

Urological Oncology

In a multi-institutional study authors from the USA and Austria attempt to determine if there are differences in several indices between African-American and white men undergoing radical prostatectomy. They did not find race to be an independent risk factor for PSA recurrence, but found that other variables commonly associated with PSA recurrence are also important in African-Americans.

Using data extracted from the Hospital Episodes database, authors from England describe national trends in radical nephrectomy between 1995 and 2002. They found a considerable increase in the annual number of radical nephrectomies, with an expected increase in the number of laparoscopic procedures. They also found a decrease in emergency admissions and length of hospital stay.

Racial differences in serum prostate-specific antigen (PSA) doubling time, histopathological variables and long-term PSA recurrence between African-American and white American men undergoing radical prostatectomy for clinically localized prostate cancer

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Accepted for publication 3 January 2005

OBJECTIVE

To determine if there are significant differences in biochemical characteristics, biopsy variables, histopathological data, and rates of prostate-specific antigen (PSA) recurrence between African-American (AA) and white American (WA) men undergoing radical prostatectomy (RP), as AA men are twice as likely to die from prostate cancer than their white counterparts.

PATIENTS AND METHODS

We established a cohort of 1058 patients (402 AA, 646 WA) who had RP and were followed for PSA recurrence. Age, race, serum PSA, biopsy Gleason score, clinical stage, pathological stage, and PSA recurrence data

were available for the cohort. The chi-square test of proportions and *t*-tests were used to assess basic associations with race, and log-rank tests and Cox regression models for time to PSA recurrence. Forward stepwise variable selection was used to assess the effect on the risk of PSA recurrence for race, adjusted by the other variables added one at a time.

RESULTS

The AA men had higher baseline PSA levels, more high-grade prostatic intraepithelial neoplasia (HGPIN) in the biopsy, and more HGPIN in the pathology specimen than WA men. The AA men also had a shorter mean (SD) PSA doubling time before RP, at 4.2 (4.7) vs 5.2 (5.9) years. However, race was not an independent predictor of PSA recurrence

($P = 0.225$). Important predictors for PSA recurrence in a multivariable model were biopsy HGPIN ($P < 0.014$), unilateral vs bilateral cancer ($P < 0.006$), pathology Gleason score and positive margin status (both $P < 0.001$).

CONCLUSIONS

This study indicates that while there are racial differences in baseline serum PSA and incidence of HGPIN, race is not an independent risk factor for PSA recurrence. Rather, other variables such as pathology Gleason score, bilateral cancers, HGPIN and margin positivity are independently associated with PSA recurrence. The PSA doubling time after recurrence may also be important, leading to the increased mortality of AA men with prostate cancer.

KEYWORDS

prostate cancer, African-American, PSA doubling time, pathological stage, radical prostatectomy, PSA recurrence

INTRODUCTION

The number of new cases of prostate cancer was estimated at 513 000 worldwide and 173 000 in the USA, accounting for 15.3% of all cancers in men in developed countries in 2000 [1]. Within the next 15 years, prostate cancer is predicted to be the most common cancer in men [1]. The incidence of prostate cancer varies widely among ethnic populations, and the rate of this disease can differ by as much as 90 times among various populations. Specifically, African-American (AA) men in the USA have the highest incidence of prostate cancer (137 per 100 000 per year) [2].

According to the 2000 USA Census, AAs comprise the second largest racial group in the USA; that AA men have a 2.5 times greater mortality from prostate cancer than white Americans (WA) has become a significant health concern in the USA [2]. This strikingly higher mortality for AA men raises several questions. Is the difference in mortality a result of diagnosis at later, more advanced disease stages? Or is it because prostate cancer is more biologically aggressive in AA men? [3]. It may also be possible that AA men are receiving different treatments for their prostate cancer than other populations [4]. In

addition, is there a role for competing causes of death such as comorbidity and age? Finally, do poverty, socio-economic status and education have a role? [4].

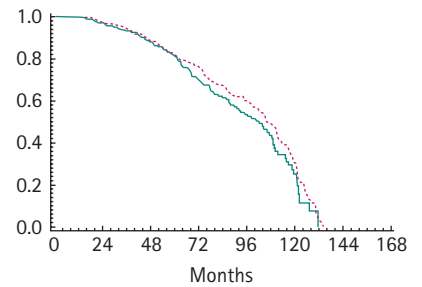
Several authors [4–10] have examined an important surrogate, PSA recurrence, as a measure of prostate cancer-specific mortality. These studies evaluated clinical and pathological variables before and after surgery, socio-economic factors, and delivery of healthcare; the results are conflicting [4–10]. Recently there has been interest in the PSA doubling time as a surrogate for the ultimate outcome of prostate cancer [11]. Differences in PSA doubling times before and after treatment among races have been studied in a few series [5], but there is no comprehensive report of this subject in AAs in an equal-access setting. To address this issue, we evaluated differences in PSA doubling times, histopathological variables, and the incidence of PSA recurrence between AA and WA men with clinically localized prostate cancer. Accordingly, the analysis was limited to patients undergoing radical retropubic prostatectomy (RP) to ensure the availability of histopathological data from the excised surgical specimen.

PATIENTS AND METHODS

This retrospective cohort study was aimed at comparing pathological stage and PSA recurrence in AA and WA men with prostate cancer and who were treated with RP at a large healthcare system in the mid-West USA, the Henry Ford Health System (HFHS), a vertically integrated healthcare system incorporating the nation's 10th largest health maintenance organization. The population served by HFHS is large and racially diverse, with $\approx 30\%$ of the patients being AA. The HFHS has a computerized medical information system and medical record database. Comprehensive data are also available from computerized health-claims databases. This study was part of an Institutional Review Board-approved project for evaluating the effect of various demographic, clinical and histopathological variables on prostate cancer recurrence.

HFHS maintains a computerized tumour registry database accredited by the American College of Surgeons. Registry staff use a thorough case-finding system, including a review of all pathology and cytology reports,

FIG. 1. Recurrence-free survival estimates by race (all ages; red, WA; green, AA).



and radiation and oncology consultations. The American Joint Commission on Cancer system is used to determine the stage of disease by evaluating tumour size, extent of invasion, microscopic involvement of lymph nodes and presence of metastases. HFHS Registry staff link this data with the Detroit area Surveillance, Epidemiology and End Results Program records, and conduct an annual follow-up for vital status and recurrence; the annual follow-up is estimated at 94%. Thus the tumour registry of the HFHS was searched for all patients with an ICD-9 code of 185 (prostate cancer), who were treated by RP and followed during the period 1 January 1990 to 31 December 2000; only men with localized cancer (i.e. a negative bone scan) were included in the study.

Patients were excluded who were not AA or Caucasian, as were those who had incomplete follow-up information. Patients who developed bone metastasis within a year of diagnosis were also excluded, as we felt that these men most likely had pre-existing metastatic disease. Patients were also excluded if they received preoperative hormonal, radiation, cryotherapy, or received immediate adjuvant hormonal or radiation therapy for extracapsular disease, including seminal vesicle involvement.

The diagnosis of cancer was established by histological examination of prostate biopsy specimens by HFHS pathologists; tumour grade was reported as Gleason score 2–10, and the disease was staged using the 1992 TNM classification.

Relevant baseline variables were recorded, e.g. race, age, clinical stage, serum PSA, biopsy Gleason score (minor and major), side(s) of positive cores, perineural infiltration (PNI), high-grade prostatic intraepithelial neoplasia (HGPIN), and prostatic inflammation.

TABLE 1 Baseline and histopathological characteristics between AA and WA

Variable	WA	AA	P
N	656	402	
Before RP			
Mean (SD):			
age, years	63.0 (6.5)	62.8 (6.9)	0.499
PSA, ng/mL	8.6 (10.3)	10.5 (12.6)	<0.001
PSA doubling time, years	5.2 (5.9)	4.2 (4.7)	0.015
Clinical stage, n (%)			
T1a	1 (<1)	0	0.032
T1b	5 (1)	3 (1)	
T1c	383 (70)	285 (78)	
T2a	128 (23)	54 (15)	
T2b	34 (6)	22 (6)	
T2c	0	1 (<1)	
T3	0	1 (<1)	
Mean (SD)			
Primary Gleason grade	3.0 (0.6)	3.1 (0.6)	0.105
Gleason score	6.2 (1.1)	6.3 (1.1)	0.168
Percentage cancer, n (%):			
PNI	35 (6)	27 (7)	0.389
HGPIN	53 (8)	50 (13)	0.025
Inflammation	12 (2)	6 (2)	0.659
Mean (SD)			
Biopsy % cancer	13.8 (14.5)	15.0 (14.5)	0.278
Positive cores			
unilateral	370 (59)	246 (62%)	0.290
bilateral	256 (41)	148 (38)	
Pathological variables, n (%)			
Stage			
T2a	85 (13)	47 (12)	0.050
T2b	370 (57)	228 (58)	
T2c	18 (3)	19 (5)	
T3a	114 (17)	49 (12)	
T3b	57 (9)	49 (12)	
T3c	8 (1)	3 (1)	
Mean (SD):			
Specimen weight, g	47.4 (19.8)	51.1 (23.4)	0.010
Primary Gleason grade	3.2 (0.9)	3.2 (0.6)	0.291
Gleason score	6.6 (1.1)	6.7 (1.2)	0.272
Percentage cancer	19.9 (15.7)	21.3 (16.4)	0.128
N (%):			
PNI	110 (17)	73 (18)	0.549
HGPIN	113 (17)	94 (24)	0.013
Inflammation	18 (3)	11 (3)	0.999
Margin positive status	181 (28)	119 (30)	0.475
Seminal vesicle invasion	57 (9)	49 (12)	0.065
Lymph node spread	21 (3)	12 (3)	0.851
PSA recurrence	196 (30)	117 (29)	0.789
Mean (SD)			
PSA doubling time, years*	9.7 (13.5)	5.9 (8.1)	0.071
Follow-up, months	75.8 (30.3)	73.6 (27.8)	0.296

*After recurrence.

Pathological variables after RP were also recorded, e.g. specimen weight, pathological stage, PNI, HGPIN, prostatic inflammation, percentage tumour, margin status, seminal vesicle involvement, and lymph node spread. The baseline (preoperative) PSA doubling time was calculated by a linear regression model using at least four PSA values.

The primary endpoint of the analysis was the difference in PSA recurrence and doubling time. PSA recurrence was defined as two or more consecutive samples with a PSA level of >0.2 ng/mL. The PSA doubling time after recurrence required at least three PSA values during the follow-up [11]. The secondary endpoints were differences in pathological variables, e.g. percentage cancer, HGPIN, PNI, inflammation, margin status, seminal vesicle invasion and lymph node spread.

A univariate analysis was used to compare the pathological variables at baseline and after RP between the racial groups. Comparisons of PSA recurrence were based on survival analysis. The Cox proportional-hazards model was used for multivariate survival analysis, which allowed an estimate of the PSA recurrence time, controlling for differences in follow-up time and risk factors that may affect survival, including confounding variables and effect modifiers. All relative risks were derived from the multivariate Cox models. Adjusted survival curves were generated using the empirical cumulative hazard estimate of the survivor function. Differences in the duration of survival were calculated by measuring differences in the adjusted survival curves at median survival. All *P* values were two-sided.

RESULTS

The baseline characteristics of the cohort of 1058 patients are summarized in Table 1. An important and surprising finding of the study was that at baseline, AA men had a shorter PSA doubling time than WA men (Table 1).

Table 1 also summarizes the study endpoints between the cohorts; even though PSA recurrence was no different between the racial groups, after PSA recurrence was diagnosed the PSA level increased at a faster rate in AA men than WA men. This was not statistically significant because the doubling time was calculable only in a few patients who eventually had PSA recurrence. However,

these data showed that there was >3 years difference in PSA doubling time between the racial groups. None of the other study endpoints, i.e. margin positivity, seminal vesicle infiltration and lymph node spread, were statistically different between the cohorts.

As shown in Table 2, AA origin was not an independent predictor of PSA recurrence in the univariate model. Other known variables, e.g. clinical stage, Gleason score, percentage cancer and pathological stage, were significantly associated with PSA recurrence. Importantly, HGPIN and specimen weights were also important predictors of recurrence. HGPIN had a hazard ratio (HR) of 1.8, and greater than margin positivity (1.76) and Gleason score (1.46; Table 2).

In the Cox proportional-hazard model race was not an independent predictor of PSA recurrence (Table 2, HR 1.21), but other variables, e.g. biopsy HGPIN, unilateral cancers in the biopsy, pathology Gleason score and positive margin status, were independent predictors of PSA recurrence. Interestingly there was a counterintuitive significant association between clinical stages T1 and T2 cancers, showing that T2 cancers had a lower HR for recurrence; we do not know the significance of this finding.

DISCUSSION

Overall mortality from prostate cancer is greater in AA than WA men; historically, this has been attributed to a more advanced tumour stage in AA men at diagnosis. More recently, increased awareness and the widespread use of PSA screening has dramatically increased the detection of earlier stage cancers. This has been associated with a clear improvement in mortality and survival rates, especially in AA men, where there has been an improvement of 21% in organ-confined disease. Some have argued that the treatment outcome has been better in WA than AA men for localized prostate cancer, but others have argued that there is no significant racial difference in treatment outcome [4–7,9,10,12].

The present study indicates that there are racial differences in baseline serum PSA, PSA doubling times, clinical and pathological stages, and the incidence of HGPIN. However, race alone did not appear to be an

TABLE 2 Univariate and multivariate modelling assessing the effect of the recorded variables on PSA recurrence

Variable	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Baseline				
AA	1.18 (0.93–1.48)	0.169	1.21 (0.89–1.64)	0.225
Age, decades	0.86 (0.72–1.03)	0.093	0.74 (0.58–0.95)	0.017
PSA	1.00 (0.99–1.00)	0.613	0.99 (0.98–1.01)	0.377
Log PSA	1.01 (0.90–1.12)	0.924	–	
Clinical stage	0.71 (0.53–0.94)	0.018	0.52 (0.36–0.73)	<0.001
Gleason (biopsy)	1.43 (1.29–1.58)	<0.001	1.11 (0.93–1.32)	0.254
Biopsy inflammation	1.15 (0.43–3.08)	0.788	0.66 (0.20–2.16)	0.493
Biopsy PNI	1.17 (0.78–1.77)	0.449	1.47 (0.87–2.48)	0.146
Biopsy HGPIN	1.80 (1.22–2.64)	0.003	1.81 (1.13–2.91)	0.014
Biopsy % cancer	1.02 (1.01–1.03)	<0.001	–	
Uni- or bilateral +ve cores	0.84 (0.67–1.07)	0.157	0.63 (0.46–0.87)	0.006
RP				
Specimen weight	0.99 (0.98–0.99)	<0.001	0.99 (0.98–1.00)	0.059
Percent cancer	1.01 (1.00–1.02)	<0.001	1.00 (0.99–1.02)	0.443
Primary Gleason grade	1.38 (1.29–1.47)	<0.001	1.39 (1.21–1.59)	<0.001
Gleason score	1.46 (1.33–1.60)	<0.001	1.34 (1.13–1.58)	<0.001
N stage	1.39 (0.86–2.25)	0.174	1.35 (0.70–2.59)	0.366
Seminal vesicles	1.58 (1.18–2.12)	0.002	0.97 (0.60–1.57)	0.910
Margin positive	1.76 (1.40–2.20)	<0.001	1.75 (1.27–2.42)	<0.001
Pathological stage	1.49 (1.19–1.87)	<0.001	0.89 (0.60–1.31)	0.548
PNI	1.08 (0.81–1.43)	0.611	1.39 (0.90–2.14)	0.138
HGPIN	0.80 (0.59–1.09)	0.162	0.84 (0.52–1.36)	0.472
Inflammation	0.65 (0.24–1.76)	0.401	0.79 (0.19–3.40)	0.756

independent risk factor for PSA recurrence. Rather, other variables, e.g. pathology Gleason score, bilateral cancers, HGPIN and margin positivity, were independently associated with PSA recurrence. The present study is unique in that it includes a significant proportion of AA patients (38%) and has many additional variables that could affect PSA recurrence. Further, we also showed that while PSA recurrence rates are no different between AA and WA men, PSA levels double much faster in the former than the latter. The biological significance of a rapid PSA doubling time is currently unknown, but given the association of a rapid PSA doubling with earlier development of metastasis [11,13], it can be postulated that after PSA recurrence, AA men may have a more aggressive course of disease. This finding is in contrast with results from a detailed study by Banerjee *et al.* [5], who reported that the mean average relative PSA velocity for AA and WA men having disease recurrence was 0.25 and 0.11 ng/mL per month, respectively ($P=0.21$). The rate of PSA increase in patients who developed disease

recurrence after RP was 18.9% per month for AA men and 16.3% per month for WAs ($P=0.73$). The present results may differ because the follow-up was longer (78 months) than that assessed by Banerjee *et al.*, where the median follow-up was 39 months. The brevity of the PSA doubling time was also noted before RP in the present series, but the significance of this finding is unknown. Several studies reported that a rapid PSA doubling time may be associated with more aggressive disease [4–7,9,10,12]. We postulate that even though PSA recurrence rates are comparable, AA men who develop PSA recurrence may have a more accelerated course of disease. This hypothesis is currently being tested at our centre in patients for whom long-term survival data are available.

Whether race is truly predictive of PSA recurrence after RP has been controversial. Earlier reports stated that race is an independent predictor of outcome, while recently many authors reported that there is

no racial disparity in progression-free survival among men with clinically localized prostate cancer. In an elegant study by Powell *et al.* [3,5,10,14–18] a subgroup of younger AA patients (aged <65 years) were evaluated, and they had a greater risk of recurrence. Using multivariate modelling, we re-examined this issue in the present cohort, but there was no statistically significant racial difference in younger AA patients. This discrepancy could be attributed to an inherent difference in the study populations; in contrast to the series of Powell *et al.*, the present had < 1% clinical stage T3 cancer.

The present findings are robust because the analysis involved patients from an equal-access system, which minimizes potential access-related issues in healthcare. Other studies [9] showed that lack of healthcare insurance and barriers to access could delay diagnosis and affect outcome. Therefore, the present study is more suitable for determining whether race is an independent factor for PSA recurrence; we conclude that race is not independently associated with PSA recurrence but must acknowledge that AA men have a shorter PSA doubling time, which may translate into more aggressive disease. Our centre is currently studying long-term data from these patients.

Another strength of the present study is that it includes several additional histopathological variables which could affect PSA recurrence. Specifically, we assessed differences in PNI, inflammation and percentage cancer in the biopsy. None of these variables was more prevalent in AA patients, but the incidence of HGPIN was significantly greater in AA men and associated with a greater incidence of PSA recurrence. An important limitation of the study is its retrospective design, but the large sample size and inclusion of several confounding variables potentially offset this limitation.

In conclusion, AA race is not an independent risk factor for PSA recurrence in patients undergoing RP, and AA men have no greater incidence of HGPIN, higher baseline PSA level, or rapid PSA doubling before RP or after

recurrence. Early PSA testing and aggressive evaluation of abnormal PSA, and of HGPIN, could result in the diagnosis of early prostate cancer and ultimately prolong survival.

ACKNOWLEDGEMENTS

Funding: Institute for Clinical Research at the Veterans Affairs Medical Center, Washington, DC.

CONFLICT OF INTEREST

None declared.

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Abbreviations: AA, African-American; WA, white American; RP, radical prostatectomy; HFHS, Henry Ford Health System; HGPIN, high-grade prostatic intraepithelial neoplasia; PNI, perineural invasion; HR, hazard ratio.