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The association between height and prostate cancer grade in the Early Stage Prostate Cancer Cohort Study

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Abstract

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Objective—We examined the relationship between height and prostate cancer grade.

Methods—The Early Stage Prostate Cancer Cohort Study is an observational cohort of 1,037 men diagnosed with early-stage prostate cancer, $T_{0–3}N_xM_0$. High-grade prostate cancer was defined as a biopsy Gleason score ≥ 7 (4 + 3). Logistic regression models were created to calculate odds ratios (OR) and 95% confidence intervals (CI) for the cross-sectional relationship between height and prostate cancer grade in the overall cohort and subpopulations.

Results—We identified 939 participants with a biopsy Gleason score. High-grade prostate cancer was diagnosed in 138 participants. Overall, participants in the highest quartile of height were more than twice as likely to have a Gleason score ≥ 7 (4 + 3) than participants in the lowest quartile of height, OR 2.14 (95% CI 1.11, 4.14), after multivariate adjustment. Participants in the highest quartile of height were more likely to be diagnosed with high-grade prostate cancer than participants in the lowest quartile of height among participants who were black, OR 8.00 (95% CI 1.99, 32.18), and participants who had diabetes mellitus, OR 5.09 (95% CI 1.30, 19.98).

Conclusions—Height is associated with increased risk of high-grade prostate cancer overall and perhaps among certain subpopulations.

Keywords

Prostatic neoplasms; Body height; Epidemiology

Introduction

Prostate cancer is a significant cause of morbidity and mortality among men. In 2010, it is estimated that 217,730 men were diagnosed with prostate cancer and 32,050 men died as a result of prostate cancer in the United States [1]. Given the large difference between the number of men who are diagnosed with prostate cancer and die from prostate cancer, it would be helpful to identify risk factors for prostate cancer that are more likely to lead to prostate cancer–related mortality. The pathologic grade of prostate cancer at diagnosis is related to the likelihood of prostate cancer mortality [2, 3].

Height is a potential risk factor for prostate cancer. A meta-analysis of 58 studies found that height was positively associated with prostate cancer [4]. However, fewer studies have examined the relationship between height and advanced prostate cancer. Among the studies that have examined this relationship, taller men appear to be at higher risk for more advanced prostate cancer than shorter men [4–6] but not all studies have found this association [7, 8], and little is known about this relationship in subpopulations of men with different risks of prostate cancer. Therefore, we examined the relationship between height and prostate cancer grade in the Early Stage Prostate Cancer Cohort. Furthermore, we explored the relationship between height and prostate cancer grade in various subpopulations of men with potentially different risk of high-grade prostate cancer.

Materials and methods

Data sources

Men were eligible for participation in the Early Stage Prostate Cancer Cohort (ESPCC) study if they were diagnosed with early-stage prostate cancer, $T_{0–3}N_xM_0$, within two and a half years prior to enrollment. In addition, eligible men had no other history of cancer, with the exception of non-melanoma skin cancer, within 5 years of enrollment and had no other major illness that would have precluded long-term participation. Men with early-stage prostate cancer were identified at 16 sites throughout the VA Healthcare System.

A total of 1,037 men participated in the ESPCC study. Participants completed questionnaires at the initial interview that asked about demographic information including age, race, current weight, and current height; medical history including diabetes mellitus; and other potential risk factors for prostate cancer progression including smoking history and family history of prostate cancer. Questions were also asked about why prostate cancer had been suspected prior to a diagnosis.

Definition of outcome

The Gleason score was identified from pathology reports at the time of diagnosis and prostatectomies that had occurred by the time of the baseline survey. We identified Gleason scores from paper reports sent to us by site coordinators and using the Automated Retrieval Console [9] to review electronic reports in the VA Healthcare System electronic medical record. The appropriate Gleason score for each participant was selected according to the criteria of the 2005 International Society of Urological Pathology Consensus Conference on Gleason grading of prostatic carcinoma [10]. High-grade prostate cancer was defined as a Gleason score ≥ 8 as well as cases where the overall Gleason score was 7 and the primary score was ≥4.

Statistical analyses

We calculated the percent of men in our cohort with and without high-grade prostate cancer as well as the mean age, weight, and height ± standard deviation. We calculated the percent of men with a self-reported age at the time of prostate cancer diagnosis that matched ± 1 year their age identified in the electronic medical record, Veterans Affairs (VA) Patient Treatment File (PTF). We also calculated the percent of men who reported having diabetes mellitus and were found to have diabetes mellitus in the VA PTF at the time of prostate cancer diagnosis. We used logistic regression to examine the relationship between height as a continuous (5 cm) marker and grade of prostate cancer. Quartiles of height were defined, <172.7, 172.7–177.7, 177.8–182.7, and >182.7 cm. We used logistic regression to examine the relationship between quartiles of height and grade of prostate cancer with the lowest quartile as the referent quartile. We calculated the median height in each quartile and used logistic regression to calculate the *p* for trend across quartiles of height for prostate cancer grade. We performed age- and multivariate-adjusted models to calculate odds ratios (OR) and 95% confidence intervals (CI). Multivariate models controlled for age (years), race (white, black, other), family history of prostate cancer (yes, no, missing), whether the prostate cancer was suspected by PSA testing (yes, no), smoking status (no, current, quit),

diabetes mellitus (yes, no), weight (kg), and site of enrollment (sites). We repeated the above procedures among groups stratified by the presence or absence of particular risk factors for high-grade prostate cancer. We dichotomized age and weight based upon the median values in the cohort. We limited the analysis to categories with ≥100 men and calculated the *p* value for the interaction term of each stratification. We also performed a sensitivity analysis among men who received a prostatectomy using height as a continuous (5 cm) marker and grade of prostate cancer at prostatectomy.

Results

Of the 1,037 participants in the ESPCC, we identified 939 with Gleason scores from biopsy pathology reports and 931 with Gleason scores and reported height. We found that the age at prostate cancer diagnosis that a participant reported and was identified in the VA PTF matched ± 1 year in 95% of the participants. We also found that a diagnosis of diabetes mellitus matched between participant's self-report and the VA PTF in 88% of participants. Overall, the mean ± standard deviation Gleason score from biopsy reports was 6.3 ± 1.1 units. The mean ± standard deviation height was 177.2 ± 7.1 cm. Taller participants were younger and heavier than shorter participants (Table 1). Taller participants were more likely to be black and report a history of diabetes mellitus than shorter participants.

We identified 138 participants with a Gleason score ≥7 (4 + 3) at biopsy. Participants in the highest quartile of height were more than twice as likely to have a Gleason score ≥ 7 (4 + 3) at biopsy than participants in the lowest quartile of height, OR 2.14 (95% CI 1.11, 4.14), and the trend across quartiles was significant, *p* trend = 0.01, after multivariate adjustment (Table 2). Although not statistically significant, every 5-cm increase was associated with an increased risk for a Gleason score ≥ 7 (4 + 3) at biopsy, OR 1.11 (95% CI 0.96, 1.29). Among the 239 men who underwent prostatectomy, every 5-cm increase was also associated with an increased risk for a Gleason score ≥ 7 (4 + 3) at prostatectomy, OR 1.07 (95% CI 0.77, 1.48), although not statistically significant.

We examined the relationship between height and prostate cancer grade in various subpopulations (Table 3). Participants younger than age 65 years had a non-significant increased risk for a Gleason score ≥ 7 (4 + 3) with every 5 cm of height, OR 1.16 (0.90, 1.50), and the participants in the highest quartile of height were more likely, although not statistically significant, to have a Gleason score ≥ 7 (4 + 3) than participants in the lowest quartile of height, OR 4.06 (0.86, 19.15). Among black participants, every 5 cm of height was associated with an increased risk for a Gleason score of ≥ 7 (4 + 3) at biopsy, OR 1.44 (1.06, 1.95). Participants in the highest quartile of height were eight times more likely to have a Gleason score ≥ 7 (4 + 3) at biopsy than participants in the lowest quartile of height, OR 8.00 (1.99, 32.18), and the trend across quartiles was significant, *p* trend < 0.01. Among participants with diabetes mellitus, every 5 cm of height was associated with an increased risk for a Gleason score of ≥ 7 (4 + 3) at biopsy, OR 1.35 (1.00, 1.81). Participants in the highest quartile of height were over five times more likely to have a Gleason score ≥ 7 (4 + 3) at biopsy than participants in the lowest quartile of height, OR 5.09 (1.30, 19.98), and the trend across quartiles was significant, *p* trend = 0.01. Among participants who weighed < 87 kg, participants in the highest quartile of height were over three times more likely to have a

Gleason score ≥ 7 (4 + 3) at biopsy than participants in the lowest quartile of height, OR 3.23 (1.24, 8.40), and the trend across quartiles was significant, p trend = 0.01. The p value for interaction was greater than 0.05 for each potential interaction.

Discussion

In the ESPCC, height appeared to be associated with increased risk of high-grade prostate cancer, Gleason score ≥ 7 (4 + 3), at biopsy. In the highest quartile of height, participants were more than twice as likely to have high-grade prostate cancer compared with the lowest quartile of height. In particular, among black participants and participants with diabetes mellitus, height was especially associated with a diagnosis of high-grade prostate cancer at biopsy.

Several potential mechanisms have been proposed for the relationship between height and prostate cancer. Insulin-like growth factor-I (IGF-I) has been found to be associated with body height in adolescence [11], and some [12, 13], but not all [14, 15], studies have found a relationship between height and levels of IGF-1 in adulthood. IGF-1 is known to be mitogenic and antiapoptotic [16], and it has been found to be positively associated with prostate cancer [17, 18]. Height has also been found to be genetically linked [19]. Therefore, genes that regulate height may also be associated with regulating prostate cancer development and progression.

IGF-1 levels may differ by age, race, and the presence or absence of diabetes mellitus. It is generally believed that levels of IGF-1 decline with increasing age [20]. McGreevy et al. reported that although plasma levels of IGF-1 were not different between black and white men, the level of IGF-binding protein-3 (IGFBP-3) and the ratio of IGF-1/IGFBP-3 were lower among black men [21]. This suggests that black men may have higher levels of bioavailable IGF-1. Although not all studies have found black men to have a lower ratio of IGF-1/IGFBP-3, several studies have found that black men have lower levels of IGFBP-3 [22–25]. Several cross-sectional studies have found elevated IGF-1 levels and decreased IGFBP-3 levels in patients with impaired glucose tolerance and diabetes mellitus [26, 27]; however, another study found decreased levels of IGF-1 among diabetic men compared with non-diabetic men [28].

One should consider several limitations of our analysis when interpreting our results. Our analysis is cross-sectional. Therefore, based upon our results, we cannot formally say that height is a risk factor for high-grade prostate cancer. However, it is difficult to imagine that high-grade prostate cancer affected a participant’s height in this cohort of men with early-stage prostate cancer. Height was self-reported. However, the correlation between measured and self-reported height is typically high although shorter men tend to overreport their height more frequently than taller men [29]. This over reporting would tend to attenuate the effect of height on prostate cancer grade toward the null hypothesis. Furthermore, we had high correlation between self-reported age and diabetes mellitus and the values for these variables identified in the electronic medical record. This suggests that the height that participants reported was likely accurate. We had small numbers of men with high-grade prostate cancer and focused our analysis on Gleason scores obtained from biopsies rather

than prostatectomy. However, we found consistent results whether we used Gleason scores obtained from biopsy or prostatectomy. We were unable to collect pathology reports from biopsies that occurred outside of the VA Healthcare System. However, we did not find a significant difference in the frequency of participants who reported that they received a majority of their care in the VA Healthcare System by quartiles of height. Our cohort was limited to men with early-stage prostate cancer. Therefore, our results are likely biased toward the null hypothesis and thus underestimate the true effect, since many cases of high-grade prostate cancer likely did not qualify for inclusion in the ESPCC. Although we found several apparent differences in the relationship between height and prostate cancer among various strata of risk factor groups for prostate cancer progression, none of the *p* values for interaction were significant. However, the interaction coefficient does not discern the balance of potential synergistic, antagonistic, or competitive relationships between variables and thus cannot rule out the presence of an interaction [30].

Conclusions

In the ESPCC, height appeared to be associated with increased risk of high-grade prostate cancer, especially among younger participants, black participants, and participants with diabetes mellitus. Future research should focus on the relationship between height and prostate cancer mortality as well as the potential mechanism for the specific relationship between height and prostate cancer grade among younger men, black men, and men with diabetes mellitus.

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Table 1

Participant characteristics by quartiles of height

Characteristics	Quartiles of height			
	< 172.7 cm *n* = 196	172.7–177.7 cm *n* = 232	177.8–182.7 cm *n* = 261	> 182.7 cm *n* = 242
Age, years, mean ± SD	65.9 ± 7.6	65.9 ± 7.9	65.3 ± 7.7	63.8 ± 7.6
Weight, kg, mean ± SD	81.1 ± 13.3	87.1 ± 17.0	91.1 ± 17.2	96.9 ± 17.5
Height, cm, mean ± SD	167.5 ± 3.2	174.0 ± 1.3	179.0 ± 1.3	186.0 ± 4.2
Race, %				
White	75.7	81.0	78.1	79.6
Black	23.3	18.2	21.5	20.0
Other	1.0	0.9	0.4	0.4
Family history of prostate cancer, %				
No	71.4	76.7	70.5	71.9
Yes	20.4	19.8	21.8	22.7
Missing	8.2	3.5	7.7	5.4
Suspected cancer due to PSA, %				
No	13.4	15.0	11.5	11.3
Yes	86.6	85.0	88.5	88.8
Smoke, %				
No	31.6	25.5	25.7	20.3
Current	15.0	20.8	16.9	19.1
Quit	53.4	53.7	57.5	60.6
Diabetes mellitus, %				
No	79.2	81.0	74.2	81.9
Yes	20.8	19.0	25.8	18.1
Received usual care in the VA				
Healthcare System, %				
No	9.0	11.2	10.1	7.1
Yes	91.0	88.8	89.9	92.9

Table 2

Odds ratios (95% confidence interval) of Gleason score ≥ 7 (4 + 3) compared with Gleason score ≤ 7 (3 + 4) at diagnostic biopsy by continuous height and quartiles of height in the overall cohort

	Continuous, 5 cm	Quartiles				*p*, trend
		< 172.7 cm	172.7–177.7 cm	177.8–182.7 cm	> 182.7 cm	
Overall						
No. of cases	138	21	30	40	47	
Age-adj	1.15 (1.01, 1.31)	Referent	1.10 (0.61, 1.97)	1.42 (0.82, 2.48)	2.02 (1.17, 3.49)	< 0.01
MV*-adj	1.11 (0.96, 1.29)	Referent	1.30 (0.67, 2.56)	1.61 (0.84, 3.08)	2.14 (1.11, 4.14)	0.01

*Multivariate model included the following covariates: age (years); race (white, black, other); family history of prostate cancer (yes, no, missing); prostate cancer suspected by PSA (yes, no); smoke (no, current, quit); diabetes mellitus (yes, no); weight (kg); site of enrollment (sites)

Table 3

Odds ratios (95% confidence interval) of Gleason score ≥ 7 (4 + 3) compared with Gleason score ≤ 7 (3 + 4) at diagnostic biopsy by continuous height and quartiles of height stratified by age, race, and presence or absence of diabetes mellitus

	Continuous, 5 cm	Quartiles				*p*, Trend	*p*, Interaction
		< 172.7 cm	172.7–177.7 cm	177.8–182.7 cm	> 182.7 cm		
Age							0.12
< 65 years, *n* = 429							
No. of cases	47	4	9	14	20		
Age-adj	1.21 (0.98, 1.49)	Referent	2.07 (0.61, 7.00)	2.56 (0.81, 8.08)	3.45 (1.13, 0.49)	0.17	
MV*-adj	1.16 (0.90, 1.50)	Referent	2.95 (0.59, 14.66)	3.52 (0.74, 16.69)	4.06 (0.86, 19.15)	0.52	
≥65 years, *n* = 498							
No. of cases	90	17	20	26	27		
Age-adj	1.12 (0.96, 1.32)	Referent	0.96 (0.48, 1.94)	1.29 (0.66, 2.53)	1.90 (0.96, 3.75)	< 0.01	
MV*-adj	1.10 (0.92, 1.32)	Referent	1.06 (0.49, 2.33)	1.32 (0.62, 2.83)	1.96 (0.90, 4.29)	0.01	
Weight							0.48
< 87 kg, *n* = 455							
No. of cases	58	13	16	15	14		
Age-adj	1.15 (0.94, 1.41)	Referent	1.11 (0.51, 2.45)	1.47 (0.66, 3.25)	2.28 (1.00, 5.20)	0.02	
MV*-adj	1.21 (0.96, 1.52)	Referent	1.56 (0.65, 3.73)	1.70 (0.69, 4.18)	3.23 (1.24, 8.40)	0.01	
≥87 kg, *n* = 471							
No. of cases, *n* = 471	79	7	14	25	33		
Age-adj	1.11 (0.93, 1.33)	Referent	1.39 (0.53, 3.70)	1.62 (0.66, 3.99)	2.13 (0.88, 5.18)	0.09	
MV*-adj	1.08 (0.88, 1.31)	Referent	1.02 (0.33, 3.08)	1.49 (0.55, 4.07)	1.70 (0.63, 4.61)	0.27	
Race							0.19
White, *n* = 727							
No. of cases	96	14	23	31	28		
Age-adj	1.08 (0.92, 1.26)	Referent	1.31 (0.65, 3.80)	1.72 (0.88, 3.37)	1.71 (0.86, 3.41)	0.04	
MV*-adj	1.03 (0.86, 1.23)	Referent	1.21 (0.56, 2.62)	1.65 (0.79, 3.46)	1.47 (0.67, 3.20)	0.14	
Black, *n* = 191							
No. of cases	40	6	6	9	19		

	Continuous, 5 cm	Quartiles				*p*, Trend	*p*, Interaction
		< 172.7 cm	172.7–177.7 cm	177.8–182.7 cm	> 182.7 cm		
Age-adj	1.37 (1.07, 1.75)	Referent	1.03 (0.28, 3.80)	1.42 (0.45, 4.51)	5.29 (1.78, 15.77)	< 0.01	
MV*-adj	1.44 (1.06, 1.95)	Referent	1.40 (0.31, 6.23)	1.56 (0.37, 6.61)	8.00 (1.99, 32.18)	< 0.01	
Family history of prostate cancer							0.56
No, *n* = 676							
No. of cases	104	15	23	32	34		
Age-adj	1.21 (1.03, 1.42)	Referent	1.21 (0.60, 2.44)	1.88 (0.96, 3.66)	2.35 (1.21, 4.59)	< 0.01	
MV*-adj	1.14 (0.94, 1.37)	Referent	1.24 (0.57, 2.69)	1.73 (0.81, 3.70)	2.00 (0.92, 4.35)	0.07	
Yes, *n* = 198							
No. of cases	27	5	6	5	11		
Age-adj	1.08 (0.83, 1.39)	Referent	0.86 (0.23, 3.22)	0.67 (0.18, 2.49)	1.71 (0.54, 5.39)	0.19	
MV*-adj	1.09 (0.81, 1.47)	Referent	0.87 (0.18, 4.23)	0.80 (0.19, 3.49)	1.90 (0.47, 7.74)	0.22	
Suspected cancer due to PSA							0.82
No, *n* = 117							
No. of cases	17	3	6	3	5		
Age-adj	1.16 (0.80, 1.70)	Referent	1.57 (0.34, 7.16)	0.88 (0.16, 4.86)	1.79 (0.37, 8.57)	0.75	
MV*-adj	1.13 (0.74, 1.72)	Referent	3.04 (0.44, 21.09)	1.41 (0.18, 11.04)	2.27 (0.34, 15.03)	0.80	
Yes, *n* = 804							
No. of cases	120	18	23	37	42		
Age-adj	1.15 (1.00, 1.32)	Referent	1.09 (0.56, 2.11)	1.63 (0.89, 2.98)	2.24 (1.23, 4.09)	< 0.01	
MV*-adj	1.10 (0.94, 1.29)	Referent	1.16 (0.56, 2.42)	1.66 (0.83, 3.31)	2.12 (1.04, 4.38)	0.01	
Smoke							0.81
No, *n* = 236							
No. of cases	34	6	3	13	12		
Age-adj	1.27 (1.00, 1.61)	Referent	0.43 (0.10, 1.85)	1.93 (0.67, 5.55)	3.32 (1.12, 9.86)	0.01	
MV*-adj	1.19 (0.89, 1.59)	Referent	0.33 (0.06, 1.81)	1.21 (0.31, 4.74)	2.71 (0.67, 11.0)	0.07	
Current or previous, *n* = 690							
No. of cases	104	15	27	27	35		
Age-adj	1.09 (0.94, 1.28)	Referent	1.43 (0.72, 2.83)	1.34 (0.68, 2.63)	1.88 (0.98, 3.64)	0.05	
MV*-adj	1.07 (1.03, 1.15)	Referent	1.53 (0.72, 3.23)	1.49 (0.70, 3.17)	1.89 (0.89, 4.04)	0.07	

	Continuous, 5 cm	Quartiles				*p*, Trend	*p*, Interaction
		< 172.7 cm	172.7–177.7 cm	177.8–182.7 cm	> 182.7 cm		
Diabetes mellitus							0.12
No, *n* = 724							
No. of cases	98	16	22	31	29		
Age-adj	1.07 (0.92, 1.25)	Referent	1.00 (0.51, 1.94)	1.53 (0.82, 2.87)	1.45 (0.77, 2.74)	0.09	
MV*-adj	1.02 (0.86, 1.22)	Referent	1.33 (0.62, 2.84)	1.74 (0.83, 3.66)	1.55 (0.71, 3.34)	0.22	
Yes, *n* = 193							
No. of cases	38	5	7	9	17		
Age-adj	1.35 (1.05, 1.75)	Referent	1.34 (0.36, 4.93)	1.13 (0.35, 3.71)	4.61 (1.48, 14.42)	< 0.01	
MV*-adj	1.35 (1.00, 1.81)	Referent	1.23 (0.28, 5.39)	1.51 (0.39, 5.84)	5.09 (1.30, 19.98)	0.01	

*Multivariate models included each of the following covariates except for the categorical variable by which the population was stratified: age (years); race (white, black, other); family history of prostate cancer (yes, no, missing); prostate cancer suspected by PSA (yes, no); smoke (no, current, quit); diabetes mellitus (yes, no); weight (kg); site of enrollment (sites)