Cancer Surveillance Series: Interpreting Trends in Prostate Cancer—Part II: Cause of Death Misclassification and the Recent Rise and Fall in Prostate Cancer Mortality

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Background. The rise and fall of prostate cancer mortality correspond closely to the rise and fall of newly diagnosed cases. To understand this phenomenon, we explored the role that screening, treatment, iatrogenic (i.e., treatment-induced) deaths, and attribution bias (incorrect labeling of death from other causes as death from prostate cancer) have played in recent mortality trends. Methods. Join point regression is utilized to assess the recent rise and fall in mortality and the relationship of total U.S. trends to those areas served by the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Cancer Registry Program. Incidence-based mortality (IBM) is estimated with the use of prostate cancer data from the SEER Program to partition (from overall prostate cancer mortality trends) the contribution of cases diagnosed since the widespread use of prostate-specific antigen (PSA) testing starting in 1987. IBM is also used to examine the contribution of stage at diagnosis to the recent prostate cancer mortality trends. Results. IBM for cases diagnosed since 1987 rose above the pre-1987 secular (i.e., background) trend, peaked in the early 1990s, and almost returned to the secular trend by 1994. This rise and fall of IBM track with the pool of prevalent cases diagnosed within the prior 2 years. IBM for cases diagnosed with metastatic disease fell starting in 1991, while IBM for those diagnosed with localized/regional disease was relatively flat. Conclusions. The rise and fall in prostate cancer mortality observed since the introduction of PSA testing in the general population are consistent with a hypothesis that a fixed percent of the rising and falling pool of recently diagnosed patients who die of other causes may be mislabeled as dying of prostate cancer. The decline in IBM for distant stage disease and flat IBM trends for localized/regional disease provide some evidence of improved prognosis for screen-detected cases, although alternative interpretations are possible. [J Natl Cancer Inst 1999;91:1025–32]

This is the second in a series of three articles on recent trends in prostate cancer incidence and mortality in the United States. The first article (1) provides an in-depth analysis of the increase in both incidence and mortality rates in the late 1980s and the early 1990s and subsequent decline in both statistics and examines the consistency of these trends with a screening effect. Since these changes occurred concurrently with the rapid dissemination of prostate-specific antigen (PSA) testing in the population (2,3), it is particularly tantalizing to attribute the decline in mortality to PSA testing. This is especially true because more definitive results on the efficacy of PSA screening from randomized screening trials will not be available for some time. However, as Hankey et al. (1) noted, great caution should be exercised in drawing such conclusions from observational data because alternative explanations exist.

In particular, in this article, we explore the possibility that incorrect attribution of cause of death may have made a substantial contribution to the recent mortality trends.

The large pool of undiagnosed prostate disease identified through autopsy studies makes the reported incidence of prostate cancer particularly susceptible to changes in the use of medical interventions such as PSA testing (4–6). Thus, increased detection of prostate cancer cases resulting from screening drives up the observed pool of prevalent cases and yields a large population of men whose death may potentially be attributed to this disease. Because prostate tumors are often slow growing and men with the disease commonly die of other causes (7), there is likely to be a certain number of men who die of causes other than prostate cancer but who mistakenly have their underlying cause of death attributed to prostate cancer merely because they were labeled as having the disease as a result of screening. We refer to this misclassification of death as attribution bias.

The rise and fall of prostate cancer mortality correspond roughly with the rise and fall in prostate cancer incidence for both whites and blacks in the United States (1). It may be that the misattribution of cause of death from a rising and falling pool of newly diagnosed prevalent cases led to the rise and fall in mortality, especially if one posits that misattribution is most likely to occur when the diagnosis of cancer is still fairly recent. Of course, earlier detection through screening, coupled with increased use of aggressive therapy, may have also contributed to the decline in the mortality rate, but much debate remains over whether PSA screening and these aggressive therapies actually reduce prostate cancer mortality (8,9). Typically, a delay is expected between the time screening is introduced and any reduction in prostate cancer mortality is realized. In the third article in this series (10), we use a simulation model to examine if the introduction of widespread PSA testing in the population starting in 1987 (2,3) could have plausibly led to a decline in mortality in the early 1990s.

Although the age-adjusted mortality rate is commonly considered to be the most objective measure of progress against cancer (11), the measure lacks focus, since incident cases from many years contribute to the deaths in a given year. Interventions, such as a new screening method or treatment, tend to

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impact cancer statistics by year of diagnosis. Hence, overall mortality presents a blurred picture of the impact of incidence-based, period-specific interventions. However, cancer registry data, which have a sufficiently long period of follow-up, allow us to partition the deaths in a given calendar year by the period of diagnosis, as well as by other factors associated with diagnosis, e.g., stage. This partitioning, in turn, allows us to bring into focus the influences of interventions on mortality. The method of partitioning cancer registry-based, disease-specific mortality rates by factors associated with the disease at diagnosis has been previously used and is referred to as incidence-based mortality (IBM) (12).

This study focuses on the contribution of cases diagnosed since the widespread introduction of PSA as a screening test starting in 1987 to overall mortality (2,3). We were interested in determining if the rise and subsequent fall in prostate cancer mortality come from cases diagnosed since 1987. In particular, if the rise can be attributed to recently diagnosed cases, then a possible explanation for the rise and at least part of the subsequent decline is the misattribution of cause of death among the rising and falling prevalent pool of newly diagnosed cases. The analysis is performed only for white men, since mortality rates for black men are considerably more variable and an IBM analysis partitions these rates even further. Also, the recent decline in prostate cancer mortality is statistically significant only for white men (1).

Prostate cancer data are obtained from the tumor registries participating in the Surveillance, Epidemiology, and End Results (SEER) Program1 of the National Cancer Institute (13). Since in this analysis we utilize mortality data only from the SEER areas, we first evaluate the representativeness of prostate cancer mortality rates based on SEER data to the total United States. Second, we compare IBM and the usual death certificate prostate cancer mortality rates in SEER to validate the use of IBM rates. Third, applying the method of IBM, we evaluate the contribution of cases diagnosed since 1987 to mortality, evaluate IBM by stage of the disease, and postulate about the role of screening, treatment, and attribution bias in these trends.

METHODS

We obtained case information on prostate cancer patients diagnosed in five states (Connecticut, Iowa, New Mexico, Utah, and Hawaii) and four metropolitan areas (Detroit, Atlanta, San Francisco–Oakland, and Seattle–Puget Sound) from 1973 through 1995. These population-based registries are participants in the SEER Program and represent approximately 10% of the U.S. population. The SEER registries provide a high-quality source of national estimates of cancer incidence and survival (13), with ascertainment of data obtained by abstracting hospital records, clinical and nursing home records, records from private pathology laboratories and radiotherapy units, and death certificates.

Malignant prostate cancer cases were coded and identified with the use of the International Classification of Diseases for Oncology (14) event code C61.9, and deaths were identified with the use of the International Classification of Disease codes 185.0–185.9 for underlying death due to prostate cancer (15). Underlying cause of death was derived from death certificates by use of an algorithm that usually takes the last line in part I of the death certificate (called the originating antecedent case) but supercedes this choice if there are certain combinations of conditions present or if there are overriding epidemiologic reasons for giving precedence to other conditions on the certificate. In these circumstances, the underlying cause of death may come from either part I (antecedent causes) or part II (contributing causes) of the death certificate (16). Prostate cancer mortality from 1973 through 1995 based on death certificates was obtained from public-use files from the National Center for Health Statistics (NCHS), Hyattsville, MD. Rates were derived by combining case data with estimated midyear population values obtained from the U.S. Bureau of the Census (Suitland, MD).

All rates in this analysis were age adjusted to the 1970 U.S. standard population to remove the effect of changes in the age distribution over time. Age-adjusted rates include all ages unless otherwise noted.

We first established mortality trends for the United States by using join point regression as described by Hankey et al. (1). These piecewise linear models (joined linear segments) on a log scale were fit to U.S. prostate cancer mortality rates to describe and compare changes in trend (17). For the identification of change points for the total United States, the trends were constrained to join at up to two points. Since this analysis involves mortality from the SEER areas, of interest is whether trends in SEER data are representative of patterns observed in the entire United States. Because a model fit to prostate cancer mortality data from the SEER areas alone had too much variability to allow identification of change points, we first identified change points for the total United States and then overlaid these change points on the trends based on data from SEER areas and the United States with SEER removed. In this way, we investigated the hypothesis that, given fixed change points, the annual percent changes in mortality rates from SEER areas are similar to those in the rest of the United States. Differences between the United States–SEER and SEER were tested by putting both series in a weighted least-squares regression model on the log of the rate with fixed join points and testing if the slopes of each segment differed significantly using a Wald test. The weights were equal to the inverse of the variance of the log rates.

Prostate cancer mortality rates based on death certificates include cases diagnosed in any prior time period. Partitioning prostate cancer mortality by year of diagnosis can provide insight into the efficacy of interventions, such as PSA screening and aggressive treatment (radiation therapy and radical prostatectomy), which impact only the portion of mortality that occurs after their introduction. IBM requires population-based cancer registry data that include current vital status and cause of death for all patients (12). By use of registry data in this manner, mortality cases identified through follow-up were partitioned by factors associated with diagnosis, i.e., year of diagnosis and stage at diagnosis. Stage-of-disease definitions used in this article are identical to those used by Hankey et al. (1). To determine the pool from which deaths (partitioned by year of diagnosis) were drawn, we calculated prevalence by year of diagnosis by using standard methods (18). This calculation counts all diagnosed patients still alive on the date that prevalence is computed and counts a portion of patients lost to follow-up utilizing their expected survival up until the prevalence date.

RESULTS

Prostate cancer mortality rates are presented by age and year of death in Fig. 1. For each age group, a accelerated increase in prostate cancer mortality rates occurred in the 1980s, peaking in 1991 or 1992 and then declining or leveling off (for ages 80+ years only). The annual percent changes in slope between SEER- and United States-based models were not statistically significantly different, except for men aged 70–79 years in the period 1985 through 1991 (two-sided \( P = .015 \)). Thus, the trends in SEER mortality are generally similar to those of the entire United States.

Fig. 2 displays incidence-based prostate cancer mortality rates based on SEER data according to year of death by the cumulative number of calendar years since diagnosis. For example, the lowest curve (labeled IBM:0) denotes the mortality rate for men dying of prostate cancer in the same calendar year in which they were diagnosed. The second lowest curve (IBM:0–1) is the mortality rate for men dying of prostate cancer in the same calendar year or the year after diagnosis, and so on. Each successive curve starts 1 year later because identification of new cases in SEER started in 1973, and so the first year we have data for IBM:0–x is 1973 + x. The top line in Fig. 2 is mortality based on usual death certificate data. More than 50% of the total death certificate mortality can be accounted for by case patients who die in the same or within the next 3 calendar years after diagnosis (IBM:0–3). By the mid-1980s, SEER had enough years of follow-up to explain essentially all prostate cancer mortality occurring in a given year. With 10–15 years of follow-back, the
IBM rates approach approximately 95% of prostate cancer mortality rates based on death certificates. For any particular person, the cause of death with the use of NCHS or SEER data sources is identical because both sources rely on the underlying cause of death from the death certificate. However, the IBM rate will never exactly equal the usual mortality rate because of various factors. For example, a nonresident at diagnosis who moves into a SEER area and dies will not be registered by SEER but will be in the NCHS death certificate mortality statistics for that area, whereas a man diagnosed while a resident in a SEER area who moves away and dies will be in SEER but not in the NCHS death certificate mortality statistics for that region (12).

Although mortality rates are not influenced by lead time bias, which occurs when a screening test advances the time of diagnosis without changing the time of death, it can influence IBM calculated by year of diagnosis. A cancer progress measure might be called lead time invariant if it is affected only by changes in the true prognosis of the patient. For example, consider a man clinically diagnosed with prostate cancer in 1992 who then dies of prostate cancer in 1994. If this man received a PSA test that led to a prostate cancer diagnosis in 1990, but his time and cause of death remained unchanged, then he would shift from IBM:2 (diagnosed 2 calendar years prior to death from prostate cancer) to IBM:4 (diagnosed 4 calendar years prior to death from prostate cancer), despite no real change in his prognosis. The usual death certificate mortality statistic is lead time invariant, since this case contributes to deaths in 1994 under either scenario.

It is possible, however, to construct an IBM measure partitioned by years since diagnosis that is lead time invariant. Assuming negligible PSA screening rates prior to 1987, we know that all screening-induced shifts in the time of diagnosis occurred in 1987 or after. The justification for negligible rates of PSA screening prior to 1987 was derived from an analysis of Medicare claims data in SEER areas (3) and showed that, for a cohort of men aged 65 years and above in 1988, less than 2% had a PSA test in the last year in 1988. The rates of PSA testing...
grew dramatically, especially starting in 1990; by 1992, about 30% of men had a PSA test within the prior year. PSA screening was introduced at different time periods in different parts of the United States [e.g., in the Seattle–Puget Sound SEER area, almost 10% of men had a PSA test in the past year by 1989; in contrast, in Utah, only about 1% had a test within the past year (3)], but testing rates prior to 1987 were negligible throughout the United States. Thus, cumulative IBM rates with the use of an anchor year of 1987 should not be influenced by lead time. For example, we computed the IBM rate for 1987 based on cases diagnosed in 1987 (IBM:0), the IBM rate for 1988 based on cases diagnosed in 1987 and 1988 (IBM:0–1), the IBM rate for 1989 based on cases diagnosed in 1987 through 1989 (IBM:0–2), and so on, until the end of follow-up in 1995 (i.e., cases diagnosed in 1987 through 1995 and dying in 1995 [IBM:0–8]). The patient who has his diagnosis shifted from 1992 to 1990 because of screening and dies of prostate cancer in 1994 despite the early diagnosis will, in both instances, be included in the IBM:0–7 statistic for the year of death 1994. Thus, this set of statistics anchored in 1987 is lead time invariant. A statistic anchored in any other year (e.g., IBM:0–3 for year of death 1994 that includes cases diagnosed in 1991–1994) will not be invariant to shifts in the time of diagnosis due to screening.

In Table 1, age-adjusted IBM rates are partitioned by year of diagnosis and year of death. The rates in the upper-left-hand triangle of the table are for patients who were diagnosed and died before the introduction of PSA screening; the rates in the lower-right-hand triangle of the table are computed only for patients diagnosed from 1987 forward, during the period of PSA screening. IBM:0 for year of death 1987 is 2.26. IBM:0–1 for year of death 1988 is computed by summing 3.71 and 1.97. These rates sum despite being age adjusted because they are derived from the same populations for a specific year of death. For IBM:0–8 in 1995, we sum the nine numbers in the last column of the table.

The purpose of including the IBM rates in Table 1 before 1987 (upper triangle) is to allow the derivation of a prescreening secular (i.e., background) trend comparison series for rates derived in 1987 and after. The secular trend for IBM:0 prior to screening is determined by the lower diagonal of the upper triangle and represents patients who were diagnosed and died in the same calendar year. Similarly, the secular trend in IBM:0–1 is derived by summing the last two values in each column for years of death 1974 through 1986 (no value can be derived for 1973 because we do not have data for cases diagnosed prior to 1973). This type of calculation continues for IBM:0–2 through IBM:0–8 with 1 less initial year included in each series.

Fig. 3 graphically compares the IBM rates before and after the start of the dissemination of PSA screening with the use of data derived from Fig. 1. The lowest line shows the IBM:0 rates for 1973 through 1986 (diamonds), and a line fit through these points is extrapolated to 1987 for comparison to IBM:0 in year of death 1987 (denoted by an “X”). Similarly, the highest line shows the IBM:0–7 rates for 1980 through 1986 (dashes), and a line fit through these points is extrapolated to 1994 for comparison to IBM:0–7 in year of death 1987 (again denoted by an “X”). The 1995 IBM:0–8 rate is excluded from Fig. 3 because the 9-year (1987–1995) extrapolation of a secular trend based on 6

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<td>3.85 3.64 2.68 2.42 1.83 1.19 1.04 0.66 0.64 0.50 0.45 0.21 0.22 0.30</td>
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<td>2.80 3.75 3.65 2.85 1.91 1.78 1.22 0.97 0.84 0.65 0.49 0.40</td>
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<td>1976</td>
<td>3.49 3.61 3.56 2.84 2.11 1.68 1.29 1.08 0.89 0.79 0.72</td>
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<td>1977</td>
<td>2.70 4.00 3.44 2.94 2.32 1.79 1.16 1.12 0.66 0.57</td>
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<td>1987†</td>
<td>2.26 3.71 3.84 3.01 2.45 2.23 1.59 1.32 1.04</td>
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<td>1995</td>
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*Rates age-adjusted to the 1970 standard population. PSA = prostate-specific antigen.
†General population PSA testing starts here.
years of data (1981–1986) was unstable. Fig. 3 clearly shows that the number of patients diagnosed since PSA screening began in 1987 rose above the prescreening secular trend, peaked in 1992, and then fell back toward the secular trend, as indicated by the vertical distance between the fitted lines and the "X." It is clear that the cases diagnosed since 1987 are the major contributors to the recent rise and fall in prostate cancer mortality.

To help interpret Fig. 3, we derived the size of the pool of prevalent prostate cancers from which the prostate cancer deaths were drawn. Fig. 4 shows the age-adjusted prevalence proportion of prostate cancer patients observed in SEER in a given year, partitioned by cumulative calendar year(s) since diagnosis. We label these curves as follows: P:0 denotes the pool of patients alive at the end of the same calendar year in which they were diagnosed, P:0–1 denotes patients diagnosed in the same or prior calendar year and still alive at the end of the current year, and so on. Rates are age adjusted to the 1970 U.S. standard population. Data source: the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program. See text for further explanation of the symbols.

Fig. 3. Prostate cancer mortality in white men by year of diagnosis. Incidence-based mortality (IBM) rates before and after the start of the introduction of prostate-specific antigen screening in 1986 are compared. IBM:0–x denotes mortality rate for patients who died up to x calendar years after diagnosis; e.g., IBM:0 is the mortality rate for men dying in the same calendar year in which they were diagnosed and IBM:0–1 is the mortality rate for men dying in the same calendar year or the year after diagnosis, and so on. Rates are age adjusted to the 1970 U.S. standard population. Data source: the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program.

Fig. 4. Age-adjusted prevalent cohort of white patients with prostate cancer in a given year partitioned by cumulative year(s) since diagnosis. Prevalence proportions are age adjusted to the 1970 U.S. standard population. P:0–x denotes cases diagnosed up to x calendar years ago and alive on December 31 of the current year; e.g., P:0 is the pool of patients alive at the end of the same calendar year in which they were diagnosed and P:0–1 is the pool of patients diagnosed in the same or prior calendar year and alive at the end of the current year, and so on. Data source: the National Cancer Institute’s Surveillance, Epidemiology, and End Results Program.

Incidence. P:0–1 peaks in 1992, and IBM rises the most above its secular trend in 1992. In fact, the rise and fall above the secular trend of IBM track closely with P:0–1.

Fig. 5 shows overall IBM partitioned into localized/regional, distant, and unstaged categories. These categories are very similar, whether they are based on clinical or pathologic information, because only a small percentage of patients are found to have distant disease after being surgically treated. A partitioning of localized and regional cases was not done, since surgery and pathologic staging lead to up-staging; i.e., clinically localized tumors are shifted to regional cases on the basis of pathologic findings. Consequently, the stage distribution of all patients in a given year will be related to the percentage of patients who were surgically treated. Fig. 5 is presented on the arithmetic scale so that it is possible to assess the importance of absolute changes in the rates. The IBM rates by stage are a partition of the total prostate cancer mortality rate; i.e., for each calendar year, the age-adjusted rates by stage add up to the total IBM rate. The IBM rates for each calendar year include the cases diagnosed only since 1973. Beginning in the mid-1980s, the trend in the age-adjusted total IBM rate is similar to the usual death certificate mortality rates. Thus, it is possible to make inferences about stage-specific contributions to the recent prostate cancer
mortality trend. One can observe a decline in the IBM for distant stage disease that occurred at approximately the same time as the decline in the incidence of distant stage disease. Localized/ regional disease and unstaged disease have increased only slightly since the mid-1980s.

**Discussion**

Attribution bias could be explaining at least part of the rise and fall in prostate cancer mortality. Mettlin and Murphy (19) argued that it seems implausible that the observed trends can be attributed to changes in the accuracy or procedures for recording cause of death. However, we do not postulate changes in the accuracy or procedures for coding cause of death, but rather we postulate a rising and falling pool of prevalent cases with a fixed proportion having misattributed causes of death among those in the prevalent pool. A number of other scenarios may be considered regarding the impact of interventions on IBM for cases diagnosed during the period from 1987 through 1994 (Fig. 3):

1) If there is a beneficial PSA-screening effect on prostate cancer mortality, this should eventually lead to a decline in prostate cancer mortality below the secular trend. This decline should not be seen for several years after the introduction of PSA screening, since no patients with screen-detected prostate cancer should die of disease-related causes during their lead time, with the exception of iatrogenic (treatment-induced) deaths.

2) The increased use of aggressive therapy may have led to a decline in mortality. The use of surgery (e.g., radical prostatectomy) is typically reserved for patients in good health, younger than 70 years, and with the disease clinically confined to the prostate (20–23). The use of radical prostatectomy increased sharply for all age groups in the 1980s through 1992 but then leveled off (24–26). Radiation therapy is used for patients with disease clinically confined to the prostate and/or surrounding tissues; some of these patients are poor candidates for radical prostatectomy (27–29). The use of radiation therapy has remained relatively constant over time, albeit it is decreasing slightly for men aged 50–69 years and is increasing slightly for men aged 70 years or older (20). In the late 1980s and early 1990s, gonadotropin-releasing hormone analogues and antiandrogenic agents were introduced, making the treatment of recurrent or advanced disease more viable to patients and clinicians. Although these new treatments may not be biologically curative, they may delay death from prostate cancer long enough for the patient to die of other causes. Although the increased use of all of these treatments could lead to declines in mortality, the analysis of IBM for cases diagnosed since 1987 was timed to capture the impact of the introduction of PSA screening rather than of any specific treatment. In fact, the continuous development and increased use of new treatments may have contributed to the declining secular trend of IBM prior to 1987 and may justify the extrapolation of the declining secular trend after 1987.

3) Surgically related iatrogenic deaths may have increased and then fallen as a result of the rising and falling incidence of prostate cancer, as well as the rising proportion of cases treated with radical prostatectomy through 1992. This is consistent with results shown in Figs. 3 and 4, in which the rise and fall of IBM track fairly closely with P:0–1. A review of the Medicare claims of 101,604 men who underwent a radical prostatectomy during the period from 1991 through 1994 indicated that 30-day mortality was 0.5% for men aged 65–69 years and approached 1% for men aged 75 years and older (30). An IBM analysis of SEER data indicates that deaths due to prostate cancer within 3 calendar months of a radical prostatectomy contribute only about 0.05 deaths per 100,000 population (age adjusted to the 1970 standard population). Although this rate increased from 0.04 per 100,000 in 1987 to 0.07 per 100,000 in 1992 and then declined back to 0.04 per 100,000 in 1995, the magnitudes of these rates are so small that they could not have influenced overall mortality. Using a tighter definition for possible iatrogenic deaths (e.g., 1 month) would have yielded even lower rates. The IBM:0 rates from Table 1 are much larger than 0.05 because only patients with a good prognosis are selected to have a radical prostatectomy. Iatrogenic deaths following surgery for prostate cancer are supposed to be coded with an underlying cause of death from prostate cancer, although there may be confusion in these circumstances as to how to complete the death certificate.

The exact mechanism or degree to which attribution bias occurs is unknown. The number of patients whose cause of death is misattributed to prostate cancer in any one year can be decomposed into three multiplicative components: (number of prevalent cases of prostate cancer) × (proportion of patients who die of other causes among the prevalent cases) × (proportion of patients whose cause of death is misattributed to prostate cancer among those who die of other causes). The second factor increases with age. For example, the probability of a white male dying of any cause within 2 years rises from 3.1% for a 60-year-old man to 7.2% for a 70-year-old man, 16.5% for an 80-year-old man, and 35.0% for a 90-year-old man (31). One can postulate that the third component rises with age (deaths among the elderly are not as thoroughly investigated) or falls with age (a cancer diagnosis is rarer among younger men and thus is more likely to be remembered and considered at the time someone fills out a death certificate). One can also postulate that the third component is higher for newly diagnosed cases and fades with time. Conversely, it may be generally accepted that patients newly diagnosed with prostate cancer (especially when screen detected) will not die of their disease for some time and that ambiguous symptoms of recurrence followed by a sudden death will lead to misattribution. Finally, it may be that the first and third components are independent or that they may vary directly with each other. For example, it is possible that increased media
attention given to prostate cancer as a result of the rapid increase in incidence rates, along with the many prominent people reported to have been treated for the disease, may have influenced the rate of reporting of prostate cancer as a cause of death. Furthermore, as physicians get used to the idea that many men with prostate cancer do not die of their disease, this bias in attribution may also be reduced. Alternatively, the prevalence of the cancer and the proportion of misattributed cases may be unrelated.

A major factor in misattribution may be a lack of understanding of how to fill out death certificates and that, as long as a diagnosis of cancer is on the patients’ medical record, the physician may incorrectly feel obligated to indicate prostate cancer somewhere on the death certificate. If prostate cancer is listed on the last line of part I of the death certificate, it will in most cases be censored as the underlying cause of death even if the person filling out the certificate mistakenly puts the true underlying cause in an earlier line.

Utilizing cases identified in the population-based tumor registries in New Mexico and Connecticut, the National Cancer Institute is currently sponsoring two studies to investigate changes in death certification for men with prostate cancer. Both studies involve a comparison of data supplied on death certificates with data obtained from patients’ medical records both in the pre-PSA era and using more recent data. Records will be examined for patients with prostate cancer reported as the underlying cause of death, as well as for those with other underlying causes of death. These studies should help quantify the magnitude of misattribution and describe the mechanisms underlying any confounding of trends caused by incorrect attribution of the cause of death of prostate cancer patients.

Of particular interest in Fig. 5 is the recent decrease in the IBM rate for distant stage disease and the relatively flat IBM for localized/regional disease. This pattern is consistent with at least two different hypotheses. Suppose early detection through PSA testing is improving the prognosis of patients who would have formerly been clinically diagnosed with distant disease and are screen detected with localized/regional disease. We should see a decline in distant stage IBM without a compensating concurrent increase in the IBM for localized/regional disease, which is consistent with what we observed. Alternatively, if PSA testing is shifting cases from distant to localized/regional disease without any improvement in prognosis, then the IBM for localized/regional disease should shift upward at the same time and by the same amount that distant disease shifted downward. However, incidence started falling beginning in 1992, which may have led to a decline in the number of cases that have a misattributed cause of death. The net effect of two opposite forces on IBM for localized/regional disease could be a flat resultant trend, which is also consistent with our observations.

The trends in IBM shown in Figs. 3 and 5 probably represent the effect of many possible forces (screening, treatment, iatrogenic deaths, and attribution bias), many of which work in opposite directions. The fact that IBM rose above its background trend starting in the PSA era suggests that a factor such as attribution bias was more than offsetting any potential early benefits in prostate cancer mortality rates resulting from early detection or treatment. A continued decline in mortality to a level below the prescreening level would provide stronger evidence of an effect of screening. However, the fact that, until now, mortality has risen and fallen back to its prescreening level suggests that the recent trends may have been affected by cause-of-death misclassification associated with the rising and falling pool of prevalent cases.

REFERENCES


(23) Zickeh C, Bergstrakh EH, Blute ML, Myers RP, Barrett D, Lieber MM, et


NOTES

*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 20, 1999; accepted April 23, 1999.