Racial Differences in Prognostic Value of Adult Height for Biochemical Progression Following Radical Prostatectomy

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Abstract

Purpose: Adult height, as a surrogate of childhood and adolescent hormone activity and diet, has been associated with the risk for development and death from prostate cancer in predominantly White populations. However, hormonal activity and diets vary between races. We examined whether height was significantly associated with biochemical progression following radical prostatectomy and whether there was an interaction between height and race.

Experimental Design: Multivariate Cox proportional hazards analysis was used to determine if height significantly predicted biochemical progression among 1,503 men (450 Black and 1,053 White) treated with radical prostatectomy between 1988 and 2003. We examined for possible interactions between height and race.

Results: Taller men (>175.3 cm) were significantly younger (P = 0.001), treated in more recent years (P = 0.02), had more clinical stage T_1 disease (P = 0.001), and were less likely to have extraprostatic extension (P = 0.02) than shorter men (≤175.3 cm). Height was not significantly related to race, preoperative serum prostate-specific antigen concentrations, biopsy or pathologic Gleason sum, positive surgical margins, seminal vesicle invasion, or lymph node metastasis. Height was significantly associated with progression among Black men [relative risk (RR), 1.67; 95% confidence interval (95% CI), 1.00-2.79] but not among White men (RR, 1.03; 95% CI, 0.77-1.38). The interaction between race and height for predicting biochemical progression was statistically significant ($P_{interaction}$ = 0.05).

Conclusions: There was an interaction between height and race in that height predicted progression for Black men but not for White men. The explanation for these findings is unclear, although lower insulin-like growth factor–binding protein-3 concentrations among Black men may be involved.

Events that occur early in life may predispose to prostate cancer and help determine the aggressiveness of the cancer later in life. However, these early events are often difficult to measure. One approach is to examine adult height, which reflects adequate caloric intake and hormonal concentrations in childhood and adolescence as well as genetic factors (1–4). Although several studies have found that adult height was a significant risk factor for developing prostate cancer (5, 6), other studies found no relationship between height and prostate cancer risk (7). Similarly, conflicting data exist regarding whether adult height increases (8), decreases (9), or has no effect (8) on the risk of prostate cancer death. Only two studies, both from the same group, studied height among men undergoing primary therapy and found that increased height was not associated with larger cancers at the time of radical prostatectomy (10, 11). However, no study to date has examined height and the risk of treatment failure following primary therapy. Given that men who develop an early biochemical recurrence after radical prostatectomy are

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at increased risk for development of metastatic disease (12) and prostate cancer–specific death (13), biochemical recurrence can be used as an intermediate end point for aggressive prostate cancer. Moreover, nearly all prior studies examining height and prostate cancer studied predominantly if not entirely White men. Thus, the association between height and prostate cancer among Black men is understudied. To determine whether increased height was associated with advanced disease and biochemical progression following radical prostatectomy, we used the multiracial Shared Equal Access Regional Cancer Hospital Database (14). Because hormonal and dietary factors that influence height vary between races (15–18), we examined whether height was equally predictive for biochemical progression among White and Black men.

Materials and Methods

Description of data registry. After obtaining institutional review board approval from each institution, data from consecutive patients (excluding patients treated with preoperative androgen deprivation or radiation therapy) treated with radical prostatectomy from 1988 to 2003 at the West Los Angeles, Palo Alto, San Francisco, and Augusta, Georgia Veterans Affairs Medical Centers, and the San Diego Naval Medical Center were combined into the Shared Equal Access Regional Cancer Hospital Database. This database includes information on patient age, race, height, weight, clinical stage, grade of cancer on diagnostic biopsies, preoperative serum prostate-specific antigen (PSA) concentrations, surgical specimen pathology (tumor grade, stage, and surgical margin status), and follow-up PSA concentrations.

Subjects. The Shared Equal Access Regional Cancer Hospital Database contains information on 2,028 consecutive patients treated with radical prostatectomy between 1988 and 2003. Men who were neither Black nor White were excluded (n = 245) due to limited numbers of men from each represented ethnicity. Men with missing height data were excluded (n = 280). These men were older, more likely to be treated in earlier years, and had significantly higher preoperative PSA concentrations, biopsy and pathologic Gleason sums, clinical stages, and incidence of extracapsular extension than the cohort analyzed. The final study population was 1,503, of which 450 were Black (30%) and 1,053 were White. Mean and median follow-up among men without progression was 50 and 39 months (range, 1-187 months). During this time, 418 patients (29%) progressed.

The prostatectomy specimens were sectioned per each institution's protocol (14). Patients were followed to determine biochemical progression defined as a single PSA of >0.2 ng/mL, two concentrations at 0.2 ng/mL, or secondary treatment for an elevated PSA concentration (19). Patients with no follow-up data (n = 52) were included for evaluating differences in preoperative and pathologic characteristics but not for biochemical progression.

Statistical analyses. Height was categorized by tertiles (≤175.3 versus >175.3 cm to <182.9 versus ≥182.9 cm). PSA (<10 versus 10 ng/mL to 20 versus >20 ng/mL) and Gleason sum (2 to 6 versus 7 versus 8-10) were examined as categorical variables using previously published cut points (20). Clinical stage T_3 was combined with clinical stage T_2 due to the limited number of men with clinical stage T_3 (n = 7) and examined as a categorical variable of T_1 versus T_2-T_3. Body mass index was calculated by dividing the weight (in kilograms) by height (in meters) squared and was examined as a categorical variable of <25 kg/m^2 for normal weight, ≥25 to <30 kg/m^2 for overweight, ≥30 to <35 kg/m^2 for mild obesity, and ≥35 kg/m^2 for moderate and severe obesity. Age (5-year intervals) and year of surgery were examined as continuous variables. Clinicopathologic characteristics were compared across the height groups using ANOVA for continuous variables or χ^2 for categorical variables. Time to biochemical progression was compared between the height categories using Kaplan-Meier plots and the log-rank test. To estimate the relative risk of progression associated with height, we used a Cox proportional hazards regression model. To verify the proportional hazards assumption, we plotted $\log(-\log[S(t)])$ versus survival time, stratified by height (≤175.3 versus >175.3 cm). The curves for the two height groups were parallel over the range of survival times, indicating no departure from the proportional hazards assumption (21). We adjusted for all clinical characteristics, including PSA, age, body mass index, year of surgery, race, clinical stage, and biopsy Gleason sum. In addition, we included a term for each center to account for possible differences between the centers. Because hormonal activity and diets, which help determine height, vary between racial groups, we tested for an interaction between height and race by including a cross-product term in the multivariate analysis. Ps were determined by changes in the likelihood ratio by inclusion of the height or interaction term, as appropriate. Significance was defined as $P < 0.05$. All clinicopathologic characteristics were similar between the centers; therefore, data from all centers were combined for analysis.

Results

Mean ± SD and median height was 178.8 ± 6.9 and 177.8 cm, respectively (range, 154.9-210.8 cm). Taller men were significantly younger (P = 0.001), more likely to be treated in recent years (P = 0.02), more likely to have clinical stage T_1 disease (P = 0.001), and significantly less likely to have extraprostatic extension (P = 0.02; Table 1). When analyzed separately by race, height was only significantly associated with younger age (P = 0.004), more recent year of surgery (P = 0.04), and clinical stage (P = 0.004) among White men (Table 2) and not among Black men (Table 3). In addition, height was significantly inversely associated with body mass index among Black men (P = 0.04) but not among White men (P = 0.69). The association between height and extraprostatic extension was similar in both races, although it did not reach statistical significance when either race was examined alone. Among the entire cohort and when each racial group was examined separately, there were no significant differences between the height groups in terms of race, preoperative serum PSA concentrations, biopsy or pathologic Gleason sum, pathologic stage, or in the prevalence of the adverse pathologic findings of positive surgical margins, seminal vesicle invasion, or lymph node metastasis.

Mean and median follow-up among men without progression was 50 and 39 months (range, 1-187 months). During this time, 418 patients (29%) progressed. On initial exploratory analysis, relative to men in the lowest height group (≤175.3 cm), men in the middle (>175.3 to <182.9 cm) height group (relative risk, 1.20; 95% confidence interval, 0.93-1.55) and men in the tallest (≥182.9 cm) height group (relative risk, 1.20; 95% confidence interval, 0.94-1.54) had similar biochemical progression risk, which was higher than men in the lowest height group. Therefore, for all further analyses, men in the two tallest groups were combined, and height was categorized as ≤175.3 versus >175.3 cm. On crude and age-adjusted analysis, taller height was associated with increased risk of biochemical progression (P = 0.05; Table 4). This association was slightly attenuated after adjustment for multiple clinical characteristics (P = 0.10; Table 4). We examined whether height was equally predictive of progression among Black and White men and found that height was a statistically significant predictor of progression among Black men (Fig. 1) but not among White men (Fig. 2; $P_{interaction}$ = 0.05). Tall Black men (>175.3 cm)

were 67% (95% confidence interval, 0-179%) more likely to recur than short Black men (≤175.3 cm), whereas among White men, the risk of progression did not differ between the two height categories beyond what would be expected by chance (>175.3 versus ≤175.3 cm; relative risk, 1.03; 95% confidence interval, 0.77-1.37).

Discussion

Hormonal and dietary factors are likely important in prostate cancer, although their exact role is still unclear. Adult height is reflective of the dietary and hormonal milieu in childhood and adolescence (1–4). No prior study has examined height as a prognostic factor for biochemical progression among men undergoing therapy for prostate cancer. Moreover, little data exist on the association between height and prostate cancer among Black men. We found that height significantly predicted progression among Black men but not among White men. These data support the link between events in childhood and adolescence and aggressiveness of prostate cancer later in life among Black men.

Adult height is reflective of a complex mixture of dietary factors and various hormonal concentrations during childhood and adolescence as well as genetics. Hormones that have been implicated in adult height include insulin-like growth factor-I (IGF-I), growth hormone, leptin, and the sex hormones testosterone and estrogen (1–4, 22). Prior studies have linked both IGF-I and leptin to prostate cancer risk (23–28). Serum IGF-I concentrations have also been linked with the risk of developing advanced-stage prostate cancer (29). Obesity and

Table 1. Clinical and pathologic features of Black and White men undergoing radical prostatectomy segregated by adult height

	Height (cm)			*P**
	≤175.3 (%)	>175.3 to <182.9 (%)	≥182.9 (%)	
No. patients	549	452	502	
Race				
White	396 (72)	317 (70)	340 (68)	0.30
Black	153 (28)	135 (30)	162 (32)	
Body mass index (kg/m^2)				
<25.0	149 (29)	128 (29)	157 (33)	0.84
25.0-29.9	237 (46)	205 (47)	217 (45)	
30.0-34.9	91 (18)	74 (17)	74 (15)	
≥35.0	37 (7)	27 (6)	30 (6)	
Mean age ± SD (y)	62.9 ± 6.5	62.6 ± 6.4	61.5 ± 6.8	0.001†
Median year of surgery	1997	1997	1998	0.02†
PSA (ng/mL)				
Median	9.7	6.9	7.5	0.21†
Mean ± SD	9.1 ± 7.2	8.7 ± 7.7	9.8 ± 9.6	
Biopsy Gleason sum (%)				
2-6	368 (71)	311 (72)	361 (74)	0.23
7	118 (23)	100 (23)	92 (19)	
8-10	36 (7)	21 (5)	37 (8)	
Clinical stage (%)				
T_1	205 (39)	202 (47)	243 (50)	0.001
T_2	320 (61)	227 (52)	242 (50)	
T_3	1 (<1)	5 (1)	2 (<1)	
Pathologic Gleason sum (%)				
2-6	287 (55)	247 (57)	277 (57)	0.60
7	176 (34)	150 (35)	168 (34)	
8-10	57 (11)	34 (8)	44 (9)	
Pathologic stage				
T_2	400 (75)	332 (75)	382 (77)	0.28
T_3	124 (23)	104 (23)	97 (20)	
T_4	12 (2)	7 (2)	16 (3)	
Positive surgical margins	154 (29)	143 (32)	172 (35)	0.12
Capsular penetration	143 (27)	117 (26)	99 (20)	0.02
Seminal vesicle invasion	43 (8)	31 (7)	42 (8)	0.69
Lymph node involvement	11 (2)	9 (2)	6 (1)	0.52

*P from χ^2 test except where noted.
†P from ANOVA.

Table 2. Clinical and pathologic features of White men undergoing radical prostatectomy segregated by adult height

	Height (cm)			*P**
	≤175.3 (%)	>175.3 to <182.9 (%)	≥182.9 (%)	
No. patients	396	317	340	
Body mass index (kg/m^2)				
<25.0	118 (32)	95 (31)	107 (33)	0.69
25.0-29.9	170 (46)	152 (50)	139 (43)	
30.0-34.9	64 (17)	43 (14)	53 (17)	
≥35.0	19 (5)	16 (5)	22 (7)	
Mean age ± SD (y)	63.5 ± 6.3	63.2 ± 6.3	62.0 ± 6.8	0.004†
Median year of surgery	1996	1997	1998	0.04†
PSA (ng/mL)				
Median	6.5	6.3	6.8	0.39†
Mean ± SD	8.6 ± 6.6	8.2 ± 7.8	9.6 ± 10.4	
Biopsy Gleason sum (%)				
2-6	260 (69)	219 (73)	250 (75)	0.30
7	87 (23)	63 (21)	57 (17)	
8-10	31 (8)	19 (6)	26 (8)	
Clinical stage (%)				
T_1	132 (35)	126 (41)	154 (47)	0.004
T_2	248 (65)	174 (57)	173 (53)	
T_3	1 (<1)	5 (2)	2 (<1)	
Pathologic Gleason sum (%)				
2-6	214 (57)	176 (58)	191 (58)	0.45
7	116 (31)	101 (33)	113 (34)	
8-10	44 (12)	25 (8)	27 (8)	
Pathologic stage				
T_2	283 (73)	233 (75)	255 (76)	0.55
T_3	96 (25)	74 (24)	71 (21)	
T_4	10 (3)	5 (2)	11 (3)	
Positive surgical margins	111 (29)	96 (31)	111 (33)	0.42
Capsular penetration	111 (29)	85 (27)	73 (22)	0.09
Seminal vesicle invasion	28 (7)	15 (5)	30 (9)	0.12
Lymph node involvement	9 (3)	5 (2)	5 (2)	0.73

*P from χ^2 test except where noted.
†P from ANOVA.

dietary factors in adolescence have also been linked with early-onset puberty and final attained height (30, 31). Adolescent obesity has been associated with the risk of developing prostate cancer, although the exact relationship is unclear (7, 32). Furthermore, nutrition at all ages directly regulates IGF-I levels (33). Given that adult height is a reflection of various hormonal and dietary factors, many of which have been linked to prostate cancer, it is quite plausible that height would be associated with prostate cancer.

Numerous studies have examined the association between adult height and risk of developing prostate cancer in predominantly White populations. Although several studies found that adult height was significantly associated with developing prostate cancer (5, 6, 34, 35), other studies found no relationship between height and prostate cancer risk (7). Importantly, one of the largest studies to date (6) as well as a recent meta-analysis (36) both found that increased height was positively associated with prostate cancer risk. Importantly, no study found increased height was associated with a decreased risk of developing prostate cancer. The limitation in these studies is that the populations being sampled were largely White men, often of Northern European heritage. Thus, the relationship between height and prostate cancer risk among Black men has not been well studied.

Several studies examined the relationship between height and risk of metastatic disease or death from prostate cancer. Using data on predominantly White men from the Health Professionals Follow-up Study, Giovannucci et al. (32) found that men in the tallest group (≥74 inches) were at 68% increased risk for metastatic disease relative to men in the shortest group (≤68 inches). A large prospective study of >135,000 men from Sweden found that men in the tallest group had a 28% increased risk of death from prostate cancer (34). Similarly, data from the Cancer Prevention Study I, a cohort of >381,000 men, of which only 2% were Black, enrolled in 1959 by the American Cancer Society for longitudinal studies on cancer, found that men in the tallest group (≥73 inches) had a 74% increased risk of prostate cancer

death relative to men in the shortest group (<65 inches; ref. 8). However, data from Cancer Prevention Study II, a cohort of nearly 435,000 men enrolled in 1982, of which only 3.5% were Black, as well as data from the National Health Interview Survey, a cohort of >110,000 men interviewed between 1986 and 1994, of which 8.7% were Black, found no relationship between height and prostate cancer mortality (8, 37). In a subset analysis, neither Cancer Prevention Study I, Cancer Prevention Study II, nor the National Health Interview Survey found a significant relationship between height and prostate cancer mortality among Black men. A recent case-control study found that both Black and White taller men had decreased risk of prostate cancer death (9). Thus, although conflicting data exists, it seems that adult height may be related to the risk of development and death from prostate cancer in predominantly White populations. The association between fatal prostate cancer and height in Black men has been understudied, although the few studies that have examined the issue suggest no significant associations (8, 37).

No prior study examined the relationship between height and biochemical outcomes following therapy for prostate cancer. Two prior studies, from the same group examining only White men, found no relationship between adult height and cancer volume in the radical prostatectomy specimen (10, 11). In the current study, height predicted progression for Black men but not for White men. There are several potential explanations for our findings. Due to the retrospective nature of our study, we are unable to differentiate among them. Therefore, for the purposes of discussion, we have chosen to primarily focus on the IGF axis because it is clearly linked to height, may differ by race, and is an area of great current interest for prostate cancer. The IGF-I/IGF-binding protein-3 (IGFBP-3) ratio in childhood and adolescence is positively associated with adult height (2). IGF-I is a mitogen for prostate cells (38) and has been associated with the risk of developing prostate cancer (23–26), although IGF-I's role in progression is less clear. IGF-I binds the IGF-I receptor and ultimately results in Akt activation (39). However, reduced PTEN or NKX3.1 expression, both of which are frequent and early events in prostate cancer, also cause Akt activation (40), thus

Table 3. Clinical and pathologic features of Black men undergoing radical prostatectomy segregated by adult height

	Height (cm)			*P**
	≤175.3 (%)	>175.3 to <182.9 (%)	≥182.9 (%)	
No. patients	153	135	162	
Body mass index (kg/m^2)				
<25.0	31 (22)	33 (26)	50 (32)	0.04
25.0-29.9	67 (47)	53 (41)	78 (50)	
30.0-34.9	27 (19)	31 (24)	21 (13)	
≥35.0	18 (13)	11 (9)	8 (5)	
Mean age ± SD (y)	61.5 ± 6.8	61.4 ± 6.5	60.5 ± 6.7	0.36†
Median year of surgery	1998	1999	1998	0.22†
PSA (ng/mL)				
Median	7.8	7.1	8.4	0.57†
Mean ± SD	10.1 ± 8.6	9.9 ± 7.5	10.2 ± 7.8	
Biopsy Gleason sum (%)				
2-6	108 (75)	92 (70)	111 (71)	0.13
7	31 (22)	37 (28)	35 (22)	
8-10	5 (3)	2 (2)	11 (7)	
Clinical stage (%)				
T_1	73 (50)	76 (59)	89 (56)	0.34
T_2	72 (50)	53 (41)	69 (44)	
Pathologic Gleason sum (%)				
2-6	73 (50)	71 (55)	86 (54)	0.68
7	60 (41)	49 (38)	55 (35)	
8-10	13 (9)	9 (7)	17 (11)	
Pathologic stage				
T_2	117 (80)	99 (76)	127 (80)	0.52
T_3	28 (19)	30 (23)	26 (16)	
T_4	2 (1)	2 (2)	5 (3)	
Positive surgical margins	43 (29)	47 (36)	61 (38)	0.25
Capsular penetration	32 (22)	32 (25)	26 (16)	0.22
Seminal vesicle invasion	15 (10)	16 (12)	12 (8)	0.42
Lymph node involvement	2 (2)	4 (4)	1 (1)	0.23

*P from χ^2 test except where noted.
†P from ANOVA.

Table 4. Relative risk and 95% confidence interval of time to biochemical progression after radical prostatectomy by height

	Relative risk (95% confidence interval)	*P**
Crude (>175.3 vs ≤175.3 cm)	1.23 (1.00-1.50)	0.05
Age adjusted (>175.3 vs ≤175.3 cm)	1.23 (1.00-1.50)	0.05
Multivariate-adjusted† (>175.3 vs ≤175.3 cm)	1.22 (0.96-1.55)	0.10
Multivariate adjusted with interaction term‡		
White (>175.3 vs ≤175.3 cm)	1.03 (0.77-1.37)	0.05§
Black (>175.3 vs ≤175.3 cm)	1.67 (1.00-2.79)	

*P value for change in likelihood ratio by inclusion of term for height, except where noted.
†Adjusted for age, race, clinical stage, preoperative PSA, year of surgery, biopsy Gleason sum, body mass index, and center.
‡Adjusted for age, race, clinical stage, preoperative PSA, year of surgery, biopsy Gleason sum, body mass index, and center and includes an interaction term, which represents the cross-product of height × race.
§P value for change in likelihood ratio by inclusion of the cross-product of height × race.

bypassing the requirement for IGF-I for continued tumor growth. Accordingly, IGF-I receptor is reduced in advanced prostate cancers (41), metastatic lesions in TRAMP mice (42), and in some human prostate cancer models (43). Because in our study all men already had prostate cancer and we examined progression as our end point, our results may have been less influenced by IGF-I than studies that examined the risk of developing prostate cancer. However, IGFBP-3, which helps regulate free IGF-I concentrations, also causes apoptosis in an IGF-I-independent fashion (44–46). Given that height is directly associated with childhood and adolescent IGF-I/IGFBP-3 ratios, shorter Black men would have lower IGF-I/IGFBP-3 ratios and thus more IGFBP-3 and less IGF-I relative to taller Black men. This increased IGFBP-3 among shorter Black men may be involved in promoting apoptosis within the tumor and thus be protective for progression, whereas the decreased IGFBP-3 among taller Black men may promote progression. Although a similar argument could be made for White men, Black boys and men have lower IGFBP-3 concentrations than their White counterparts (15–18, 47). These racial differences in IGFBP-3 concentrations may result from *IGFBP3* gene polymorphisms that are sensitive to retinoid regulation (48) or due to decreased serum vitamin D among Black people (49). These polymorphisms have recently failed to show a relation to prostate cancer; however, this was analyzed in a small sample of almost entirely White men (50). The overall higher IGFBP-3 concentrations in White men may result in the slight IGFBP-3 concentration differences between tall and short men being less important for cancer progression among White men than in Black men.

Additional explanations for our findings include differences in caloric intake or socioeconomic status between different heights and races. Ultimately, the relationship among adolescent hormones, diet, adult height, and prostate cancer progression later in life is likely complex and probably involves interplay between multiple environmental and genetic factors. Further research is needed to better understand these relationships. Moreover, although we controlled for multiple potential confounding effects, perhaps a confounding effect that we were unable to control for could explain these results.

A limitation to the current study was that the mean follow-up was relatively short. More studies using diverse and larger patient populations are needed to confirm these findings. All patients in the current study had prostate cancer and underwent surgery for their disease. Therefore, although the current findings suggest

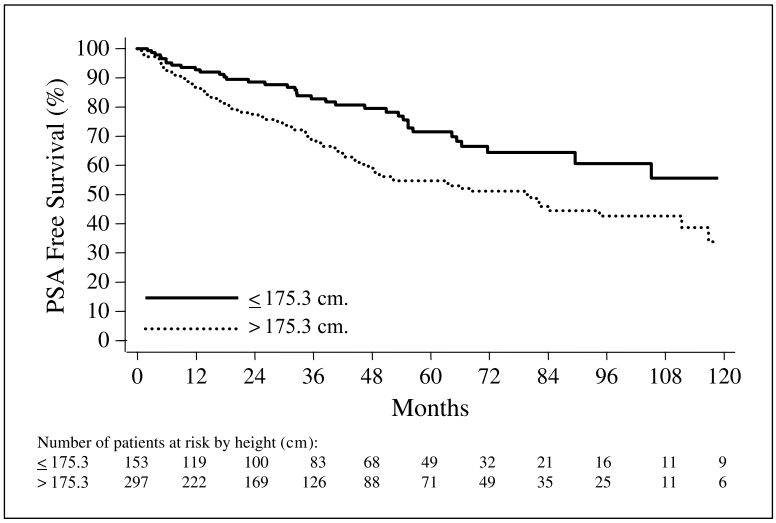

Fig. 1. Actuarial 10-year Kaplan-Meier estimates of biochemical progression rates of Black men treated with radical prostatectomy segregated by height.

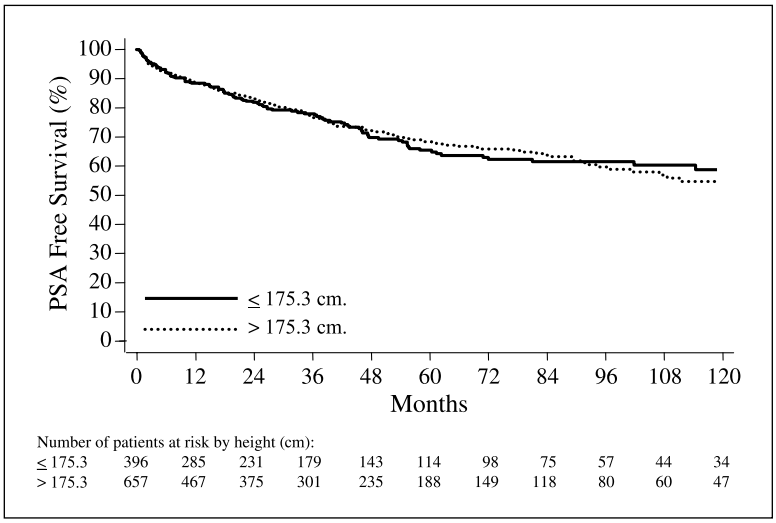

Fig. 2. Actuarial 10-year Kaplan-Meier estimates of biochemical progression rates of White men treated with radical prostatectomy segregated by height.

tallness may be associated with more aggressive prostate cancers among Black men, we are unable to comment on any possible relationship between adult height and the risk of developing prostate cancer. Additionally, this study exclusively looked at biochemical progression and did not analyze mortality from prostate cancer, although early biochemical progression has been associated with greater risk for metastasis and death from prostate cancer (12, 13).

In conclusion, in a multiracial cohort of men undergoing radical prostatectomy, height was significantly associated with biochemical progression among Black men but not among White men. Although the explanation for these findings is unclear, we speculate that racial differences in the IGF axis may be involved. More research is needed to further examine the association between height and prostate cancer, particularly among Black men.

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