Modeling the Impact of the Decline in Distant Stage Disease on Prostate Carcinoma Mortality Rates

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BACKGROUND. The incidence of distant stage prostate carcinoma was relatively flat until 1991 and then started declining rapidly. This decline probably was caused by the shift to earlier stage disease associated with the rapid dissemination of prostate specific antigen (PSA) screening. Prostate carcinoma mortality rates started falling at approximately the same time. In this article, the authors model the potential impact of this stage shift on prostate carcinoma mortality rates given various assumptions concerning the survival of patients with screen-detected local-regional disease.

METHODS. The authors used the CAN*TROL 2 computer model to shift each deficit in the number of patients with distant stage disease to local-regional stage disease and modeled the implications on mortality using a set of base, optimistic, and pessimistic survival assumptions. A base survival assumes that a patient with screen-detected local-regional disease of a certain histologic grade has the same prognosis as a patient with clinically detected local-regional disease of same grade (i.e., an assumption of no length bias for patients with screen-detected disease), whereas the optimistic and pessimistic scenarios assume that survival is better or worse, respectively, than the base survival (i.e., complete cure for patients with favorable grade for the optimistic scenario and no improvements in survival for patients with unfavorable grade for the pessimistic scenario).

RESULTS. Model results were compared with observed mortality trends. Rising age-adjusted mortality rates peaked in 1991 for white males and in 1993 for black males and then fell 21% and 13% for white males and black males, respectively, from 1990 through 1999. Under the modeled stage-shift intervention, mortality rates would fall 18%, 8%, and 19% for both white males and black males under the base, pessimistic, and optimistic assumptions, respectively.

CONCLUSIONS. It is impossible to know what the mortality trends would have been in the absence of the introduction of PSA screening. However, under the base assumption, it appears that the decline in distant stage disease can have a fairly sizable and rapid impact on population mortality. The optimistic scenario is not much improved over the base scenario, which is indicative of the facts that the survival of patients diagnosed with clinical local-regional prostate carcinoma is quite good and that further survival improvements can have only a marginal impact. Under the pessimistic scenario, it appears that something else must be responsible for much of the decline in mortality. Screening trial results from the United States and Europe may verify and isolate the size of any mortality benefit associated with PSA screening. Trial results eventually can be put back into these population models to help quantify the impact of screening, treatment, and other factors on population trends. ***Cancer* 2002;95:870–80.**
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Age-adjusted prostate carcinoma mortality increased in the United States over the last several decades, with an accelerated increase in the late 1980s. Mortality peaked in 1991 for white males and 1993 for black males and then started declining, and that decline has continued through the most recent U.S. data in 1999. These changes in the prostate mortality rates occurred concurrently with the rapid dissemination of prostate specific antigen (PSA) testing, which was approved by the Food and Drug Administration (FDA) in 1986 for monitoring disease status and in 1994 for aiding in the detection of prostate carcinoma in men age $\geq$ 50 years.[1] The incidence of prostate carcinoma started rising rapidly in 1989, followed by a precipitous decline starting in 1992 for white males and in 1993 for black males.[2] Legler et al.,[3] using Medicare claims data for an aging cohort of men age $\geq$ 65 years in 1988, showed that PSA usage started rising rapidly by 1990, and first-time usage peaked in the same year that incidence peaked.

Several reports[4–7] have investigated the association of a beneficial effect of screening on the recent decrease in prostate mortality rates. Hankey et al.[4] noted that unequivocal causal association, especially in the absence of definitive trial results, is difficult to obtain from observational data, because alternative explanations may exist. For example, the increased use of aggressive therapies (e.g., surgery and androgen-deprivation [AD] therapies) may be playing a role in the decline. Feuer et al.[5] postulated that the rise in mortality starting in the late 1980s may have been due to incorrect attribution of causes of death associated with the growing prevalent pool of men with prostate carcinoma who died of other causes, some of which deaths were attributed mistakenly to prostate carcinoma merely because the patients were diagnosed with the disease. If misattribution occurs when the diagnosis of carcinoma is still fairly recent, then the rising *and falling* pool of newly diagnosed patients may be associated with both the rise and the fall in mortality rates. Etzioni et al.[6] showed that the mortality rate declines through 1994 could be attributed totally to PSA screening only if screening was at least as efficacious as hypothesized in the U.S. Prostate, Colorectal, Lung, and Ovarian (PLCO) Cancer Screening Trial and if the average lead time (the amount of time that the diagnosis is shifted due to screening) was on the short end of believable alternatives (i.e., approximately 3 years). However, prostate mortality rates still are falling and have reached levels below those observed before the diagnostic use of PSA testing,[7] which may be an important sign of a benefit of PSA testing.[8,9] In addition, the decline of distant stage disease (i.e., prostate carcinoma with distant metastases at the time of diagnosis) from 1991 onward almost certainly reflects the stage shift expected from early detection of prostate carcinoma using PSA testing (Fig. 1).

The objective of this study was to quantify the magnitude of the link between the decrease in distant disease at the population level and the decline in prostate carcinoma mortality rates in the U.S. We divide patients with disease that was detected through PSA screening testing into three types: Type I, patients shifted from distant disease to localized-regional disease; Type II, patients shifted within local-regional disease; and Type III, patients with disease that never would have been detected clinically but was detected through screening as local-regional disease, i.e., overdiagnosed patients.

In this article, we modeled the potential size and timing of a mortality gain associated with the detection of disease in Type I patients. Early detection in Type III patients does not impart any mortality benefit. Because Type I patients are likely to have been closer to death than Type II patients at the time they would have been diagnosed clinically, the potential impact of this group on mortality is likely to be sooner than any potential mortality benefit from Type II patients. Modeling provides a unique opportunity to focus on the potential mortality gains from this important subset of patients.

MATERIALS AND METHODS

CAN*TROL Computer Modeling

To model the impact of the decline of distant stage disease on prostate carcinoma mortality, we used the CAN*TROL 2 computer model.[9] CAN*TROL originally was developed for the Cancer Unit of the World Health Organization in the early 1980s to calculate the effects of cancer control activities. A mainframe program (Year 2000 model[10]) and, later, a Windows descendant of the program (CAN*TROL 2) were developed by the National Cancer Institute to assist in the development of *Cancer Control Objectives for the Nation: 1985–2000*[10] and *Healthy People 2000*.[11]

The CAN*TROL 2 model tracks the population over time through various conditions, from *healthy*, to various *possible disease stages at diagnosis*, a *cured state*, and, finally, *death from disease or other causes*. At the start of each new cycle (1 calendar year), new births are added to the disease free population, and individuals may shift from the healthy state, to a disease state, or to death from other causes based on proportions derived from observed population-based statistics. Once a person is assigned a certain stage of disease after diagnosis, that stage will never change, regardless of whether the disease progresses. The prognosis postdiagnosis is modeled using stage specific relative survival curves. Individuals

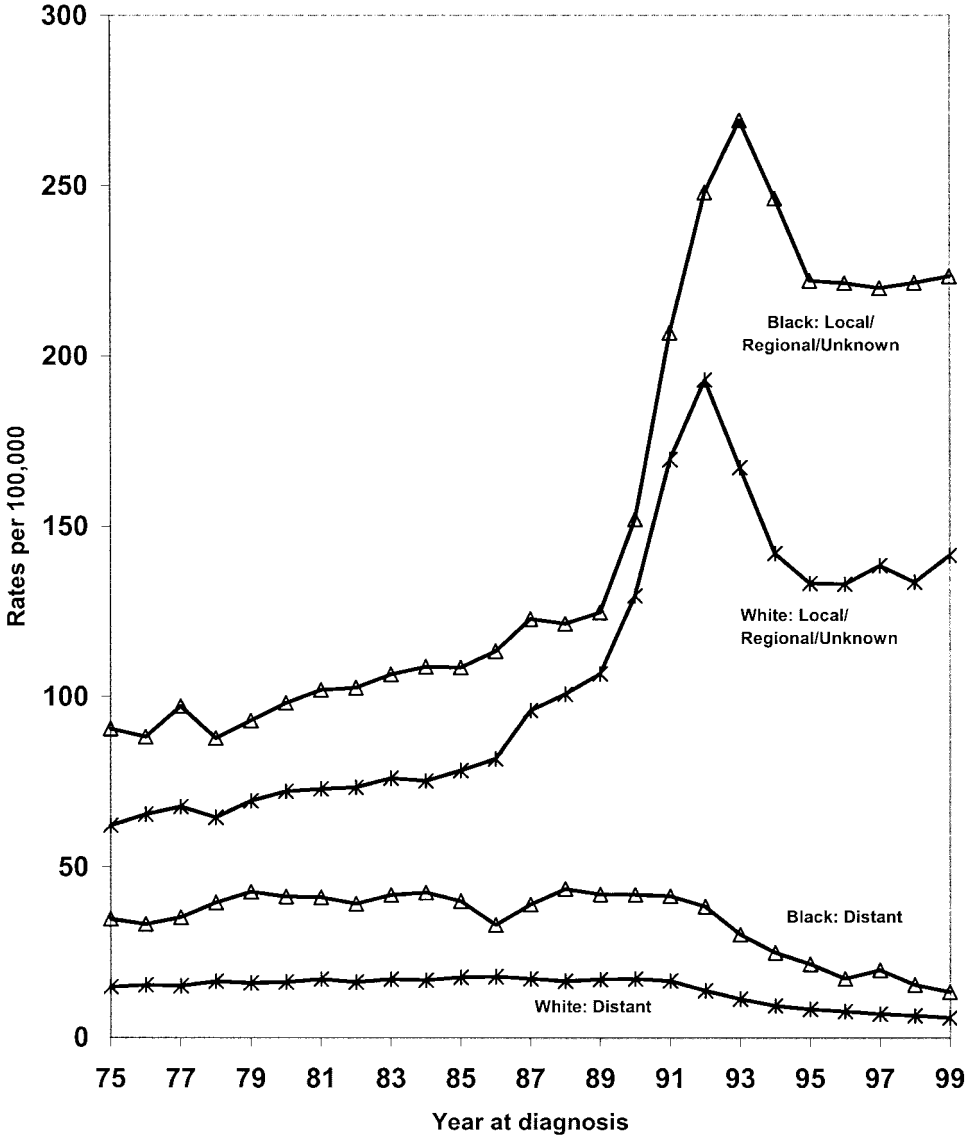

FIGURE 1. SEER prostate carcinoma incidence age-adjusted to the 1990 U.S. standard million population by age and stage.

are *aged* 1 year every cycle, so that the proper mortality rates from causes other than the disease of interest can be applied to the population. Users define a set of initial conditions, and three possible types of interventions (primary prevention through changes in incidence, treatment through changes in survival, and screening through a stage shift and possible changes in survival within stage). Occupancy of the states at baseline is seeded using a 20-year run of the model under the initial conditions. From the baseline year forward, CAN*TROL projects mortality in both the presence and the absence of the defined disease control intervention.

Stage and Grade

Prostate carcinoma incidence, survival, and stage distribution were obtained from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program. Prostate carcinomas are classified as localized, regional, distant, or unstaged using the SEER historic staging system. Localized disease indicates an invasive tumor confined to the prostate with no penetration of the capsule, regional disease indicates a tumor that has involved the regional lymph nodes and/or has penetrated the prostatic capsule with or without direct extension beyond the limits of the prostatic capsule into surrounding organs or tissues, distant disease refers to a tumor that has spread to parts of the body remote from the primary tumor, and unstaged disease indicates that there was insufficient information on the medical record to stage the tumor. Staging is based on pathologic information from surgery, if available; otherwise, clinical findings

are used. Local and regional disease were not separated for this analysis, because the ability to diagnose regional disease is a function of a patient's choice to undergo surgery. Because the grade of the tumor is an important prognostic factor even within stage, stage shifts associated with screening were assumed to occur within grade categories.

The grade of a tumor was coded from the final pathologic diagnosis in the pathology report obtained from the hospital medical record or, if it was not available from the final diagnosis, from the microscopic description. Gleason scores were converted to grade as follows: Gleason scores of 2–4 were converted to Grade 1 (well differentiated), Gleason scores of 5–7 were converted to Grade 2 (moderately differentiated), and Gleason scores of 8–10 were converted to Grade 3 (poorly differentiated or undifferentiated). When only a Gleason pattern was given, a score of 1 or 2 was converted to Grade 1, a score of 3 was converted to Grade 2, and score of 4 or 5 was converted to Grade 3.

For the purposes of the CAN*TROL model, the stages of disease at diagnosis were defined using the following six historic stage-histologic grade combinations: distant stage, well to moderate grade; distant stage, poor to undifferentiated grade; distant stage, unknown grade; local/regional/unknown (L/R/U) stage, well to moderate grade; L/R/U stage, poor or undifferentiated grade; and L/R/U stage, unknown grade. Patients with unknown stage were combined with local-regional disease, because, on average, they have a similar prognosis.

Stage-Shift Assumption

Incidence, survival, and mortality from all causes of death other than prostate carcinoma and stage-grade distribution during 1980–1986 provided data for the pre-PSA testing (baseline) period in CAN*TROL 2. Incidence of distant disease was relatively flat until 1991. To isolate the impact of the decline in distant disease on mortality (i.e., the impact of Type I patients), we estimated the stage distribution induced by shifting patients from distant disease to local-regional disease from 1991 onward while keeping overall incidence at its baseline (1980–1986) level. Although the shift from distant disease to local-regional disease actually induced a temporary increase in incidence, we avoided modeling this increase by only changing the stage of diagnosis and the subsequent prognosis, but not the time of diagnosis. Certainly, the deficit in distant stage disease represents individuals with disease that was screen detected at some previous time that was unknown, but our model assumed that the survival advantage of an earlier diagnosis began at the original time of diagnosis with distant disease, so the model was not affected by the lack of knowledge of the time of screen detection.

To calculate the stage shift, we computed the average annual number of patients by stage-grade in the base years (1980–1986) weighted to the 1990 U.S. race specific male populations. For each year from 1991 onward, we calculated the number of patients with distant stage disease by grade, again weighted to the 1990 U.S. race specific male population. For each observed decrement in the number of patients with distant stage disease over the base years, the same number of patients were shifted to local-regional disease, assuming that grade remained constant. Figure 2 shows the stage shift assumed for each grade category for black males and white males. For example, for white males, the percentage of distant disease with well to moderately differentiated tumors declined from 6% to 1% of all patients, causing a concurrent increase in L/R/U with well to moderately differentiated tumors from 53% to 58%. These resultant stage shifts were applied in CAN*TROL 2.

Survival Assumptions

Using what is termed our *base assumption*, we assumed that a patient with screen-detected local-regional disease of a certain histologic grade had the same prognosis as a patient with clinically detected local-regional disease of the same grade (i.e., an assumption of no length bias for patients with screen-detected disease). To avoid exaggerating estimates of survival with the effects of lead time, all survival estimates are from the prescreening era, i.e., 1980–1986 (Fig. 3). In addition, a clinically plausible *optimistic* scenario was run using the assumption that a patient with screen-detected disease shifted from distant disease to local-regional disease was cured if they had a favorable grade tumor (i.e., well or moderately differentiated), whereas patients with unfavorable grade tumors (i.e., poorly differentiated, undifferentiated, or unknown) still had a local-regional survival curve according to their tumor grade. In a *pessimistic* scenario, we assumed that patients with unfavorable grade tumors had no benefit early detection, whereas patients with favorable grade tumors still had a local-regional survival curve according to their tumor grade. These latter two assumptions allowed for the possibility that length bias was operating for patients with disease that was detected early through PSA screening.

To better understand these survival assumptions, suppose a man who would have been clinically diagnosed with a well to moderately differentiated distant stage tumor is shifted to local-regional disease through screening. If we assume a specified lead time (we have chosen 5 years for the purposes of illustra-

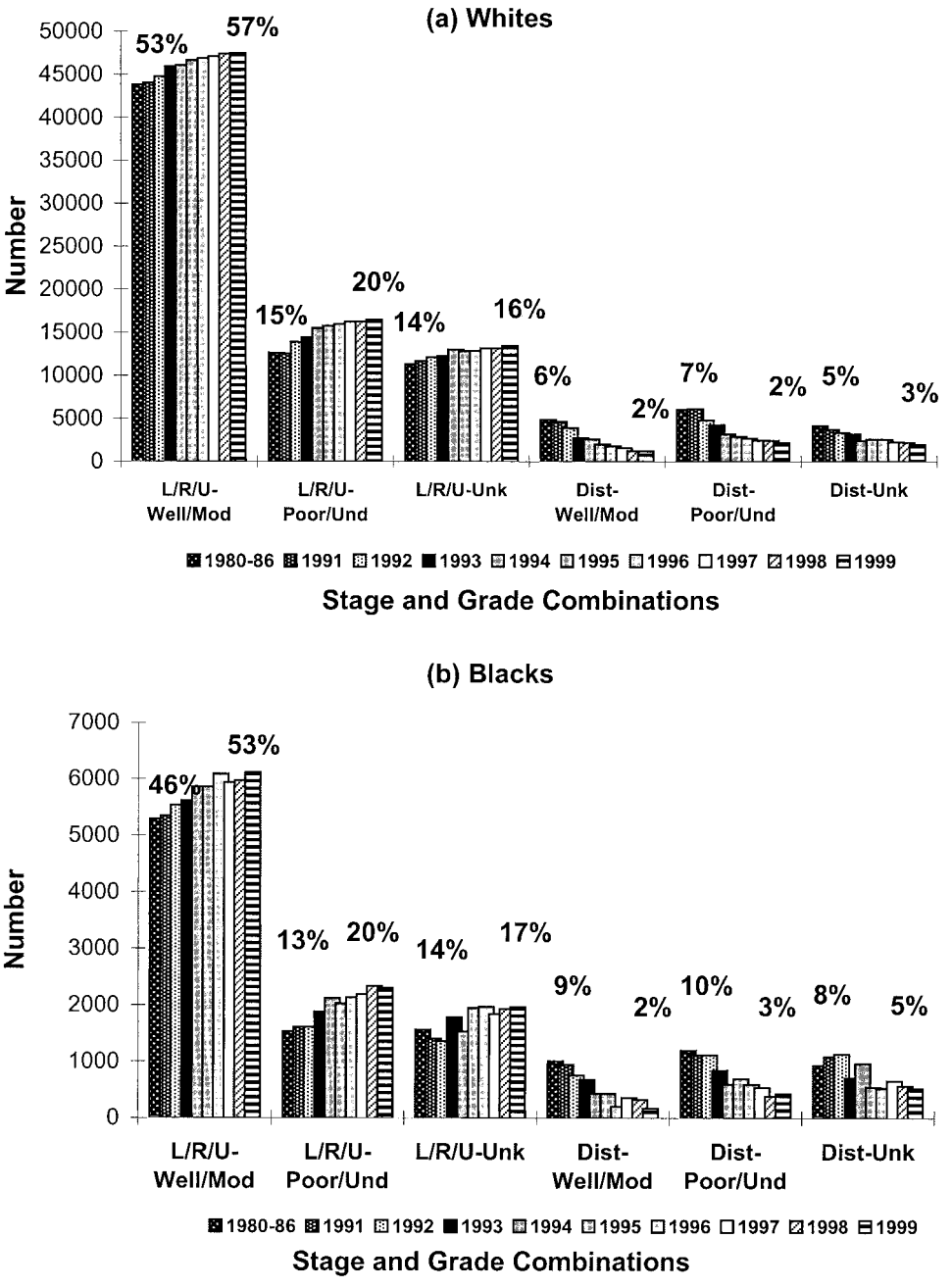

FIGURE 2. The observed incidence of distant prostate carcinoma (Dist) and the expected incidence of local-regional prostate carcinoma (L/R) assuming that the only increase in the incidence of local-regional disease was due to the shift from distant disease to local-regional disease. The numbers are weighted to the race specific U.S. male 1990 population. Percentages indicate the stage distribution. L/R/U: local/regional/unknown; Poor/Und; poor/undifferentiated; Well: well differentiated; Mod: moderately differentiated; Unk: unknown.

tion), our base survival assumption would imply that this man would be shifted from the survival curve shown by the dotted line with starbursts in Figure 4 to the curve shown by the solid line with triangles. No one can die of disease during their lead time; thus, the disease specific or relative survival curve[12] of a patient with screen-detected disease does not start to decline until the end of their lead time. It is the shift in the time of diagnosis associated with screening that temporarily raises incidence. Because almost no one is diagnosed by screening with distant disease, it is reasonable to assume that each decline in distant stage disease represents a shift of a patient from distant disease to local-regional disease. Thus, for each decline in the number of patients with distant stage disease, a corresponding patient is shifted to an improved local-regional survival curve. For each patient of this type, we know when the patient's disease would have been detected clinically in the absence of screening, but we do not know the time of screen detection. Because we know that the relative survival curve cannot start to decline prior to the time of clinical diag-

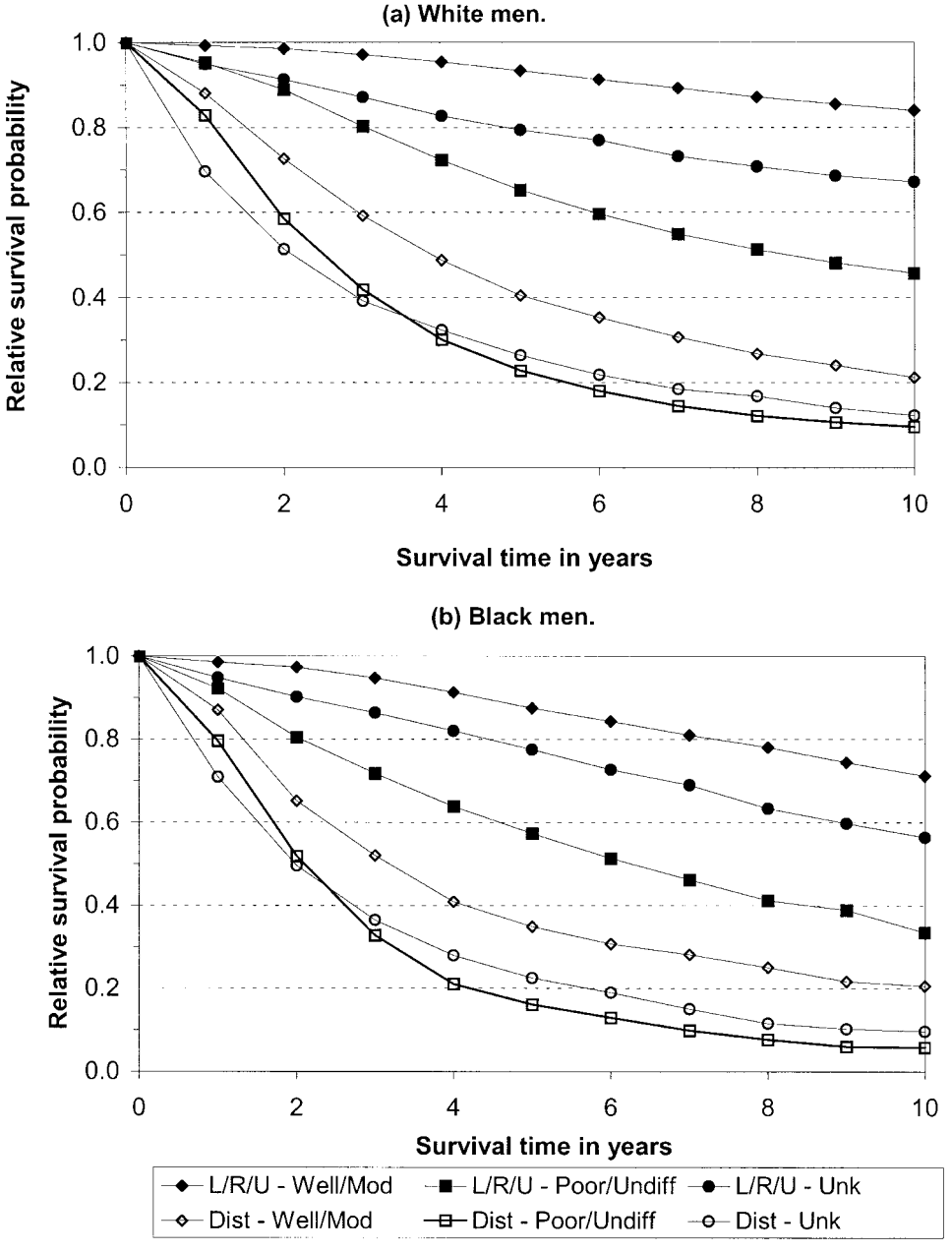

FIGURE 3. SEER relative survival of patients with diagnosed prostate carcinoma during 1980–1986 by stage-grade combinations. L/R: local-regional disease; Dist: distant disease; L/R/U: local/regional/unknown; Poor/Undiff; poor/undifferentiated; Well: well differentiated; Mod: moderately differentiated; Unk: unknown.

nosis, we place this person on an improved local-regional survival curve initiated at the time their disease would have been detected clinically rather than at the time of screen detection. Because this model does not shift the time of diagnosis for patients with screen-detected disease, there is no need to input estimates of lead time or to model any increase in incidence above its prescreening level.

RESULTS

CAN*TROL 2 was run to compute the intervention mortality rates and counts under each scenario, i.e., the base case, the pessimistic scenario, and the optimistic scenario. For comparison, CAN*TROL 2 also calculated the reference mortality rates and counts under the hypothesis that the stage-grade distribution is the same as the distribution during the pre-PSA testing period (1980–1986). The impact of the intervention was determined by calculating the percent difference between the baseline and intervention mortality rates with respect to the intervention mortality rates. These percent differences are shown in Table 1. Under the modeled stage-shift intervention, mortality rates would fall 18%, 8%, and 19% for white

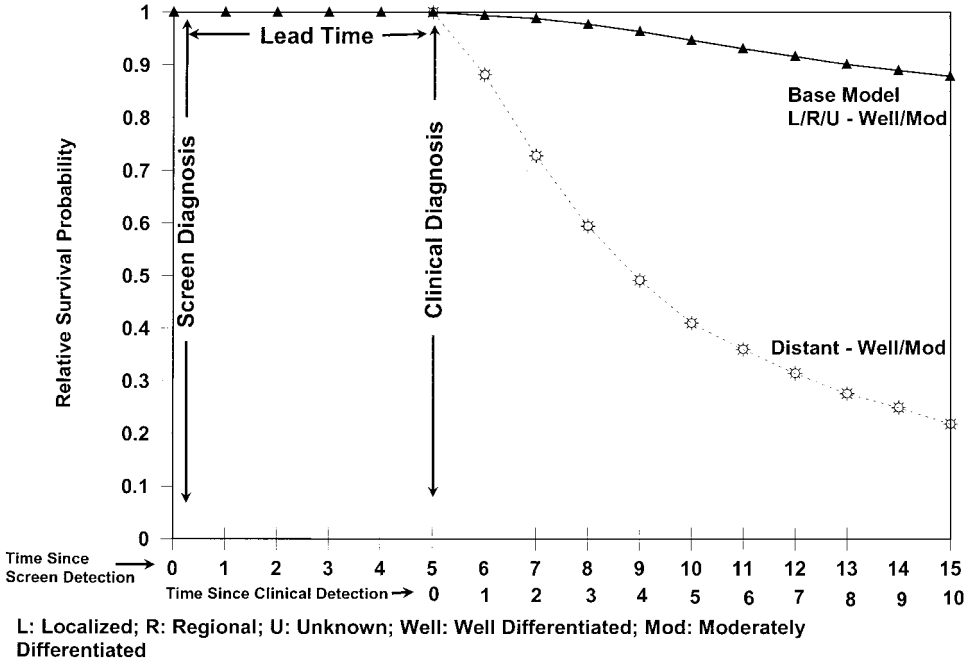

FIGURE 4. Shift of diagnosis time and prognosis assumptions.

TABLE 1
Observed U.S. Age-Adjusted Mortality Rates and the Percent Decline in Mortality Rates Due to the Observed Shift from Distant to Local-Regional Prostate Carcinoma under Three Survival Assumptions: Base, Pessimistic, and Optimistic

	White males				Black males			
		Percent Difference[a]				Percent Difference[a]		
Year	U.S. mortality rates[b]	Base	Pessimistic	Optimistic	U.S. mortality rates[b]	Base	Pessimistic	Optimistic
1990	32.38	—	—	—	71.42	—	—	—
1991	32.98	0	0	0	71.47	0	0	0
1992	32.75	1	1	1	72.48	0	1	1
1993	32.55	4	2	4	73.80	2	2	4
1994	31.91	7	3	7	72.06	5	3	7
1995	30.72	10	4	10	70.12	9	4	10
1996	29.45	13	6	13	70.37	12	6	13
1997	27.85	15	7	15	65.76	15	7	15
1998	26.54	17	7	17	64.20	16	7	17
1999	25.59	18	8	19	61.80	18	8	19

Base: clinical local-regional survival; pessimistic; clinical local-regional survival for favorable grade tumors and no benefit for tumors of unfavorable grade; optimistic: cure for favorable grade tumors and clinical local-regional survival for tumors of unfavorable grade.

[a] (Reference rate − intervention rate)/intervention rate.

[b] The observed U.S. mortality rates (per 100,000 males) were age adjusted to the 1990 U.S. standard million.

males and black males under the base, pessimistic, and optimistic assumptions, respectively. White males had a drop in the percentage of patients with distant stage disease from 18% to 7% (a drop of 11 percentage points), whereas black males went from 27% to 10% (a drop of 17 percentage points) (Fig. 2). However, compensating for the larger change in stage distribution for black males is the smaller survival improvement for black males (a base case difference in 10-year survival for black patients of 51, 47, and 28 percentage points, respectively, for patients with well to moderately differentiated, poorly differentiated or undifferentiated, and unknown grade tumors compared with 63, 55, and 36 percentage points for white males) (Fig. 3). These two factors seem to just compensate each other to produce a comparable percent decline in mortality associated with the stage shift. To give these results some perspective, these percent differences are

then multiplied by the observed U.S. mortality rates and added to the observed rates, i.e., *observed U.S. rate × (1 + [(CAN*TROL reference rate − CAN*TROL intervention rate)/CAN*TROL intervention rate)*.

Because the observed U.S. rate can be interpreted as the rate that occurred in the presence of the intervention, the intervention rates cancel in the above equation, and the resulting rate can be interpreted as the rate that would have been observed if the modeled intervention had never occurred (i.e., the modeled secular trend in the absence of screening). Figure 5 graphically displays observed U.S. mortality and the mortality rates if the intervention had not occurred under all three scenarios. The area between each curve and the U.S. observed mortality rates represents deaths averted under the assumption of each scenario. The optimistic and base scenarios have the highest curves, followed by the pessimistic scenario. This is because the mortality impact of the decline in distant stage disease is the largest when survival improves the most. Under the pessimistic scenario, it appears that something else must be responsible for much of the decline in mortality. Under the base assumption, it appears that the decline in distant stage disease can explain much of the observed decline in mortality. The optimistic scenario is not much improved over the base scenario, which is indicative of the fact that the survival of patients who are diagnosed with clinical local-regional stage disease is quite good, and further survival improvements can have only a marginal impact. Although the modeled impact of the decline in distant stage disease on mortality is approximately the same for black males and white males (Table 1), the impact of this intervention on the observed mortality trends (Figure 5) seems to go further above the secular trend for black males than for white males. This is due to the fact that the observed mortality decline for black males is smaller and of shorter duration compared with that observed for white males (16.3% for black males from 1993 to 1999 vs. a 22.4% decline for white males from 1991 to 1999).

DISCUSSION

Etzioni et al.[6] modeled the potential impact of PSA screening on prostate carcinoma mortality through 1994 using a direct approach. This direct approach required assumptions about 1) the dissemination of PSA screening in the population, 2) cancer detection rates for PSA screening, 3) lead time, and (4) survival postlead time for patients with screen-detected disease. By indirectly modeling the potential mortality decline as a function of the observed decline in distant stage disease, this report required only assumptions concerning survival postlead time for patients with screen-detected disease. Specifically, no assumptions were necessary concerning lead time, a quantity for which estimates vary widely.[13–15] This model requires two other assumptions, namely that 1) the flat incidence trends for distant disease that occurred from at least 1973 (the beginning of SEER data collection) until 1990 would have continued in the absence of screening, and 2) the decline in distant stage disease starting in 1991 represents a screening-induced shift of patients from distant disease to local-regional disease.

Modeling provides a useful synthesis of the current state of knowledge and uncertainty. Although models may be too simplified, unreal, and even false in some respects, they force us to confront possibilities that otherwise would not have occurred.[16] Using this model, we have shown that it is not too early for a PSA-induced decline in distant stage disease to cause a substantial portion of the observed mortality decline. For white males, it appears that, under the pessimistic and base assumptions, mortality rates would have been flat until 1994 in the absence of the intervention and then would have started to decline. For black males, mortality actually would rise until 1996 under the optimistic and base assumptions in the absence of the intervention. In the absence of randomized trial evidence, it is difficult to know which of the three survival scenarios is the most realistic. It is possible that a patient with screen-detected L/R/U disease who did not have symptoms until it was distant disease would have a more aggressive tumor compared with a patient with symptom-detected L/R/U disease. This argues for the more pessimistic assumption. Alternatively, a patient with distant disease that is screen detected as L/R/U must not have a tumor that is growing too quickly; otherwise, it probably would have avoided detection in screenings at fixed intervals. This would argue for the base scenario and possibly for the optimistic scenario. One cannot entirely rule out the possibility that the shift from distant disease to local-regional disease results in no improvement in prognosis and, thus, has no impact on mortality

We have assumed that the grade of a tumor does not change over time; however, this is not known. If grade becomes worse as the tumor grows, then screening could shift a distant poorly, differentiated tumor to a local-regional, well to moderately differentiated tumor. Thus, the impact on mortality may be even greater than the result shown here.

In almost every scenario shown in Figure 5, there must be another component responsible for some of the decline in mortality. Although this analysis focused on patients who shifted from distant disease to L/R/U disease (i.e., Type I patients), there certainly

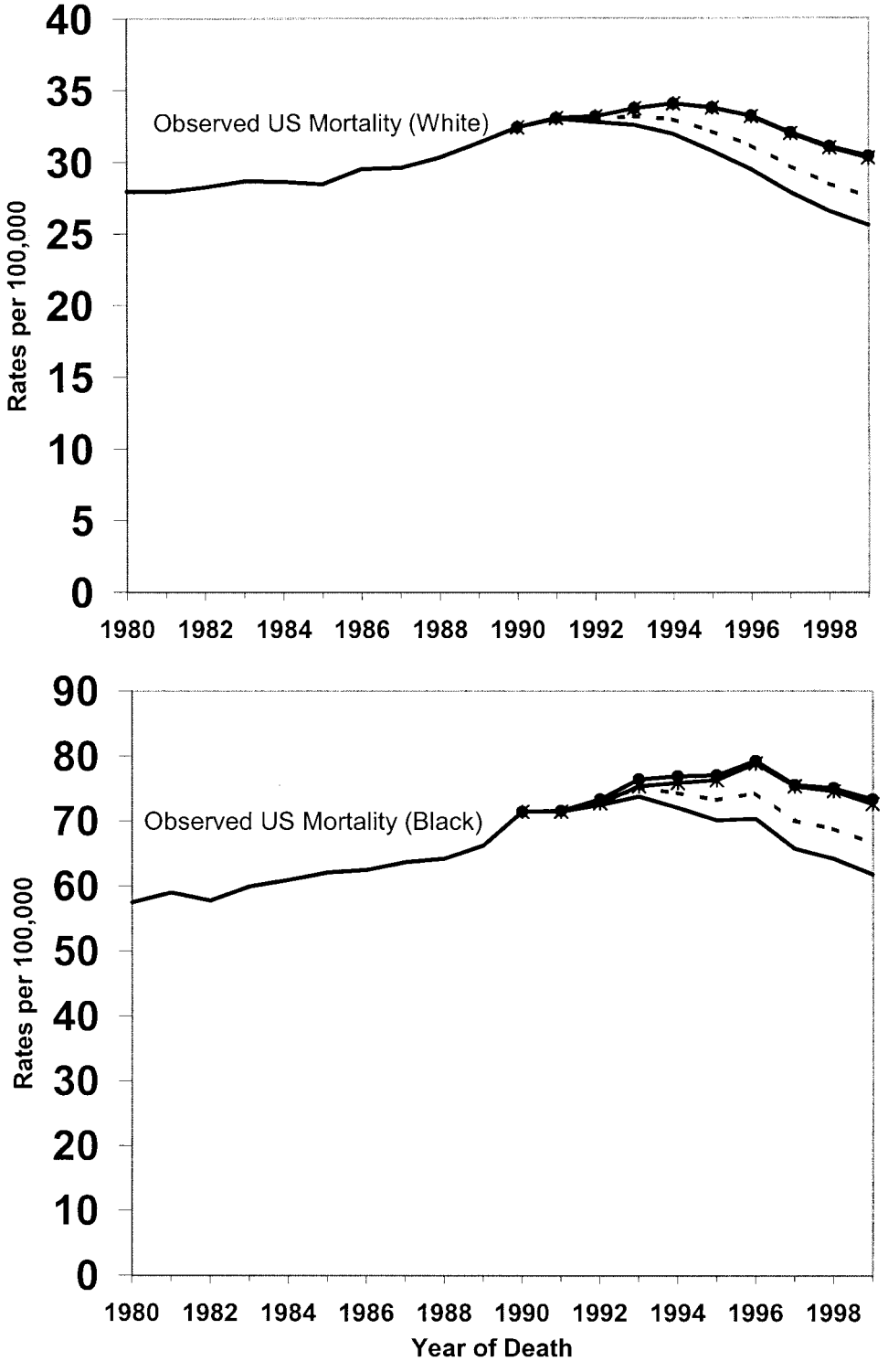

FIGURE 5. The effect of a stage shift on prostate carcinoma mortality rates for white men and black men by year of death under three survival assumptions for shifted patients. The areas between each curve and the U.S. mortality rates (solid lines) represent deaths averted. Dashed line: pessimistic (clinical local-regional survival for favorable grade and no benefit for unfavorable grade); solid line with asterisks: base (clinical localized/regional survival); solid line with dots: optimistic (cure for favorable grade and clinical local-regional survival for unfavorable grade).

may be another component of the decline in mortality associated with Type II patients (i.e., patients with a within-stage shift from L/R/U disease to earlier in the course of L/R/U disease). Feuer et al.[4] showed that, even in the prescreening era, more prostate carcinoma deaths were attributable to patients who were diagnosed with local-regional disease than to patients with distant disease at the time of diagnosis, despite the large prognostic advantage of a diagnosis of local-regional disease. Of course, this is due to the fact that

the number of patients with local-regional disease is much larger than the number of patients with distant disease, which more than compensates for the differences in prognosis. If, in fact, it is true that mortality gains for Type I patients are observed before mortality gains for Type II patients, then a second wave of mortality gains associated with Type II patients still may occur. There is probably overlap between the mortality impact of Type I patients and Type II patients. The size of any benefit associated with Type II patients depends ultimately on any prognostic advantage of earlier detection in the course of local-regional disease.

There are certainly other factors related to changes in the treatment of patients with prostate carcinoma that may explain some portion of the decline in mortality. The proportion of patients with prostate carcinoma who undergo radical prostatectomy (RP) increased dramatically until 1992 and then leveled off.[17] If RP results in an improved prognosis, an assumption that has yet to be established in clinical trials, then this may be driving mortality rates down. The introduction of new gonadotropin-releasing hormone analogues and oral antiandrogenic agents in the late 1980s has made AD therapy more popular than when the only alternative to AD therapy was orchiectomy. Long-term adjuvant AD therapy with radiation therapy for patients with locally advanced disease has shown survival benefits over AD at the time of disease progression.[18] Although this affects a relatively small group of patients, possible benefits of short-term adjuvant AD therapy will affect a larger prognostic group, and dissemination may be greater due to less severe side effects. Finally, promising results from a trial[19] showed that adjuvant AD for patients with lymph node positive disease after undergoing RP has a survival benefit over AD at the time of clinical disease progression.

This model shifted patients from distant disease to local-regional disease within histologic grade groupings. Observed histologic grade is a function of the amount of tissue available for examination, and the amount of tissue available for examination is a function of the treatment modality. Thus, changes in treatment modality over time may slightly confound the results of this modeling effort. Another potential confounding factor is the changing incidence of patients with disease of unknown stage.[4] Although we combined these patients with the group of patients with local-regional disease because of their similar prognosis, it is difficult to know the role these patients actually play in the stage shifts induced by PSA screening.

Assessing the impact of PSA screening in the population presents an especially difficult task, because the population use exploded in 1990, whereas the U.S. PLCO Cancer Screening Trial started accruing patients in 1993,[20] and the European Randomized Study of Screening for Prostate Cancer[21] did not start accruing patients until 1994. Population data and trials should be viewed as partners rather than competitors in our search to determine the efficacy and population impact of treatment, screening, and prevention modalities. The results of our study and those of Etzioni et al.[6] suggest that there may be a subset of patients with shorter lead times who are having an impact on early population mortality declines. Thus, trial results may show some declines earlier than originally anticipated. Trial results will give us a mortality benefit associated with screening isolated from other factors, which is impossible in a population setting. These results can be put back into our population models to help isolate the impact of screening, treatment, and other factors on population trends.

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