Fall 10-2008

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Abstract

Prostate cancer is the most frequently diagnosed cancer in males in the United States, accounting for an estimated 186,320 new cases in 2008. There are striking racial or ethnic differences in prostate cancer incidence and mortality rates in the United States, with Black males 1.6 times more likely to be diagnosed and 2.4 times more likely to die with prostate cancer than Whites. Stage at diagnosis is a key prognostic factor for prostate cancer survival, with African-Americans generally diagnosed at a more advanced stage. To identify factors that explain the race-stage disparity in prostate cancer, we conducted a population-based case-case study of 251 African-American (46%) and White (54%) prostate cancer cases diagnosed in Connecticut between January 1987 and October 1990. Multivariate logistic regression was used to identify potential explanatory factors, including clinical, sociodemographic, medical care, insurance, digital rectal examination screening history, and lifestyle factors. Cox proportional hazards models assessed the impact of study variables on race differences in long-term survival. Modifiable factors such as screening practice and sociodemographic factors accounted for >60% of the race difference in prostate cancer stage at diagnosis. Histologic grade (Gleason score) accounted for comparatively less. Survival analyses confirmed the importance of tumor characteristics, education, and insurance in explaining observed race differences in survival. Although cases were identified before the widespread use of prostate-specific antigen (PSA) screening, the results should also be relevant to countries that have large underserved populations and/or disparities in access to medical care and cancer screening. (Cancer Epidemiol Biomarkers Prev 2008;17(10):2825–34)

Introduction

Prostate cancer is the most frequently diagnosed cancer in males in the United States, with an estimated 186,320 cases to be diagnosed in 2008 (1). With increasing global development, prostate cancer is an important source of cancer death, even in developing countries. Worldwide, 3 African countries and 3 Latin American countries rank among the top 10 countries with the highest prostate death rates. Although the United States is ranked 28th with respect to prostate cancer mortality rates, there are striking racial differences in prostate cancer incidence and mortality rates among American men (2, 3). In the United States, for the years 2000 to 2004 (most recent data), the average annual age-adjusted incidence rates (per 100,000) of prostate cancer were 161.4 in White males and 255.5 in African-American males. Over the same period, the average annual age-adjusted mortality rates (per 100,000) for prostate cancer were 25.6 and 62.3, respectively, for White and African-American males (3).

Stage at diagnosis is a key predictor of survival from prostate cancer. Between 1996 and 2003, the 5-year relative survival rate was 100% among men diagnosed with prostate cancer at either a localized or regional stage, but only 32% among men with distant stage disease (1). In an analysis of National Cancer Institute Surveillance, Epidemiology and End Results (SEER) data (4), later stage at diagnosis had the largest impact on explaining the Black-White difference in prostate cancer mortality. Although there is a much more favorable stage distribution in the PSA (prostate specific antigen) screening era, African-American men are still somewhat less likely to be diagnosed with localized prostate cancer compared with White men (89% versus 92%, respectively; ref. 1).

This population-based case-case study was designed to evaluate race differences in stage at diagnosis for prostate cancer and to identify factors that might explain the observed differences. Potential explanatory variables considered in this study included a wide range of sociodemographic, access to health care, cancer screening history, clinical, and selected lifestyle factors. Understanding the role of these factors in the observed race difference in prostate cancer stage at diagnosis from a time before PSA screening may shed light on the smaller but persistent race difference in prostate stage at diagnosis and survival

Received 3/4/08; revised 6/24/08; accepted 7/28/08.

Grant support: National Cancer Institute, NIH Program Project Grant (5-P01-CA42101), and The Patrick and Catherine Weldon Donaghue Medical Research Foundation (DF 01-025).

Note: M.G.M. Curnen has now retired but was affiliated with the Yale University School of Medicine during the study period.

The authors assume full responsibility for data analyses and interpretation.

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doi:10.1158/1055-9965.EPI-08-0203

that exists despite widespread prostate cancer screening in men today.

Materials and Methods

The Study Population. This investigation was part of a larger study in which race differences in several cancers that disproportionately burden African-Americans were investigated. The method was the same for all sites and has been previously described (5, 6). Between January 1987 and October 1990, using a rapid case-ascertainment system, we identified all men with newly diagnosed prostate cancer from the 22 Connecticut hospitals in which 98% of all African-American cancer cases in Connecticut were diagnosed. A comparison of African-American prostate cancer cases ascertained by our surveillance system to those listed (with some delay) in the Connecticut Tumor Registry (CTR) (and diagnosed in these same 22 hospitals) during the study period indicated that all but 7 prostate cancer cases occurring in African-American men were identified by our surveillance efforts, resulting in >98% complete enumeration. Approvals of the institutional review boards of Yale University School of Medicine, the State of Connecticut Department of Public Health, and all participating hospitals have been maintained throughout the study period.

Eligibility was limited to men for whom this was a first malignancy (except nonmelanoma skin cancer) and who self-identified as African-American or White, spoke English, and were <80 years old at the time of diagnosis. Of the 414 eligible men who were identified, 251 (60.6%) were included in this study (115 African-American, 136 White). There were no significant race differences in overall participation ($P = 0.97$). However, race was related to reasons for nonparticipation. Physician refusal to allow contact with their patients was cited for 16 (21.3%) of 75 African-American and 35 (39.8%) of 88 White nonparticipants. Inability to contact occurred for 9 (12.0%) of 75 African-American nonparticipants compared with 3 (3.4%) of 88 White nonparticipants. There were no significant differences by race in patient refusal or death occurring before patient contact (7).

Data Collection. Participants were interviewed in their homes using a standardized instrument administered by trained interviewers. Of the 251 cases, 119 (47.4%), 100 (39.8%), and 32 (2.7%) were interviewed within 3 months, 3 to 6 months, and >6 months of their diagnosis, respectively. Time from diagnosis to interview did not differ by race ($P = 0.40$) or stage at diagnosis ($P = 0.71$). The instrument was a modified version of the questionnaire used in the National Cancer Institute's Black/White Cancer Survival Study (8) and covered a wide range of variables, including sociodemographic, health history, medical care, and psychosocial factors. We abstracted hospital medical records to obtain complete information on the size and extent of the tumor, diagnostic work-up, and medical history. With informed consent obtained at the time of the in-home interview, photocopies of pathology reports, operative reports, admission notes, discharge summaries, referral correspondence, and staging reports were obtained. Further information was obtained when necessary from physicians' office records.

Stage at Diagnosis. Prostate cancer stage at diagnosis was assigned to each case independently by two of the authors (W.L. and R.D.) using the American Urological Association staging system, the tumor-node-metastasis staging system established by the American Joint Committee on Cancer (9), and the SEER Extent of Disease System (10). Using a systematic process and detailed medical record search for information on all diagnostic procedures (including but not limited to a review of bone scan, CT (Computed Tomography) scan, and rectal exam results), our reviewers were able to assign a stage at diagnosis to 25 of 26 cases that were left unstaged by the Connecticut Tumor Registry (because of missing data). Only one case was dropped from our analysis because of the inability to assign a stage at diagnosis. Differences in interpretation were resolved by case conference. Based on an evaluation of the impact of staging criteria on the observed African-American–White difference in stage at diagnosis using these same data, we concluded that the American Urological Association system would provide the most accurate staging of cases for the purpose of assessing racial differences (7). Furthermore, the American Urological Association staging system is consistent with the Whitmore-Jewett System (11, 12), the system most widely used at the time of our case enrollment. With minor differences, it is comparable with the tumor-node-metastasis staging system that is more common today.

Two notable exceptions in stage at diagnosis assignment include the following: (*a*) the American Urological Association system takes elevation of prostatic acid phosphatase into consideration whereas the tumor-node-metastasis system does not and (*b*) the tumor-node-metastasis system takes into account histologic grade whereas the American Urological Association staging system does not. The American Urological Association staging system defines four stages of prostate cancer (A, B, C, D). No palpable lesion is evident in stage A. In stage B, the tumor is confined to the prostate. In stage C, the tumor is localized to the periprostatic area. Finally, stage D indicates metastatic disease. The primary outcome in all analyses is a dichotomous variable: localized (stages A and B) versus nonlocalized (stages C and D). This dichotomy has been associated with substantial differences in survival and has been used in previous studies (13, 14).

Other Measures. Race, the primary independent variable, was based on self-identification at the time of interview; only persons reporting race as Black, African-American, or White were included in this investigation. Sociodemographic factors included age (45-64, 65-70, and 71-79 years), marital status (single versus married or living as married), and three measures of socioeconomic status: education (1-8, 9-12, and >12 years), occupational rank based on Duncan's (15, 16) socioeconomic index (SEI), (tertiles, 4-20, 21-46, and 47-88), and family income (<$13,000, $13,000-$24,999, >$24,999). Medical care factors included having a regular doctor (no, yes), number of doctor visits (0, ≥1) over the year before diagnosis, and usual type of appointment (walk-in, scheduled appointment). A health care barrier index (high versus low, where high indicated more barriers) was constructed from items that assessed mode of transportation, required transportation time, difficulty in making

Table 1. Selected characteristics of prostate cancer cases by race: Connecticut 1987 to 1990

Variable*	African-American (n = 115)†		White (n = 136)†		OR‡	95% CI
	n[2]	%	n[2]	%		
Sociodemographic factors						
Age (y)						
45-64	31	27.0	25	18.4	2.25	1.16-4.36
65-70	47	40.8	44	32.4	1.93	1.09-3.44
71-79	37	32.2	67	49.3	1.00	
Marital status						
Single	40	34.5	22	16.2	3.08	1.67-5.68
Living as married	75	65.2	114	83.8	1.00	
Education (y)						
1-8	42	37.5	17	12.5	17.50	6.98-43.8
9-12	57	50.9	65	47.8	4.50	2.12-9.52
>12	13	11.6	54	39.7	1.00	
Occupational rank						
Lowest tertile (14-20)	57	50.0	23	16.9	4.79	4.68-20.5
Middle tertile (21-46)	39	34.2	50	36.8	3.01	1.51-6.03
Highest tertile (47-88)	18	15.8	63	46.3	1.00	
Family income (US $)						
<13,000	27	26.2	15	11.5	6.67	2.86-15.6
13,000-24,999	40	38.8	46	35.1	2.61	1.36-5.03
>24,999	36	35.0	70	53.4	1.00	
Medical care factors						
Regular doctor						
No	25	21.7	11	8.1	2.91	1.35-6.26
Yes	90	78.3	124	91.9	1.00	
Number of doctor visits						
0	23	20.4	13	9.6	2.52	1.19-5.31
≥1	90	79.6	123	90.4	1.00	
Appointment type						
Walk-in	15	13.5	8	5.9	2.52	1.01-6.28
Scheduled	96	86.5	127	94.1	1.00	
Barrier index						
High score	68	59.7	57	41.9	2.02	1.20-3.38
Low score	46	40.3	79	58.1	1.00	
Understanding of insurance coverage						
Poor	16	15.1	11	8.2	3.46	1.44-8.33
Moderate	51	48.1	43	31.9	2.60	1.47-4.62
Good	39	36.8	81	60.0	1.00	
Screening history						
DRE						
Never	24	21.0	16	11.8	2.24	1.10-4.54
Ever	90	79.0	120	88.2	1.00	
Lifestyle factors						
Smoking status						
Current smoker	25	22.1	22	16.2	1.37	0.76-2.46
Ex-smoker	58	51.3	67	49.3	1.51	0.71-3.21
Never smoker	30	26.6	47	34.5	1.00	
Alcohol consumption						
Heavy	30	26.6	26	20.0	0.94	0.43-2.04
Light	55	48.7	80	61.5	0.58	0.30-1.12
Never	28	24.8	24	18.5	1.00	
BMI						
Highest tertile	44	38.6	41	30.2	1.33	0.71-2.49
Middle tertile	35	30.7	49	36.0	0.96	0.51-1.81
Lowest tertile	35	30.7	46	33.8	1.00	
Clinical factors						
Histologic grade§						
Poorly differentiated	29	26.1	24	18.3	1.67	0.89-3.12
Moderate and well-differentiated	82	73.9	107	81.7	1.00	
Comorbid conditions						
≤3	62	53.9	56	41.2	1.52	0.91-2.53
>3	53	46.1	80	58.8	1.00	

Abbreviations: OR, odds ratio; DRE, digital rectal examination.
* See Materials and Methods for definition.
† Sample size fluctuates due to missing data.
‡ Age-adjusted odds ratio, with 95% CI, obtained from multiple logistic regression.
§ Gleason score 8, 9, 10 (poorly differentiated) versus Gleason score 5, 6, 7 (moderate) and Gleason score 2, 3, 4 (well differentiated).

Table 2. Association between race and prostate cancer stage at diagnosis (American Urological Association staging system): Connecticut 1987 to 1990

Stage at diagnosis*	African-American (n = 115)		White (n = 136)		OR†	95% CI
	n	%	n	%		
Nonlocalized	69	60.0	58	42.7	2.02	1.21-3.38
Localized	46	40.0	78	57.4	1.00	

*American Urological Association staging system: nonlocalized (stages C and D) versus localized (stages A and B).
†Crude odds ratio, with 95% CI, obtained from logistic regression.

medical appointments, waiting time for scheduling an appointment, office waiting time, and satisfaction with care. Although several questions related to the extent and quality of health insurance coverage, the only insurance variables that were effective in discriminating between patients with different outcomes were those that assessed the understanding of insurance policy based on two questions (''has anyone ever explained your insurance coverage to you or given you something to read about it?'' and ''Do you feel that you understand your insurance coverage or would you like to know more?''). Prostate screening history (never versus ever) was ascertained in reference to digital rectal examination but not the PSA screening test because this test was not widely used for screening purposes at this time (17) and was not available for most of our cohort. Clinical factors included histologic grade of tumor and comorbidity as potential explanatory variables. As in the case of stage at diagnosis, histologic grade was determined by study investigators (R.D. and W.L.), with differences resolved by case conference. Using data from pathology reports, histologic grade was classified using the Gleason method, dichotomized in these analyses as poorly differentiated (Gleason score 8, 9, 10) versus moderately (5, 6, 7) or well-differentiated (2, 3, 4), reflecting the designations in use at the time of this investigation.

Like the remainder of the potential explanatory factors, information on comorbidity was elicited from in-person interview. Using a comorbidity index that included 25 chronic health conditions, the variable was categorized as ≤3 versus >3 comorbid conditions. Body mass index (BMI) from self-reported usual adult height and weight was categorized as low, medium, or high based on tertiles of distribution. (A continuous measure of BMI and categories that correlate with overweight, severely overweight, and/or obese were tested and did not change the reported results.) Lifestyle factors included smoking status (current or ex-smoker who smoked regularly for at least 6 months versus never smoker) and alcohol consumption (heavy, light, and never, where heavy and light were defined as greater than or less than the mean, respectively, for those who reported some consumption in the year preceding their cancer diagnosis).

Statistical Analysis. Unconditional logistic regression was the primary tool used for data analysis. Age-adjusted odds ratios and 95% confidence intervals (95% CI) are generally reported. Possible explanatory variables were identified theoretically and empirically. Based on the existing literature, our *a priori* assumption was that screening (digital rectal examination) and histologic grade would each partially explain the observed association between race and stage at diagnosis. Other explanatory variables were identified empirically by examining bivariate associations between candidate variables and race and the outcome variable, stage at diagnosis, with χ^2 tests ($P < 0.05$; not presented) as well as logistic regression models adjusted only for continuous age. Analyses stratified by race were done to determine whether effects on stage at diagnosis were consistent for African-Americans and Whites.

Variables significantly related to both race and stage at diagnosis were tested further in age-adjusted models to assess change in the race-stage odds ratio. Meaningful change was defined as a 10% change in the estimated odds ratio for the race-stage association, where the change-in-estimate is computed as [(adjusted odds ratio - unadjusted odds ratio) / (unadjusted odds ratio - 1)] × 100 (18).

In a series of models in which digital rectal examination screening and histologic grade were first introduced into multivariate models, all variables determined to have explanatory potential by the methods described above were tested individually. Entry order presented in the final model was determined by the relative contribution of each variable in explaining the age-adjusted race-stage association in the simpler models. Adjustment for hospital of diagnosis (n = 22) was not made to the final models because its inclusion in simpler models did not substantially alter the reported results.

Finally, Cox proportional hazards regression (hazards ratios and 95% CI are reported) was used to examine the role of stage at diagnosis and other factors in observed race differences in survival from colorectal cancer.

Results

Patient Characteristics by Race. Compared with Whites in this population-based study of men with newly diagnosed prostate cancer, African-Americans were younger, less likely to be married or living as married, and of lower socioeconomic status (education, occupational rank, and family income; Table 1). Access to health care was significantly poorer in African-American men compared with White men as measured by a single medical care index (not shown) as well as individual items, that is, they were less likely to have a regular doctor, less likely to have visited a doctor in the year before diagnosis, and less likely to have made an appointment (versus walk-in) with a doctor's office when seeking medical care. African-Americans also reported a greater number of logistic barriers to receiving care (e.g., transportation problems, longer wait times for appointments), and were substantially less likely to

Table 3. Selected characteristics of prostate cancer cases by stage at diagnosis: Connecticut 1987 to 1990

Variable*	Nonlocalized* (n = 127)†		Localized* (n = 124)†		OR‡	95% CI
	n†	%	n†	%		
Sociodemographic factors						
Age (y)						
45-64	29	22.8	27	21.8	1.00	0.52-1.91
65-70	44	34.7	47	37.9	0.87	0.49-1.52
71-79	54	42.5	50	40.3	1.00	
Marital status						
Single	32	25.2	30	24.2	1.06	0.59-1.87
Living as married	95	74.8	94	75.8	1.00	
Education (y)						
1-8	37	29.6	22	17.9	2.08	1.01-4.31
9-12	57	45.6	65	52.9	1.03	0.57-1.88
>12	31	24.8	36	29.3	1.00	
Occupational rank						
Lowest tertile (14-20)	50	39.4	30	24.4	1.99	1.06-3.74
Middle tertile (21-46)	40	31.5	49	39.8	0.98	0.53-1.79
Highest tertile (47-88)	37	29.1	44	35.8	1.00	
Family income (US $)						
<13,000	21	17.8	21	18.1	1.23	0.59-2.58
13,000-24,999	47	39.8	39	33.6	1.44	0.80-2.60
>24,999	50	42.4	56	48.3	1.00	
Medical care factors						
Regular doctor						
No	23	18.1	13	10.6	1.85	0.89-3.86
Yes	104	81.9	110	89.4	1.00	
Number of doctor visits						
0	18	14.2	18	14.8	0.96	0.47-1.94
≥1	109	85.8	104	85.2	1.00	
Appointment type						
Walk-in	12	9.7	15	12.3	0.76	0.32-1.83
Scheduled	112	90.3	107	87.7	1.00	
Barrier index						
High score	67	53.2	58	46.8	1.28	0.78-2.11
Low score	59	46.8	66	53.2	1.00	
Understanding of insurance coverage						
Poor	16	13.3	11	9.1	1.99	0.85-4.66
Moderate	53	44.2	41	33.9	1.75	1.02-3.02
Good	51	42.5	69	57.0	1.00	
Screening history						
DRE						
Never	26	20.6	14	11.3	2.08	1.03-4.21
Ever	100	79.4	110	88.7		
Lifestyle factors						
Smoking status						
Current smoker	25	19.8	22	17.9	0.66	0.31-1.39
Ex-smoker	53	42.1	72	58.5	0.44	0.25-0.79
Never smoker	48	38.1	29	23.6	1.00	
Alcohol consumption						
Heavy	34	28.1	22	18.0	1.53	0.71-3.29
Light	61	50.4	74	60.7	0.82	0.43-1.57
Never	26	21.5	26	21.3	1.00	
BMI						
Highest tertile	39	31.0	46	37.1	0.74	0.40-1.36
Middle tertile	44	34.9	40	32.3	0.98	0.53-1.80
Lowest tertile	43	34.1	38	30.7	1.00	
Clinical factors						
Histologic grade§						
Poorly differentiated	43	35.8	10	8.2	6.35	3.04-13.44
Moderate and well-differentiated	77	64.2	112	91.8	1.00	
Comorbid conditions						
≤3	70	55.1	48	38.7	1.93	1.16-3.22
>3	57	44.9	76	61.3	1.00	

* See Materials and Methods for definition.
† Sample size fluctuates due to missing data.
‡ Age-adjusted odds ratio, with 95% CI, obtained from multiple logistic regression.
§ Gleason score 8, 9, 10 (poorly differentiated) versus Gleason score 5, 6, 7 (moderate) and Gleason score 2, 3, 4 (well differentiated).

Table 4. Relation of race to stage at diagnosis before (model I) and after (model II) adjustment for potential explanatory variables: Connecticut 1987 to 1990

Explanatory variable*	Model †	OR for race effect (African-American vs White) ‡	95% CI	Percentage of change, estimated OR§
Sociodemographic factors				
Marital status (n = 251)	I	2.02	1.21-3.38	
	II	1.98	1.16-2.41	-3.9
Education (n = 249)	I	2.00	1.19-3.36	
	II	1.80	1.02-3.18	-20.0
Occupational rank (n = 250)	I	2.06	1.23-3.45	
	II	1.80	1.03-3.17	-24.5
Family income (n = 234)	I	1.73	1.01-2.95	
	II	1.70	0.97-2.99	-4.1
Medical care factors				
Regular doctor (n = 250)	I	2.00	1.19-3.35	
	II	1.89	1.12-3.19	-11.0
Number of doctor visits (n = 249)	I	2.12	1.26-3.56	
	II	2.12	1.26-3.56	-0.0
Barrier index (n = 250)	I	1.99	1.19-3.33	
	II	1.94	1.15-3.27	-5.0
Understanding of insurance coverage (n = 235)	I	1.89	1.11-3.19	
	II	1.69	0.98-2.90	-22.5
Screening history				
DRE (n = 250)	I	1.98	1.18-3.32	
	II	1.87	1.11-3.15	-11.2
Lifestyle factors				
Smoking status (n = 249)	I	2.02	1.21-3.32	
	II	2.18	1.28-3.71	+15.7
Alcohol consumption (n = 243)	I	2.03	1.20-3.42	
	II	1.96	1.16-3.33	-6.8
BMI (n = 250)	I	1.98	1.18-3.32	
	II	2.04	1.21-3.38	+6.1
Clinical factors				
Histologic grade (n = 249)	I	2.09	1.24-3.53	
	II	1.95	1.12-3.40	-12.8
Comorbid conditions (n = 251)	I	2.02	1.21-3.38	
	II	1.93	1.14-3.24	-8.8

* See Materials and Methods for definition.
† Model definitions: I includes race and age as predictors and II includes race, age, and specified explanatory variable as predictors. For each set of models (I & II), the odds ratio for model I changes slightly to reflect small differences in sample size in the selected explanatory variables.
‡ Age-adjusted odds ratio, with 95% CI, obtained from multiple logistic regression.
§ [(race II odds ratio - race I odds ratio) / (race I odds ratio - 1)] × 100.

report that they were well informed about the extent of their insurance coverage. A significantly greater proportion of African-Americans than Whites reported never having had a screening digital rectal examination. There were no significant differences between African-American and White men with respect to lifestyle factors (smoking, alcohol), BMI, or comorbidity. Compared with 18% of White men, 26% of African-American men were diagnosed with poorly differentiated tumors (Gleason score), although this difference was not statistically significant.

Race Difference in Prostate Stage at Diagnosis. Consistent with trends reported even in the most recent SEER registry data (1), racial differences in stage at diagnosis were observed in our population-based sample (Table 2). With 69 African-Americans (60.0%) and 58 Whites (42.7%) diagnosed with nonlocalized cancer, African-Americans were significantly more likely than Whites to be diagnosed with cancer that had progressed beyond a localized stage (unadjusted odds ratio = 2.02; 95% CI, 1.21-3.38). One concern was the potential for race differences in incidental diagnoses of prostate cancer resulting from possible race differences in transurethral resection of the prostate for treatment of benign prostatic hyperplasia. With 22% of cases in African-Americans and 21% in Whites diagnosed with prostate cancer as an incidental finding (7), this potential source of bias was dismissed.

Patient Characteristics by Prostate Stage at Diagnosis. The associations between potential explanatory variables and stage at diagnosis are shown in Table 3. Those with nonlocalized and localized prostate cancer were statistically similar with respect to age, marital status, family income, health care utilization, lifestyle factors, and BMI. Patients with nonlocalized disease were substantially more likely to have lower socioeconomic status based on education and occupational status, to be less informed about their insurance coverage, and less likely to have ever had a screening digital rectal examination. Men with later-stage cancers were less likely to report comorbid conditions in these age-adjusted analyses and considerably more likely (significantly) to have high grade tumors (odds ratio = 6.35; 95% CI, 3.04-13.44). No statistically significant interactions with race were identified.

Explaining the Race Difference in Prostate Stage at Diagnosis. Shown in Table 4 are the changes in estimate for the age-adjusted race-stage odds ratio after adjusting

for each individual explanatory variable. Among sociodemographic factors, occupational rank, and education reduced the odds ratio by >20%. Regarding health care utilization factors, having a regular doctor resulted in a meaningful reduction in the odds ratio for the race-stage association (-11.0%), as did considering oneself to be well informed about one's insurance coverage (-22.5%). Adjustment for screening digital rectal examinations in the previous 2 years reduced the odds ratio by 11.2%. Of the clinical factors, only histologic grade showed some explanatory potential, reducing the odds ratio for race-stage by 12.8%.

In Table 5, we present the model that best explained the observed race difference in stage at diagnosis based on the criteria outlined above (Methods, Statistical Analysis) as well as a conceptual framework in which it was hypothesized that the observed associations with stage at diagnosis were likely mediated by either race differences in screening history or by race differences in the aggressiveness of the tumor (measured here as histologic grade). Beginning with a model that reflected this conceptual framework, adjusting only for age, the race-stage odds ratio was 1.83 (95% CI, 1.06-3.15). Adjustment for having ever received digital rectal examination before diagnosis reduced the race-stage association by 14.5% (the magnitudes of the changes in estimate shown here differ slightly from those in Table 4 because of differences in sample size available for specific analyses). Including histologic grade with digital rectal examination in the model reduced the odds ratio by 28.9%. With the addition of education, this odds ratio was reduced by a total of 58%. Although occupational ranking looked promising as an explanatory factory from the unadjusted change-in-estimate models, because of its strong correlation with education, it was not statistically significant in the final models. Finally, with the addition of the variable that measured how well informed these subjects were about their insurance coverage, the odds ratio was further reduced. In summary, the race-stage odds ratio was maximally reduced from 1.83 (95% CI, 1.06-3.15) to 1.21 (95 % CI, 0.64-2.30) when these 4 variables were simultaneously included in the model, resulting in a 74.7% reduction in the magnitude of the odds ratio for the race-stage association.

Acknowledging that the likely overlap between factors that predict histologic grade and those that predict stage at diagnosis could result in models that are overcontrolled once histologic grade is entered, we also conducted analyses in which the order of variables selected into multivariate models was determined by the relative contribution of each in explaining the race-stage association. Although this series of models is not presented, education, insurance, and digital rectal examination explained 65.4% of the race-stage association. The explanatory effect of these factors is comparable with that described in previous model (74.7%), suggesting a relatively minor role for histologic grade in explaining the later stage at diagnosis observed in African-American men.

Prostate Cancer Survival. As a follow-up to this analysis, we looked at whether tumor characteristics (stage and grade) alone were responsible for the observed race differences in long-term survival from colorectal cancer. Although not presented here, with a maximum of 15 years of follow-up, 70% of the original cohort (n = 175) had died (all-cause mortality) by 2002. Adjusting only for their younger age at diagnosis, African-Americans had significantly poorer survival rates than did Whites (hazards ratio, 1.53; 95% CI, 1.13-2.08). Adjustment for more aggressive tumor characteristics (higher stage and tumor grade) explained some, but not all, of the race difference in survival (hazards ratio, 1.26; 95% CI, 0.92-1.73). With further adjustment for socioeconomic status and our insurance measure, we were able to completely explain the observed race difference in survival (hazards ratio, 1.03; 95% CI, 0.71-1.49).

Discussion

To the authors' knowledge, this is one of a few population-based studies that have systematically examined explanatory factors for the racial disparity in stage at diagnosis of prostate cancer. Consistent with

Table 5. Multivariate models explaining the race-prostate cancer stage at diagnosis association: Connecticut 1987 to 1990 (n = 223)

Model	Predictor variables*	OR†	95% CI	Cumulative percentage of change, estimated OR‡
I	Race	1.83	1.06-3.15	
II	Race	1.71	0.98-2.97	-14.5
	DRE	1.91	0.88-4.16	
III	Race	1.59	0.88-2.86	-28.9
	DRE	2.24	0.99-5.03	
	Histologic grade	6.04	2.79-13.07	
IV	Race	1.36	0.73-2.55	-58.0
	DRE	2.00	0.88-4.57	
	Histologic grade	5.90	2.72-12.81	
	Education	1.77	0.82-3.82	
V	Race	1.21	0.64-2.30	-74.7
	DRE	1.93	0.84-4.43	
	Histologic grade	5.90	2.71-12.86	
	Education	1.78	0.82-3.87	
	Understanding of insurance coverage	1.65	0.91-2.99	

* See Materials and Methods for definition.
† Age- and specified variable–adjusted odds ratio, with 95% CI, obtained from multiple logistic regression.
‡ [(fully adjusted odds ratio - race + age odds ratio)/(race + age odds ratio - 1)] × 100.

previous work (20-26), we observed that African-Americans were twice as likely as Whites to be diagnosed at a more advanced stage of disease. We also observed that African-Americans were disadvantaged in terms of survival.

Unlike other studies (22, 23), the current study was able to explain more than half of the observed race difference in stage at diagnosis, rendering it not statistically significant. However, adjustment for individual explanatory factors produced relatively modest modifications of the race-stage association, indicating that this is a complex relationship that cannot be explained by any single factor. Although adjustment for a few variables reduced the association to nonsignificance, our goal was to identify the set of variables that could maximally reduce the stage difference between African-American and White men. By accounting for racial differences in use of screening digital rectal examination, histologic grade of tumors, level of education, and the degree to which men are informed about their insurance coverage, we were able to explain up to 75% of the excess risk for late stage at diagnosis of prostate cancer in African-American compared with White men. Although we cannot rule out missed associations secondary to limited statistical power, we were able to rule out an explanatory role for obesity and smoking history, both of which have been reported to be associated with advanced or fatal prostate cancer in a large cohort study (27). We also ruled out multiple measures of access to and previous medical care as well as alcohol consumption. Although more aggressive prostate cancer has been associated with a positive family history (27), we could not assess this variable in this study because only seven African-Americans reported prostate cancer in any male relative.

Because low socioeconomic status is known to impact access to care and is also more common in African-Americans, socioeconomic factors have been hypothesized to explain the observed racial difference in stage at diagnosis for prostate cancer. We observed that education level had a meaningful impact on the race-stage relation, but consistent with previous reports (21-24, 28), adjustments for race differences in education level did not entirely explain the stage disparity. Despite the availability of a number of factors hypothesized to mediate the effect of education (e.g., medical care and lifestyle factors), we were unable to identify the precise mechanism through which education operates. One potential pathway could include a mediating role for nutritional factors. Although much of this work has considered the role of diet on prostate cancer risk, some work has shown a link between dietary fat (29-33), caloric intake (27), and α-linolenic acid (27, 34, 35) and advanced prostate cancer. Recent reports from one of these groups have shown tomato sauce consumption to be protective against advanced and fatal prostate cancer (27, 36). Although it is likely that the effect of nutritional and dietary factors is mediated by hormones and other growth factors, it is also possible that genetic polymorphisms play a role in the development of an aggressive phenotype (27, 37). Acknowledging the likelihood of substantial race differences in selected nutritional factors, and possibly the prevalence of selected genetic polymorphisms, we were not able to explore these pathways because neither dietary data nor blood samples were collected in this investigation.

Understanding one's insurance coverage, but none of the actual health care utilization variables, had an impact on the association between race and stage at diagnosis in a multivariate context. Other support for the importance of insurance comes from a study by Conlisk et al. (38), in which an association between stage and health insurance status was observed, but only among African-American men. Of note, we collected information on whether participants had insurance and type of insurance, but the only important explanatory variable was the one that assessed the degree to which an individual was informed about their insurance coverage. This variable likely reflects both access to care and familiarity, and, possibly, comfort level with using the health care system, suggesting that insurance coverage alone may not be sufficient to ensure improved health outcomes. Support for this interpretation comes from a Veterans Affairs Medical Centers study, a setting in which access to care is theoretically equalized, and insurance and other financial barriers to screening and medical care are minimized or eliminated. In that study, African-American men were still more likely to be diagnosed with distant-stage cancer and to have poorer survival than White men (26).

Conceptually, of the extensive socioeconomic and medical care factors considered, prostate cancer screening was expected to play an important role in explaining the race stage at prostate cancer diagnosis association. Ever having had a screening digital rectal examination before diagnosis had a meaningful impact on the race-stage association, yet the measured impact was not as large as anticipated (11.2%). It is interesting to note that this finding of a relatively minor explanatory effect of screening digital rectal examination is similar to results reported for breast cancer patients enrolled in this same study. In that analysis, adjustment for mammography screening accounted for only 9.2% of the racial difference in stage at diagnosis of breast cancer (5). As has been suggested in the case of breast cancer, there may be racial differences in the benefits received from the same screening procedures that relate to systematic differences in patient tracking and follow-up care for positive screening tests (39-41).

A comparison of the two approaches used in multivariate modeling confirms the explanatory importance of socioeconomic, insurance, and medical factors. However, the effect of histologic grade, a measure of tumor differentiation, on the race difference in stage at diagnosis was somewhat limited once these other variables were in the model. This may be due in part to the lack of a statistically significant difference in the proportion of poorly differentiated tumors between African-Americans and Whites, as has been reported by others (25).

Together, socioeconomic factors, understanding of health insurance, and screening history factors played a substantial explanatory role in the later stage at diagnosis in African-American compared with White men. Although racial disparities in socioeconomic status and insurance (however measured) have persisted in the years since this cohort was diagnosed, a substantial change in prostate screening has occurred, with the now widespread use of PSA testing in the United States

and other developed countries. As noted earlier, prostate screening at the time of the enrollment of our study subjects was primarily limited to digital rectal examination. An analysis based on a sample of men enrolled in Medicare showed that no more than 2% of White men and 1% of Black men aged 65 years and older were receiving PSA testing 1 year into our study enrollment, and 6% or fewer African-American men (and slightly more White men) received this test in 1990, the last year of our enrollment (42).

Changes in the distribution of stage at diagnosis have also occurred since the time of our study enrollment, much of it attributable to increased PSA screening. Whereas estimates based on SEER data for 1974 to 1985 show that approximately 21% (Blacks, 25.4%; Whites, 20.4%) of all prostate cancer cases were diagnosed at a distant stage, the most recent data show that only 5% of all cases (African-Americans, 6%; Whites, 4%) were diagnosed with distant-stage prostate cancer (1). Assuming that factors that influenced digital rectal examination screening are similar to those that influence PSA screening, these results, taken together with race differences in education and familiarity with insurance coverage in explaining the race-stage association, underscore the need for a more active role on the part of health care systems to improve access to care and screening (and presumably, timely and appropriate follow-up to ensure maximum benefit from screening) in traditionally underserved populations. Furthermore, our results may have important implications for health care in countries in which digital rectal examination, rather than PSA testing, is the primary screening tool or in which there are subpopulations that are traditionally underserved by the existing health care system.

As in all retrospective studies, potential limitations include the possibility of recall bias. This should be minimized in the current study because cases were compared with cases and not controls. Similarly, substantial detection bias is unlikely because the comparisons made to registry data (one of the SEER sites) showed virtually identical stage distribution between study participants and nonparticipants, that is, 58% of White and 47% of African-American nonparticipants were diagnosed with localized prostate cancer compared with 59% of White and 47% of African-American study participants (7). In addition, information on method of diagnosis was ascertained (e.g., transurethral resection of the prostate) and did not differ across race groups. Unequal diagnostic evaluation is also unlikely to be a factor in stage assignment between the race groups because extent of diagnostic evaluation (such as lymph node examination or bone scan) was comparable among African-Americans and Whites. Finally, although there was some variation among cases in time lapsed between diagnosis and interview, potentially introducing variability in the quality of interview information, any resulting misclassification would have been nondifferential with respect to race because the period from diagnosis to interview did not vary by race or stage at diagnosis.

These potential limitations are balanced by the many strengths of the study. First, it was population-based, with near-complete coverage of all prostate cancer cases in Connecticut. Second, compared with some other population-based interview studies, we had a relatively large number of African-American prostate cancer cases, thus increasing statistical power. Third, many past studies derived their information on stage at diagnosis from tumor registries rather than standardized review. Liu et al. (7) found that approximately 23% of prostate cancers in the CTR were incorrectly staged. The current study corrected such errors by making use of a standardized protocol for the staging of cases done by study physicians who were blinded to patient information. Fourth, in-person interviews were conducted using a comprehensive instrument to obtain information on a wide range of potential explanatory variables not usually collected in hospital- or registry-based studies. Finally, by linking our data to survival information, we were able to confirm the importance of the variables studied here on race differences in survival. We showed that race differences in stage at diagnosis and tumor grade contributed significantly to the race differences in prostate cancer survival. However, it was not until we accounted for their disadvantage with respect to socioeconomic status and insurance coverage that we were able to fully explain the poorer observed survival in African-American compared with White men.

Conclusions. These results suggest that the disadvantage with respect to stage at diagnosis of prostate cancer observed in African-American men compared with White men reflected racial disparities in socioeconomic status and access to health care more than strong biological differences and are therefore potentially mutable. Identification of these causal pathways is especially important for the goal of developing interventions to reduce or eliminate the race difference in prostate cancer stage at diagnosis and survival. Continued efforts to improve access to care, insurance coverage, and prostate screening in African-American men, particularly now that the PSA screening test is widely available, may lessen race differences in morbidity and mortality substantially. Although these cases were identified before the widespread use of PSA screening, the results may also be relevant to countries that have large underserved populations and/or disparities in access to medical care and cancer screening.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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Certain data used in this study were obtained from the Connecticut Tumor Registry located in the Connecticut Department of Public Health. The author(s) assume(s) full responsibility for analyses and interpretation of these data. We thank the Connecticut Institutions, including Stamford Hospital, for their participation.

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Cancer Epidemiol Biomarkers Prev 2008;17:2825-2834.