Prostate cancer is the most common noncutaneous cancer in men in the United States. During 1998, it is estimated that 184,500 new cases will be diagnosed (1). The age-adjusted incidence rate of prostate cancer in U.S. black men is more than 30% higher than in white men, and the age-adjusted mortality rate in blacks is more than twice as high (2). Moreover, the most recent data (3–5) from the national Surveillance, Epidemiology, and End Results (SEER) Program show that after diagnosis with prostate cancer, black men have substantially shorter survival than white men, even when diagnosed at the same cancer stage. Such stage-specific comparisons indicate that the poorer survival of black men with prostate cancer is not simply a result of diagnosis at later stages. These data have led some to hypothesize that the survival disadvantage in blacks is due to biologic factors rather than racial differences in access to health care.

This hypothesis (hereafter called the biologic hypothesis) predicts that black men with prostate cancer present with a less favorable distribution of tumor stage and grade than do white men, regardless of whether the comparisons are made among men in the general population or in populations with equal access to health care.

As an alternative to the biologic hypothesis, some investigators have proposed that the racial survival disadvantage for black men is due to decreased access to care, with decreased opportunities for early diagnosis and treatment (hereafter called the access hypothesis). This hypothesis is based on studies of equal-access health care systems, such as those administered by the Departments of Veterans Affairs (6,7) and Defense (8), which have consistently found no stage-specific racial survival differences.

In contrast to the biologic hypothesis, the access hypothesis predicts that racial differences in tumor stage and grade will be more similar in equal-access populations than in the general population. Both hypotheses predict equal survival for black and white men if the analysis adjusts for both stage and grade. However, analyses adjusting for stage but not grade give different predictions for equal-access and general population health care settings. The biologic hypothesis predicts that the survival disadvantage for black men should be observed in both settings. The access hypothesis, however, predicts that racial survival differences should be present in the general population but not in populations with equal access to health care.

To test these two alternative hypotheses, we analyzed survival data for black and white men diagnosed with prostate cancer in the San Francisco Bay Area region of northern California. All cases occurred among men residing in five Bay Area counties participating in the SEER program. Within this population, we analyzed data separately for members and nonmembers of a large health maintenance organization, the Kaiser Permanente Medical Care Plan (Northern California Region).

Methods

Study Population and Data Sources

We used cancer registry data from two defined populations to compute prostate cancer death rates for black and white men. The San Francisco Bay Area

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986 ARTICLES

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region of the National Cancer Institute’s SEER Program includes the populations of Alameda, Contra Costa, San Francisco, San Mateo, and Marin counties (hereafter referred to as the San Francisco Bay Area) in the state of California. Essentially all new cancer cases occurring among residents of these counties are registered, and the registry includes information on patient demographics, tumor characteristics, initial course of treatment, and survival. Since SEER implemented a modification in the rules for coding localized stage prostate cancer in 1983, we included in this study only case patients with localized stage prostate cancer that was diagnosed in or after 1983. However, the coding rule modification did not impact regional or distant stage cases, and so we included all case patients with regional and distant stage cancer diagnosed in or after 1973. SEER data regarding all new cases of prostate cancer in the San Francisco Bay Area were available through December 1992, with follow-up information available through December 1993 (9).

The SEER registry in the Bay Area is operated by the Northern California Cancer Center, which provided a separate computerized file containing only new prostate cancer cases occurring among members of the Kaiser Permanente Medical Care Program (Northern California Region) through June 1995. Kaiser Permanente is a large group-model health maintenance organization that provides comprehensive medical care services to all enrolled members. The Northern California Region of Kaiser Permanente (hereafter called Kaiser) serves more than 2.5 million enrolled members through 15 hospitals and 30 free-standing outpatient clinics.

The present study used data regarding 5263 incident case subjects with prostate cancer who were San Francisco Bay Area Kaiser members and 16 019 case subjects who were not Kaiser members. Only data regarding cases of invasive prostate cancer that occurred in white and black men aged 35 years and older were used.

Stage Categories

All cases of prostate cancer were coded as one of the following stages at diagnosis: localized (cancer confined entirely to the prostate gland); regional (cancer extends into tissues surrounding the prostate or to regional lymph nodes); or distant (cancer extends to beyond regional lymph nodes, to bones, or to other sites) (10). When information was insufficient to assign a stage, cases were denoted as unknown stage. This staging scheme (10) has been used by the SEER Program since its inception in 1973. When comparing the SEER staging scheme (10) to the American Urological Association (AUA) System of Staging (11), localized stage corresponds approximately to stages A1 through B; regional stage is approximately equal to C though D1; and distant stage is equivalent to D2.

Grade Categories

Prostate tumors were assigned a histopathologic grade according to the International Classification of Disease for Oncology, 2nd ed. (12). Tumors were classified as grades 1 (well differentiated), 2 (moderately differentiated), 3 (poorly differentiated), 4 (undifferentiated), or unknown.

Statistical Analysis

We conducted the following statistical tests to compare baseline characteristics of white and black men with prostate cancer: Student’s t test comparing age at diagnosis; chi-squared test of association between race and cancer stage; and chi-squared test of association between race and tumor grade. We also conducted chi-squared tests of association between race and initial prostate cancer treatment (cancer-directed surgery and radiation therapy) within strata defined by cancer stage and Kaiser membership status. These analyses were performed using SAS statistical software (SAS Institute, Inc., Cary, NC) (13).

We computed crude death rates in whites and blacks by dividing the total numbers of deaths (from all causes) by the total numbers of person-years of follow-up, with person-years calculated on the basis of the dates of diagnosis and death or censoring. Case subjects were censored if they were lost to follow-up or if they were alive on June 30, 1995 (Kaiser members) or December 31, 1993 (nonmembers). To adjust for racial differences in age, we first computed age- and race-specific death rates for six age intervals (35–44, 45–54, 55–64, 65–74, 75–84, and 85 years and older), where men whose follow-up crossed age intervals contributed person-years to each of the appropriate intervals. Maximum likelihood estimates of the adjusted death rate ratio and 95% confidence intervals (CIs) were computed using Poisson regression methods implemented in the SAS procedure PROC GENMOD (SAS Institute, Inc.) (14).

Analyses were performed for each cancer stage and for all cancer stages combined, with separate analyses for Kaiser members and nonmembers with prostate cancer. Information for nonmembers was obtained by subtracting—within each race/stage/age stratum—the number of deaths and person-years of follow-up for Kaiser members with prostate cancer from the corresponding figures for all Bay Area cases. When computing death rates for nonmembers with prostate cancer, we restricted our analyses to cases occurring through December 1992. This enabled us to divide the SEER survival data (age-specific numbers of deaths and person-years of follow-up) into those obtained from Kaiser members and nonmembers.

We also compared the death rates in San Francisco Bay Area black and white men with prostate cancer in analyses where the underlying cause of death was restricted to prostate cancer. Specifically, these analyses included only men whose underlying cause of death was listed as code 185 (malignant neoplasm of the prostate), using the coding scheme of the International Classification of Diseases (versions 8 and 9).

To estimate absolute survival time for white and black case subjects in the Kaiser cohort, we followed the methodology described by Kelsey et al. (15). We began by computing—for white case subjects—the all-cause death rates for each age/stage stratum, using the six age categories described above and the three stage categories (local, regional, and distant). We computed μ as the unweighted average of these 18 death rates. The risk of death at time t, R(t), was computed as R(t) = 1 − e−μt, where t was in years. Median survival was computed by finding the value of t satisfying the relation, R(t) = 1 − e−μt = 0.5. We estimated the average death rate for black Kaiser cases with prostate cancer as rμ, where r was the estimate of the death rate ratio (black men versus white men, adjusted for age and stage). With the use of the exponential risk function above, we computed median survival for black Kaiser members with prostate cancer as the value of t corresponding to R(t) = 0.5 for black subjects.

Results

Baseline Racial Differences

Black men were diagnosed with prostate cancer at younger ages than white men in both the Kaiser member and nonmember cohorts (Table 1). In both cohorts, age at diagnosis for black men was approximately 2 years earlier than for white men. For men of both races, Kaiser members were diagnosed at younger ages than nonmembers.

Black men were also more likely than white men to have distant stage cancer at diagnosis, regardless of Kaiser membership. Among Kaiser members and nonmembers, approximately one in five black men presented with metastatic cancer as opposed to approximately one in seven white men. In both races, the proportion of localized stage cases was higher in Kaiser members than nonmembers, although the stage advantage for Kaiser members was larger for white men than for black men. The proportion of patients with unknown stage was much lower in Kaiser members, possibly indicating that cases occurring among Kaiser members received more thorough staging than those occurring in nonmembers. Black men had a significantly greater proportion of higher grade tumors than white men in both Kaiser members and nonmembers, supporting the hypothesis that prostate cancer is a more aggressive disease in black men. Again, the proportion of patients with unknown grade was much lower for case subjects in the Kaiser cohort, possibly indicating more complete pathologic investigation of tumors in Kaiser members.

Racial Survival Differences

Among Kaiser members and nonmembers, black men had substantially poorer survival after diagnosis with prostate cancer, as shown by the elevated death rate ratios (DRRs) observed when black men are compared with white men (Table 2). The
DRRs were substantially elevated for all stages combined, and within nearly all stages, among both Kaiser members and nonmembers. In six of the eight comparisons shown, the DRR elevations were statistically significant, as indicated by 95% CIs that exclude unity.

Among Bay Area men with prostate cancer, black men had higher mortality than white men, among both Kaiser members (black men 28% higher) and nonmembers (black men 22% higher), even after adjusting for racial differences in age and cancer stage. Stage-specific comparisons reveal similar DRR elevations for localized and regional stage cancer among both Kaiser members and nonmembers. However, findings for distant stage cancer among Kaiser members differed dramatically from those for nonmembers. Among Kaiser members with distant stage cancer, we observed a DRR of 1.27 (95% CI 1.07–1.50), while for nonmembers we observed a DRR of 1.01 (95% CI 0.91–1.12).

For Kaiser members with prostate cancer, we also carried out

### Table 1. Baseline racial differences among San Francisco Bay Area* men with prostate cancer who were and were not members of the Kaiser Permanente Medical Care Plan

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whites</td>
<td>Blacks</td>
</tr>
<tr>
<td>No. of case subjects</td>
<td>3994</td>
<td>796</td>
</tr>
<tr>
<td>Mean age at diagnosis, y</td>
<td>70.6</td>
<td>68.5</td>
</tr>
<tr>
<td>Stage at diagnosis, %§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Localized</td>
<td>62.6</td>
<td>55.2</td>
</tr>
<tr>
<td>Regional</td>
<td>16.7</td>
<td>17.3</td>
</tr>
<tr>
<td>Distant</td>
<td>15.7</td>
<td>21.9</td>
</tr>
<tr>
<td>Unknown</td>
<td>5.0</td>
<td>5.7</td>
</tr>
<tr>
<td>Tumor grade, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (well differentiated)</td>
<td>20.0</td>
<td>12.8</td>
</tr>
<tr>
<td>2 (moderately differentiated)</td>
<td>49.0</td>
<td>51.8</td>
</tr>
<tr>
<td>3 (poorly differentiated)</td>
<td>22.1</td>
<td>25.5</td>
</tr>
<tr>
<td>4 (undifferentiated)</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>7.5</td>
<td>8.4</td>
</tr>
</tbody>
</table>

*Includes the counties of Alameda, Contra Costa, San Francisco, San Mateo, and Marin in the state of California. The data were collected under the Surveillance, Epidemiology, and End Results Program.

†To permit meaningful results for the stage and grade distributions, regional and distant stage cases in the table are restricted to those diagnosed from January 1983 through June 1995 (Kaiser members) or from January 1983 through December 1992 (nonmembers). This is because only localized stage cases diagnosed from January 1983 through June 1995 (Kaiser members) or from January 1983 through December 1992 (nonmembers) are included in the present study (see "Methods").

‡Racial differences in age were evaluated using Student’s t test. Racial differences in cancer stage and tumor grade were evaluated using the chi-squared test of association.

§In localized stage cases, the tumor is confined to the prostate gland. In regional stage cases, the tumor extends beyond the prostate capsule or has spread to regional lymph nodes. In distant stage cases, the tumor has spread beyond regional lymph nodes, to bones, or to other sites.

DRRs were substantially elevated for all stages combined, and within nearly all stages, among both Kaiser members and nonmembers. In six of the eight comparisons shown, the DRR elevations were statistically significant, as indicated by 95% CIs that exclude unity.

Among Bay Area men with prostate cancer, black men had higher mortality than white men, among both Kaiser members (black men 28% higher) and nonmembers (black men 22% higher), even after adjusting for racial differences in age and cancer stage. Stage-specific comparisons reveal similar DRR elevations for localized and regional stage cancer among both Kaiser members and nonmembers. However, findings for distant stage cancer among Kaiser members differed dramatically from those for nonmembers. Among Kaiser members with distant stage cancer, we observed a DRR of 1.27 (95% CI = 1.07–1.50), while for nonmembers we observed a DRR of 1.01 (95% CI = 0.91–1.12).

For Kaiser members with prostate cancer, we also carried out

### Table 2. Racial survival differences among San Francisco Bay Area* men with prostate cancer who were and were not members of the Kaiser Permanente Medical Care Program

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All stages†</th>
<th>Localized</th>
<th>Regional</th>
<th>Distant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whites</td>
<td>Blacks</td>
<td>Whites</td>
<td>Blacks</td>
</tr>
<tr>
<td>Deaths (all causes)</td>
<td>14 472</td>
<td>2814</td>
<td>9139</td>
<td>1700</td>
</tr>
<tr>
<td>Person-years (P-Y) of observation</td>
<td>101.5</td>
<td>124.7</td>
<td>63.6</td>
<td>69.4</td>
</tr>
<tr>
<td>Crude death rate (per 1000 P-Y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted death rate ratio§ (95% confidence interval)</td>
<td>1.28 (1.14–1.44)</td>
<td>1.23 (1.01–1.51)</td>
<td>1.30 (0.97–1.75)</td>
<td>1.27 (1.07–1.50)</td>
</tr>
<tr>
<td>Nonmembers, 1973–1992‡</td>
<td>5242</td>
<td>975</td>
<td>1657</td>
<td>268</td>
</tr>
<tr>
<td>Deaths (all causes)</td>
<td>47 235</td>
<td>7308</td>
<td>24 030</td>
<td>3562</td>
</tr>
<tr>
<td>Person-years (P-Y) of observation</td>
<td>111.0</td>
<td>133.4</td>
<td>69.0</td>
<td>75.2</td>
</tr>
<tr>
<td>Crude death rate (per 1000 P-Y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted death rate ratio§ (95% confidence interval)</td>
<td>1.22 (1.14–1.30)</td>
<td>1.24 (1.09–1.41)</td>
<td>1.48 (1.29–1.68)</td>
<td>1.01 (0.91–1.12)</td>
</tr>
</tbody>
</table>

*Includes the counties of Alameda, Contra Costa, San Francisco, San Mateo, and Marin in the state of California. The data were collected under the Surveillance, Epidemiology, and End Results Program.

†In localized stage cases, the tumor is confined to the prostate gland. In regional stage cases, the tumor extends beyond the prostate capsule or has spread to regional lymph nodes. In distant stage cases, the tumor has spread beyond regional lymph nodes, to bones, or to other sites.

‡Only localized stage cases diagnosed from January 1983 through June 1995 (Kaiser members) or January 1983 through December 1992 (nonmembers) are included in the present study. Regional and distant stage cases were diagnosed from January 1973 through June 1995 (Kaiser members) or from January 1973 through December 1992 (nonmembers) (see "Methods").

§Comparing black men with white men. Result for all stages is adjusted for age and stage. Results for separate stages are adjusted for age.
absolute comparisons of survival duration. The median survival time for white Kaiser case subjects was 4.0 years. After adjusting for racial differences in age and stage, the median survival time for black Kaiser case subjects was 3.1 years. Thus, age- and stage-adjusted median survival was 10.6 months shorter for black Kaiser members with prostate cancer.

Treatment Differences by Race

We analyzed racial differences in the use of the most common therapies for prostate cancer (cancer-directed surgery and radiation therapy) by cancer stage. Among Kaiser members with localized stage cancer, we found a nonsignificant tendency for black men to undergo cancer-directed surgery and/or receive radiation therapy slightly more frequently than did white men (black men, 81.6% versus white men, 78.6%). Among Kaiser case subjects with regional and distant stage cancers, we observed a nonsignificant tendency for black men to undergo cancer-directed surgery and/or receive radiation therapy) by cancer stage. Among Kaiser members with prostate cancer.

Stage—black men, 77.2% versus white men, 80.2%, \( P = .48 \); regional stage—black men, 22.2% versus white men, 25.2%, \( P = .44 \). Among Kaiser nonmembers, we did not observe any consistent racial patterns in the use of these treatments (local stage—black men, 87.8% versus white men, 85.2%, \( P < .01 \); regional stage—white men, 94.5% versus black men, 91.5%, \( P = .05 \); and distant stage—black men, 60.9% versus white men, 54.3%, \( P = .02 \).

It must be remembered, however, that SEER only includes data on initial therapies. Thus, we were unable to investigate racial differences in treatments given after the initial therapy.

Causes of Death

Since the death rates in Table 2 are based on all causes of death, it might be argued that the DRR elevations among black men are actually due to racial differences in the risk of death from causes other than prostate cancer, e.g., death from cardiovascular disease. If this were so, one would expect a disappearance of the racial differences in Table 2 in analyses based only on deaths from prostate cancer. In such analyses, for example, the DRR for all stages combined, adjusted for age and stage, should be close to 1.00.

Prostate cancer was listed as the underlying cause of death for 51.0% of case subjects in the present study. We computed death rates for all Bay Area white and black men with prostate cancer, based only on deaths from prostate cancer. After adjusting for racial differences in age and cancer stage, the ratio between these death rates (black men versus white men) was 1.26 (95% CI = 1.16–1.38). Thus, the value of the DRR is unchanged when the rates are based only on deaths from prostate cancer. This provides definitive evidence that the elevated all-cause death rate in black men in the present study is not accounted for by increased risk of death from causes other than prostate cancer.

Discussion

While previous studies in equal-access medical care systems have suggested that inequalities in access to health care might explain the poorer survival in black men with prostate cancer, this study provides substantial evidence against that hypothesis. Independent of Kaiser membership status, black men diagnosed with prostate cancer in the San Francisco Bay Area had poorer survival than white men. For all cancer stages combined, the death rate among black men was higher than among white men: among Kaiser members, the rate in black men was 28% higher; and among nonmembers, the rate in black men was 22% higher. In nearly all stage-specific comparisons, death rates among black men with prostate cancer were substantially higher than corresponding rates among white men, demonstrating that the poorer survival in black men is not merely a result of later stage at diagnosis.

In the report from the Department of Defense medical care system (8) and one of the reports from the Veterans Affairs system (6), the investigators controlled for racial differences in tumor grade when testing their main hypotheses. The investigators treated tumor grade as if it were a potential confounding variable, which would bias results toward null findings if higher tumor virulence in black men represented a causal explanation for the poorer prostate cancer survival in this group. While another report from the Veterans Affairs system (7) did not adjust for tumor grade, the investigators used data from only 358 white men and 383 black men with prostate cancer. Particularly in stage-stratified survival analyses, the study was handicapped by the poor statistical power to detect racial survival differences. The present study used data from 17,241 white men and 2,823 black men with prostate cancer. Whereas the present study was conducted among members of the general community and a large health maintenance organization, all previous investigations in equal-access settings were conducted among current and former members of the U.S. military. Equal prostate cancer survival in white and black men in the Department of Defense and Veterans Affairs studies might be related to racial similarities in selection factors for military service.

As noted earlier, the SEER staging scheme (10) employs only three stages as compared with the AUA system of staging (11), which uses five stages. Therefore, within each of the three broader SEER stages used in the present study, racial differences in survival still could exist if white men in a given stage were diagnosed on average at an earlier point in the history of their cancer. Systematic racial differences in survival within stages could plausibly arise, even in equal-access health care systems, if there were important racial differences in factors such as frequency of contact with health care providers. An important point is that equal-access health care systems can only guarantee equality of covered benefits for enrolled members (16), not equality in the frequency of use of all forms of care. While some degree of residual confounding by stage undoubtedly exists in these data, it is unlikely that this factor could substantially account for the findings. This is because the magnitude of the age- and stage-adjusted racial difference in median survival among Kaiser members (10.6 months) is quite large relative to the median survival of 4.0 years for white men. Thus, the degree of residual confounding within SEER stages would have to be implausibly large to account for these findings.

The present findings could be explained by racial differences in either or both of two factors: tumor aggressiveness or treatment. The observation that black men had a significantly greater proportion of higher grade prostate tumors supports the hypothesis that prostate tumors tend to be more virulent in black men.
The inconsistent findings with respect to treatment differences argue against this explanation for the study results. Additionally, it must be noted that, at present, there exists fundamental controversy over the effect of treatment on prostate cancer survival (17).

Increased mortality among black men from causes of death other than prostate cancer is unlikely to explain these findings, since black men had a higher death rate, even when the underlying cause of death was restricted to prostate cancer. In addition, investigators from the Greater Bay Area Cancer Registry (18) have also reported survival differences in Bay Area white and black men with localized and regional stage prostate cancer using relative survival rates (19) to adjust for background racial differences in mortality. Since white and black Kaiser members are probably more homogeneous with respect to socioeconomic status—a strong predictor of general mortality rates—that members of the general Bay Area population, it is less likely that the findings for Kaiser members could be due to racial differences in death rates from causes other than prostate cancer.

Finally, screening-related biases (lead-time bias and length bias) would not adequately explain these findings since they affect only screen-detected cases. [Lead-time bias arises when cancers are diagnosed earlier but there is no change in the date of diagnosis.] For prostate cancer, the great majority of screen-detected cases are localized stage cancer of longer duration and affect only screen-detected cases. Length bias refers to the propensity for screening to artifactually lengthen their survival time, separate explanations would still have to be sought to explain the results for regional and distant stage cancer.

In addition to experiencing poorer survival than white men with prostate cancer, black men were diagnosed at more advanced stages than white men; this was evident among both Kaiser members and nonmembers. Diagnosis at more advanced stages in black men may be due to unequal tendencies for white and black men to be screened for early stage cancer or to a tendency for tumors to spread beyond the prostate more rapidly in black men.

Thus, black men with prostate cancer had poorer stage-specific survival than white men, even in a large equal-access medical care system. These results argue strongly that racial differences in prostate cancer survival are not due solely to inequalities in access to health care. The findings are most compatible with the hypothesis of increased tumor virulence in black men.

References


Notes

*Editor’s note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.*

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