 1980s and into the 1990s could have contributed to the shift in the grade distribution toward higher grades during the period of increasing incidence before 1992. This would have been due to the reported tumor grade being related to the amount of tissue available for review by the pathologist. In SEER data, it has been observed that, among patients with localized disease, the grade distribution of patients surgically treated tends to be higher than that of patients receiving other treatments. Thus, it is possible that, during the period of increasing incidence, relatively more tumors were classified as moderately differentiated or higher because of the larger amount of tissue available as the result of a radical prostatectomy. The extent to which the increase in the percentage of surgically treated patients explains the incidence trends by grade will require further study.

Other factors that likely contributed to a shift toward higher tumor grades during the period of increasing incidence include an increase in the number of biopsies performed (SEER coding rules call for taking the highest tumor grade from multiple biopsy specimens that include cancer) and a decline in the rates of transurethral resection of the prostate since around 1988 in age groups 65 years and older (29) as treatment for benign prostatic hypertrophy. Transurethral resections of the prostate frequently lead to the incidental diagnosis of low-grade prostate cancer.

Finally, in the analysis of the recent decrease in prostate cancer mortality, the antecedent acceleration in the trend merits some attention (Fig. 1). If this observation is an artifact associated with the rising and falling pool of newly diagnosed cases (e.g., a certain proportion of the pool could have a misclassified cause of death), then it would have implications for establishing the importance of the recent mortality decrease. It may be that the rates are returning to some background trend after having been perturbed by such an artifact. This possibility is explored in detail in the second paper in this series by Feuer et al. (18), which concludes that misclassification of cause of death is contributing to some extent to the increase and subsequent decline in prostate cancer mortality.

In addressing the various possible effects of PSA testing on prostate cancer incidence and mortality, it is necessary to provide evidence of the extent to which PSA testing has been done in the general population. Data on PSA testing rates based on Medicare data for a cohort of men who were 65 years or older in 1988 have been reported elsewhere for the SEER areas (3). The percent of white men receiving a PSA test in a given calendar year increased from 1.2% in 1988 to nearly 40% of those living in 1994. The percent of white men receiving a first PSA test peaked in 1992 at 19% and subsequently declined, tracking with the increase and decrease in the prostate cancer incidence trend. Thus, the rapid increase and subsequent slowdown in first-time PSA testing may also be contributing to the increase followed by the recent decrease in prostate cancer incidence in SEER areas.

To fully explore whether the patterns of PSA testing plausibly correlate with the recent mortality decline requires consideration

of the natural history of the disease and the plausible survival benefit, i.e., the amount by which screening reduces the likelihood that a person with the disease will die of prostate cancer. In the third paper of this series, Etzioni et al. (19) present a computer model that explicitly links population screening behavior and expected mortality declines under specified assumptions. The model identifies values for mean lead time and survival benefit under which utilization of the test at levels similar to those recorded in the population could explain the decline in population mortality observed through 1994. Even if we assume quite substantial improvements in survival due to screening, the model suggests that mortality declines of the order of those observed by 1994 would be anticipated only under extremely short lead times.

In conclusion, there is little uncertainty that PSA testing has left its mark on the vital statistics for prostate cancer. Several factors, especially the decline in the incidence of and mortality from distant stage disease, hold out the promise that PSA testing may lead to a sustained decline in prostate cancer mortality. However, as the preceding discussion and the subsequent papers in this series clearly demonstrate, population data are complex, and it is difficult to confidently attribute relatively small changes in mortality to any one cause. Thus, extreme caution should be exercised when making inferences about the effects of screening on prostate cancer mortality from these data.

It is important to consider the implications of a continued sustained decline in prostate cancer mortality that appears to be due to screening. Some might question the need for obtaining final results from ongoing trials for testing the efficacy of PSA screening. It is important to point out that these trials are necessary to better understand the relationship of a specified controlled intervention, the potential for overdiagnosis and treatment, and any resultant mortality decline.

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## NOTES

<sup>1</sup>*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically to the NCI on a biannual basis, and the NCI makes the data available for analysis.

Manuscript received January 8, 1999; revised April 7, 1999; accepted April 15, 1999.