

BODY MASS INDEX AS A PREDICTOR FOR
GLEASON SCORE UPGRADING FROM
BIOPSY TO PROSTATECTOMY

by

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ABSTRACT

Objective: Gleason scores are often higher in radical prostatectomy (RP) specimens compared biopsy. Obese men are at a higher risk of death from prostate cancer therefore body mass index (BMI) may be an important predictor of Gleason sum upgrading.

Methods: Between 1993 and 2014, 16,904 men underwent RP at Johns Hopkins and were eligible for this analysis. Upgrading was defined as any increase in Gleason sum and also as upgrading to a higher Gleason sum group: 2-6, 3+4, 4+3, and 8+. The association between higher BMI and upgrading was evaluated in multivariable-adjusted analyses. Separate analyses were performed in Caucasian and African American men and subsets of men with Gleason sum 6 disease, and in men with Gleason sum 6 with stage T1 or T2a, and PSA<10ng/mL.

Results: In total, 21% of men upgraded to a higher Gleason sum at RP compared to at biopsy and 8% downgraded. After adjusting for factors that were associated with upgrading, men who were overweight had a 14% higher odds of upgrading (95% CI 1.03, 1.25) and men who were obese had a 24% higher odds of upgrading (95% CI 1.10, 1.39). The association between BMI and upgrading was present among Caucasian, but not African American men (overweight OR = 0.90, 95% CI 0.64, 1.28); obese OR=1.01 95% CI 0.69, 1.49). In Caucasian and African American men with Gleason sum 6, stage T1 or T2a, and PSA <10ng/mL, there was a positive association between obesity and upgrading. Addition of BMI to multivariable-adjusted analyses did not significantly improve prediction of upgrading from Gleason sum 6 prostate cancer.

Conclusions: Overweight and obesity were associated with a higher odds of upgrading between biopsy and RP in Caucasian men. In men with low risk disease, who may be eligible for active surveillance – Gleason 6 prostate cancer with PSA < 10 ng/mL and clinical stage of T1 or T2a – obesity was associated with an increased odds of upgrading in both African American and Caucasian men. Our work may inform treatment decision-making for overweight and obese men, including African American obese men, newly diagnosed with prostate cancer.

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TABLE OF CONTENTS

ABSTRACT.....	ii
ACKNOWLEDGMENTS	iv
TABLE OF CONTENTS.....	v
LIST OF TABLES.....	vi
LIST OF FIGURES	vii
BACKGROUND	1
METHODS	3
Study Population.....	3
Assessment of obesity.....	4
Assessment of upgrading and downgrading	4
Statistical Analysis.....	5
RESULTS	7
Baseline Patient Characteristics.....	7
Association between BMI and upgrading.....	7
Association between BMI and downgrading and upgrading separately in Caucasian and African American men.....	9
Association between BMI and downgrading and upgrading separately in Caucasian and African American men with biopsy Gleason sum 6 Prostate Cancer	9
Does BMI add to the prediction of upgrading in men with biopsy Gleason sum 6 prostate cancer?.....	10
DISCUSSION	10
CONCLUSIONS.....	15
REFERENCES	16
TABLES	18
FIGURES.....	28
APPENDIX.....	30
CURRICULUM VITAE.....	32

LIST OF TABLES

Table 1. Demographic and clinical characteristics of men who underwent prostate biopsy and radical prostatectomy.....	18
Table 2. Unadjusted and multivariable-adjusted associations between BMI categories and upgrading of Gleason sum from biopsy to prostatectomy.....	19
Table 3. Multivariable-adjusted association between BMI categories and upgrading of Gleason sum from biopsy to prostatectomy, separately in African-American and Caucasian men.....	20
Table 4. Unadjusted and multivariable-adjusted associations between BMI categories and upgrading of Gleason sum group from biopsy to prostatectomy.....	21
Table 5. Multivariable-adjusted association between BMI categories and upgrading of Gleason sum group from biopsy to prostatectomy, separately in African-American and Caucasian men.....	22
Table 6. Multivariable-adjusted association between BMI and change in Gleason sum in Caucasian men.....	23
Table 7. Multivariable-adjusted association between BMI and change in Gleason sum in African-American men.....	24
Table 8. Multivariable-adjusted association between BMI and change in Gleason sum in Caucasian men with biopsy Gleason 6 disease.....	25
Table 9. Multivariable-adjusted association between BMI and change in Gleason sum in African-American men with biopsy Gleason 6 disease.....	25
Table 10. Multivariable-adjusted association between BMI and upgrading in Caucasian and African-American men with clinical tumor stage \leq T2a and PSA<10 ng/mL.....	26
Table 11. Multivariable-adjusted association between BMI and upgrading in Caucasian and African-American men with biopsy Gleason sum 6 disease, clinical tumor stage \leq T2a, and PSA<10 ng/mL.....	27

LIST OF FIGURES

Figure 1. Inclusion and exclusion of subjects in analyses, 1993-2014, Johns Hopkins Hospital.....	28
Figure 2. Receiver operating characteristic curves for men with Gleason sum 6 prostate cancer in Caucasian and African American men, 1993-2014, Johns Hopkins Hospital.....	29
Figure 3. Trends in the proportions of selected characteristics over time, 1993-2014, Johns Hopkins Hospital.....	31

BACKGROUND

For nearly 50 years, Gleason score grading of prostatic tumors has been used in clinical practice as a method for distinguishing between indolent and aggressive forms of prostate cancer. (1) Over this time period, modifications have been made to the Gleason grading system to keep up with improvements in the diagnosing of prostate cancer, and it remains an important predictor of long-term clinical outcomes such as recurrence and prostate cancer-specific mortality. (1) For these reasons, treatment decisions for the management of prostate cancer are often made based on the Gleason score from biopsy specimens at the time of diagnosis. One particular challenge in treatment decision-making is the frequency in discrepancy between Gleason sums, a pathological indicator of tissue differentiation status that is prognostic, measured in biopsy and prostatectomy specimens. Prior studies investigating the correlation of Gleason score obtained from biopsy and surgical specimens have found that as many as 40% of men experience upgrading in Gleason sum of their prostate cancer. (2-5) These differences in Gleason sum between biopsy and surgical specimens have previously been attributed to missing the highest graded region of cancer during biopsy as well as inter- and intra-pathologist variation, and progression of tumor. (2-5)

Upgrading is of particular concern for men with biopsy Gleason 6 prostate cancer, who because of their lower predicted risk of death from prostate cancer, may be weighing the risks versus benefits of active surveillance compared with immediate treatment with curative intent. (6,7) Yet, men with biopsy Gleason sum 6 disease have been found to be at the highest risk of upgrading. (8-10)

Here we studied the association between body fatness as measured by body mass index (BMI) and upgrading. The reason we focused on obesity is that higher BMI is associated with an increased risk of death from prostate cancer and is associated with larger prostate volume, higher blood plasma volume, and lower PSA levels. (11-14) As a result, higher BMI may be an important predictor of Gleason score upgrading between biopsy and prostatectomy. One study found that overweight and obese men were more likely to experience upgrading than those with BMI less than 25, however, the ability to stratify analyses based on race and Gleason score was limited by low sample size (15). Another study in European men found no relationship between BMI and Gleason score upgrading, and the authors acknowledge this may be due to a lower average BMI in their sample compared to American cohorts. (8) Two other studies investigating upgrading among men with Gleason 6 prostate cancer found associations with BMI, but again analyses were not stratified by race to investigate the effect of BMI separately among African American and Caucasian men. (16, 17)

In the United States in 2012, nearly 75% of men aged 60 or older have a BMI greater than 25, and 32% were categorized as obese, which makes it even more important to understand the impact of BMI on biopsy findings. (18) Thus, we hypothesized that the likelihood of upgrading would be greater in men with higher compared with lower BMI even for the same biopsy Gleason sum disease. Further, we addressed whether the association between BMI and the odds of upgrading differed between black and white men because black men have a higher risk of upgrading and black men in the US have higher BMI.

METHODS

Study Population

We conducted a retrospective cohort analysis of men with clinically-localized prostate cancer who underwent radical prostatectomy (RP) at Johns Hopkins Hospital between January 1, 1993, when PSA-based prostate cancer screening was fully routine in the US, and December 1, 2014. We excluded from the analysis men whose biopsy or prostatectomy specimens did not contain prostate cancer, Gleason sum was not available, or the prostate cancer had a histology other than adenocarcinoma (n=200). Men with missing or extreme values for height or weight were excluded (n=3,618). Men missing clinical tumor stage or pre-surgical PSA were excluded (n=430). Shown in Figure 1 are the exclusions, which left 16,904 men in the study population.

Information on age, race, preoperative height, preoperative weight, any family history of prostate cancer, preoperative PSA, surgery year, clinical tumor stage (T1, T2a, T2b, T2c, and T3), biopsy Gleason score, pathologic stage, and Gleason score on radical prostatectomy was abstracted from the medical records. Number of biopsy cores taken, number of biopsy cores with cancer, and highest percentage of cancer of any core were also recorded in the established database when available. For men with Gleason sum 7 in the biopsy or in the prostatectomy specimen, we used the primary and secondary Gleason patterns to sub-classify them as having either 3+4 or 4+3 prostate cancer.

The follow-up of this cohort was approved by the Institutional Review Board at the Johns Hopkins School of Medicine. This analysis was additionally approved by the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health.

Assessment of obesity

Body mass index (BMI) was calculated as measured at their pre-surgery visit: weight in kilograms divided by the square of height in meters. We categorized the men as normal weight ($<25 \text{ kg/m}^2$), overweight ($25 \text{ to } < 30 \text{ kg/m}^2$), and obese ($\geq 30 \text{ kg/m}^2$) (ref CDC). Only 30 men were considered to be underweight ($\text{BMI} < 18.5 \text{ kg/m}^2$); they were included in the normal weight group.

Assessment of upgrading and downgrading

Upgrading Gleason sum between the biopsy and prostatectomy was defined two ways. First, upgrading was defined as having a higher Gleason sum in the prostatectomy specimen compared to biopsy. Nineteen men found to have Gleason 10 prostate cancer at biopsy were excluded because they were incapable of upgrading to a higher sum (Figure 1).

For the second definition, we first separated men into four biopsy Gleason sum groups: group 1 – 2 to 6; group 2 – 3+4; group 3 – 4+3; and group 4 – 8 and higher. Then, the second definition was having a higher Gleason sum category in the prostatectomy specimen compared to biopsy. Downgrading was similarly defined: having a lower Gleason sum or lower Gleason sum group in the prostatectomy specimen than in the biopsy. 812 men were excluded from the second definition for upgrading because they were in the highest Gleason sum category (Gleason sum 8 or higher) at biopsy and therefore could not achieve the outcome. Records for four men did not have primary and secondary scores (three with Gleason sum 7 and one with sum 5) and therefore they were dropped from all analyses using Gleason sum groups to determine upgrading (Figure 1).

These two definitions of upgrading (or downgrading) do not always correspond; for example, a man diagnosed with 3+4 disease on biopsy, but who was found to have 4+3 disease in the prostatectomy specimen would meet criteria for upgrading under the second definition but not for the first. Conversely, a man with Gleason sum 5 from biopsy and sum 6 from prostatectomy would be considered to have upgraded according to the first definition but not the second.

Statistical Analysis

To characterize the men and to begin to identify potentially confounding factors, we calculated the mean or prevalence of demographic and clinical characteristics among the three BMI categories (<25 , 25 to <30 , and ≥ 30 kg/m²). We determined the statistical significance of any differences in the means or prevalences across BMI categories using linear regression for continuous variables (age at diagnosis, pre-surgery PSA, year of surgery, biopsy Gleason sum) and multinomial logistic regression for categorical variables (race, clinical tumor stage, change in Gleason sum, change in Gleason Group).

We included in the analysis only men who were upgraded or who had no change. Using the first outcome definition, men who were downgraded based on sum were excluded as were men with Gleason sum 10 because they could not be upgraded, which left 15,582 men in the analysis. Using the second outcome definition, men who were downgraded based on category were excluded as were men with Gleason sum group 4 (Gleason sums 8 to 10) because they could not be upgraded, which left 14,871 men in the analysis. To evaluate the association between BMI and upgrading using either the first or second outcome definition (versus no change), we entered into a logistic regression

model indicator variables for overweight (25 to <30 kg/m²) and obese (≥ 30 kg/m²); the reference group was normal weight (<25 kg/m²). We present unadjusted and multivariable-adjusted (race, clinical tumor stage, biopsy Gleason sum, pre-surgery PSA [transformed using log₂], age at surgery, year of surgery) odds ratios (ORs) and 95% confidence intervals. We considered the influence of additionally adjusting for number of biopsy cores taken, number of biopsy cores with cancer, and highest percentage of cancer in those with available information. We considered the influence of 2005 change in the Gleason grading system on the results by stratifying the main analysis using a cutpoint of 2005 year of surgery.

Because African-American men are more likely to be upgraded, we repeated the main analyses separately in African-American and in Caucasian men. We expanded these analyses to simultaneously model upgrading by one or by two or more Gleason sum levels (e.g., 6 to 7) and downgrading (both versus no change) using multinomial logistic regression separately in African-American and in Caucasian men.

We performed additional sub-analyses for BMI and upgrading separately in African-American and Caucasian men to inform decision-making about active surveillance for obese men: (1) men with biopsy Gleason sum 6 disease, (2) men with low clinical tumor stage (\leq T2a) and PSA (<10 ng/mL), and 3) men with both (1) and (2); downgrading was not investigated because of small sample size.

We calculated the area under the receiver operating characteristic (ROC) curve (AUC), to assess whether BMI added to the predictive capacity of demographic and clinical factors for upgrading among men with biopsy Gleason sum 6 prostate cancer and men with Gleason 6 prostate cancer, T1 or T2a stage, and PSA < 10 ng/mL. All analyses

were performed in Stata version 13.1 (StataCorp, College Station, TX). Statistical tests were two-sided and $p < 0.05$ was considered to be statistically significant.

RESULTS

Baseline Patient Characteristics

Demographic and clinical characteristics for the 16,904 men in the study population are reported in Table 1. The number of men excluded for each of the reasons as described above are displayed in Figure 1. The majority of the men in the study population were Caucasian (86%), had T1 disease (73%), biopsy Gleason 6 prostate cancer (68%), and with median PSA of 5.4 ng/mL. Of those with T1 disease, 76 were staged as either T1a or T1b, and 12,182 (99%) had T1c prostate cancer.

55% of the men were overweight and 19% were obese. There were statistically significant differences in racial composition, surgical year, and biopsy Gleason score between men in different BMI categories. With increasing BMI group, the sample contained a higher percentage of African American men, underwent surgery later, and had higher proportions of Gleason 7 prostate cancer in biopsy specimens. Distribution of clinical tumor stage from DRE across BMI groups appeared similar. Based on Gleason sum, 21% of the men were upgraded and 8% were downgraded. Based on Gleason sum group, 24% were upgraded, and 8% were downgraded.

Association between BMI and upgrading

The association between BMI and upgrading is reported in Table 2. Men who were overweight had a 12% higher odds of upgrading (95% CI 1.02, 1.23) based on

Gleason sum and those who were obese had a 15% higher odds of upgrading (95% CI 1.03, 1.29) compared to those with a normal BMI (p-trend = 0.016). After adjusting for factors that were associated with upgrading (Table 2), men who were overweight had a 14% higher odds of upgrading (95% CI 1.03, 1.25) and men who were obese had a 24% higher odds of upgrading (95% CI 1.10, 1.39) (p-trend < 0.001). The association between BMI and upgrading based on Gleason sum was present among Caucasian, but not African American men (overweight OR = 0.90, 95% CI 0.64, 1.28); obese OR=1.01 95% CI 0.69, 1.49) (Table 3).

The association between BMI and upgrading based on Gleason sum groups (Table 4) was consistent with the association for upgrading based on Gleason sum. Being overweight or obese was associated with an increased odds of upgrading to a higher Gleason sum group by 11% or 19%, respectively. As for upgrading based on Gleason sum, BMI was not associated with upgrading based on Gleason sum groups in African-American men, but was positively associated in Caucasian men (Table 5). In the men with information, the results for BMI and upgrading were not notably different when adjusting for number of biopsy cores taken, number of cores with cancer, or the highest percentage of cancer of any core (data not shown). The main results for BMI and upgrading did not differ before and at or after 2005, when the modified Gleason grading system was adopted (data not shown).

Association between BMI and downgrading and upgrading separately in Caucasian and African American men

The multivariable-adjusted association between BMI and downgrading and upgrading separately in Caucasian and African American men is shown in Tables 6 and 7, respectively. Among only Caucasian men, being overweight was associated with increased odds of upgrading one level compared to those with a normal BMI, and marginally significant for upgrading two or more levels. Being overweight was possibly positively associated with downgrading (OR=1.13, 95% CI 0.96, 1.33). Being obese compared to normal BMI was associated with an increased odds of upgrading 1 level by 22% (95% CI 1.07, 1.40) and 2 or more levels by 60% (95% CI 1.14, 2.25).

In African American men, being overweight and obese were inversely associated with downgrading. BMI was not associated with upgrading 1 level, but we could not rule out that BMI was associated with upgrading 2 or more levels.

Association between BMI and downgrading and upgrading separately in Caucasian and African American men with biopsy Gleason sum 6 Prostate Cancer

Tables 8 and 9 show the multivariable-adjusted association between BMI and change in Gleason sum in Caucasian and African-American men with biopsy Gleason 6 disease. In Caucasian men with Gleason 6 disease obesity was inversely associated with downgrading (OR=0.56, 95% CI 0.31, 1.00), while both overweight and obesity were positively associated with upgrading based on Gleason sum. In African American men with Gleason 6 disease, overweight and obesity appeared to be positively associated with upgrading; the number of men who were downgraded was too small to draw conclusions.

Table 10 shows the association between BMI and upgrading among African-American and Caucasian men with clinical tumor stage $\leq T2a$ and PSA < 10 ng/mL. Positive associations between obesity, but not overweight, and upgrading were observed in both racial groups. When additionally restricted to Gleason sum 6 disease, a possible positive association between obesity (compared with combined normal and overweight) and upgrading based on Gleason sum was observed in both racial groups.

Does BMI add to the prediction of upgrading in men with biopsy Gleason sum 6 prostate cancer?

For upgrading based on Gleason sum in Caucasian men with biopsy Gleason sum 6 prostate cancer, the AUC for PSA, clinical tumor stage, age, and year of surgery was 0.6650. When we added BMI, the AUC changed to 0.6652. ROC curves are shown in Figure 2. These results were similar in Caucasian and African American men with biopsy Gleason sum 6 prostate cancer.

DISCUSSION

In this retrospective study of 16,904 men who underwent prostatectomy at Johns Hopkins Hospital in 1993-2014 following a biopsy-confirmed diagnosis of prostate cancer, being overweight or obese was associated with an increased odds of upgrading to a higher Gleason sum. Taking into account factors that are associated with upgrading, overweight men had a 15% increased odds of and obese men had a 25% increased odds of upgrading. Our work may inform treatment decision-making for overweight and obese men newly diagnosed with prostate cancer.

After stratifying into groups based on race, the results for Caucasian men were very similar to results from the entire sample, which was expected since the population under study was 86% Caucasian. However, among African American men no associations between upgrading and the overweight and obese BMI categories were found. Therefore all further analyses were stratified by race to compare the associations between BMI category and upgrading in Caucasian and African American men. No prior studies were found that investigated the association of BMI with upgrading separately within African American men to compare findings.

In multivariable-adjusted multinomial analyses, the odds ratios for overweight and obese BMI categories were stronger for upgrading two or more Gleason sum levels than upgrading one level for both Caucasian and African American men. Interestingly, in multinomial analyses, being overweight appeared to be associated with a decreased odds of downgrading in African American men, an association not seen among Caucasian men. Although the odds ratios did not meet statistical significance, obesity appeared to be associated with a decreased the odds of downgrading Gleason sum in both race groups.

The study by Freedland and colleagues in 2007 had similar findings: being overweight was associated with an increased odds of upgrading between Gleason sum groups by 44% compared to BMI less than 25 and for obese men the odds were 89% higher. (15) These stronger odds ratios may be due to differences in the underlying populations, as their sample had a higher proportion of men with T2 or T3 disease (42% vs. 27%), had higher PSA (median 6.4 vs. 5.4), and worse biopsy Gleason sum (47% with Gleason 7 or higher vs. 30%).

Contrary to our results, a study from Tilki and colleagues in 2011 included BMI as a continuous covariate and did not find an association with upgrading between Gleason sum groups. (8) Of note, their sample was derived from a European cohort, which may have different screening and diagnosis practices than in the United States.

In a study by Vora et al in a population with a high percentage of African American men (37%), they found that each 1 unit increase in BMI was associated with a 3.6% increased odds of upgrading from low risk prostate cancer (p-value=0.02). (16) Another study by Truong and colleagues found that being obese increased odds of upgrading by 90% (p-value=0.047) in another cohort of men with low risk prostate cancer, however, race was not included in multivariable models as their sample was almost entirely Caucasian. (17)

The positive association of higher BMI category with upgrading of Gleason sum or to a higher Gleason sum group is consistent with the hypothesis that upgrading may result from incomplete sampling of the highest graded portion of the tumor. As men with higher BMI tend to have larger prostates, the cores obtained from needle biopsy would represent a smaller percent of the prostate sampled, therefore increasing the chances of missing the worst tumor. (12)

Predictive ability of BMI was explored in a sample of men with biopsy Gleason sum 6 prostate cancer. This population represents men for whom active surveillance may be considered based on previous long-term studies following men for progression of disease and death from prostate cancer. (6-7, 19) Within this sample, obesity compared to normal BMI was associated with an increased odds of upgrading, a relationship not seen in overweight versus normal BMI. When analyses were re-run in the same sample but

only including BMI as a binary variable at the cutoff for obesity (30 kg/m²), Caucasian men experienced a 15% increased odds of upgrading (95% CI: 1.00, 1.32) and obese African American men a 31% increased odds (95% CI: 0.92, 1.87) compared to their non-obese counterparts.

A study by Sundi et al. investigated the association of obesity with worse pathological outcomes at the time of surgery, including increased Gleason sum, higher clinical tumor stage, or positive surgical margins and found that among 87 African American men, obesity was associated with an increased odds of upgrading by 24%, although it failed to reach significance (p-value=0.642) probably due to low sample size. This study also found a huge disparity in the location of the highest grade tumor within the prostate in African Americans compared to Caucasian men. African American men were much more likely to have their worst disease located in the anterior of the prostate, the furthest location from the point of entry for biopsy needles, which may explain in part why they are more likely to upgrade between timepoints compared to Caucasian men. (19)

Addition of BMI to models with PSA, clinical tumor stage, age, and year of surgery did not improve the predictive capacity for upgrading to a higher Gleason sum. The study by Truong and colleagues explored the predictive ability of their multivariable model including PSA density, obesity, number of positive cores, and maximum core involvement in samples of men from the University of Wisconsin, University of Chicago, and University of Miami and found them to have areas under the curve of 0.753, 0.677, and 0.672, respectively. (17)

Due to the large sample size in this study, we were able to stratify analyses on race and investigate the association of higher BMI with upgrading of Gleason sum separately among African American and Caucasian men. Additionally, the large sample size allowed assessment of the relationship within different eras of time over the past 20 years, when the prevalence of overweightness and obesity increased in the United States.

(18)

As this study was performed among men who underwent prostatectomy at Johns Hopkins Hospital, it is limited in its ability to extend findings to settings beyond large, academic cancer centers. Another limitation of the study was the limited information on number of positive cores found during biopsy, which indicates multi-focal prostate cancer, another characteristic that has been found to be associated with upgrading. Maximum percent involvement of any one core was also not considered in the main analyses due to missing data. Although sensitivity analyses were performed to compare the associations with upgrading before and after inclusion of these variables, it is not certain that they do not add important information to models.

Additionally, men with Gleason 6 or lower with other low risk clinical features may not actually represent those eligible for active surveillance because everyone in the study sample underwent prostatectomy and the exact reason why surgery was indicated is not captured on a case-by-case basis. Also, all prediction analyses were performed within the same sample of men, therefore no calibration diagnostics were calculated following ROC curves.

CONCLUSIONS

Overweight and obesity were associated with a higher odds of upgrading of Gleason sum between biopsy and prostatectomy in Caucasian men. In men with low risk prostate cancer, who may be eligible for active surveillance – Gleason 6 prostate cancer with PSA < 10 ng/mL and clinical stage of T1 or T2a – obesity was associated with an increased odds of upgrading in both African American and Caucasian men. Our work may inform treatment decision-making for overweight and obese men, including African American obese men, newly diagnosed with prostate cancer.

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TABLES

Table 1. Demographic and clinical characteristics of men who underwent prostate biopsy and radical prostatectomy, 1993-2014, Johns Hopkins Hospital.

		Body Mass Index Categories			
Characteristic	Total n=16,904	Normal n=4,417	Overweight n=9,332	Obese n=3,155	p-value
Age at diagnosis, mean (SD)	58 (6.6)	59 (6.9)	58 (6.5)	57 (6.4)	<0.001
Race					<0.001
	Caucasian	3,850 (87%)	8,022 (86%)	2,622 (83%)	
	African-American	266 (6%)	848 (9%)	409 (13%)	
	Other	301 (7%)	462 (5%)	124 (4%)	
Clinical Tumor Stage					0.652
	Any T1	3,192 (72%)	6,783 (73%)	2,283 (72%)	
	T2a	884 (19%)	1,746 (19%)	582 (19%)	
	T2b	303 (7%)	644 (7%)	231 (7%)	
	T2c	62 (1%)	118 (1%)	46 (1%)	
	Any T3	16 (<1%)	41 (<1%)	13 (<1%)	
Pre-surgery PSA, mean (SD)	6.7 (5.1)	6.5 (5.0)	6.7 (5.2)	6.7 (5.0)	0.033
Year of Surgery, mean (SD)	2004 (5.9)	2003 (6.0)	2004 (5.8)	2005 (5.8)	<0.001
Biopsy Gleason Sum					<0.001
	2 - 5	88 (2%)	138 (1%)	42 (1%)	
	6	3,063 (69%)	6,370 (68%)	2,037 (65%)	
	3+4	799 (18%)	1,710 (18%)	620 (20%)	
	4+3	293 (7%)	659 (7%)	270 (9%)	
	8	113 (3%)	312 (3%)	119 (4%)	
	9	60 (1%)	142 (2%)	66 (2%)	
Change in Gleason Sum					0.617
	Any Downgrade	338 (8%)	760 (8%)	224 (7%)	
	No Change	3,193 (72%)	6,539 (70%)	2,222 (70%)	Ref
	Any Upgrade	886 (20%)	2,033 (22%)	709 (23%)	0.016
Change in Gleason Group					0.937
	Downgrade	324 (8%)	678 (8%)	215 (7%)	
	No Change	2,971 (70%)	6,021 (68%)	1,989 (67%)	Ref
	Upgrade	948 (22%)	2,177 (24%)	765 (26%)	0.001

Table 2. Unadjusted and multivariable-adjusted associations between BMI categories and upgrading of Gleason sum from biopsy to prostatectomy, 1993-2014, Johns Hopkins Hospital.				
Upgrade in Gleason Sum (n=15,582)				
Variable		n (# upgrade)	Univariable OR (95% CI)	Multivariable* OR (95% CI)
BMI Category	Normal	4,079 (886)	Reference	Reference
	Overweight	8,572 (2,033)	1.12 (1.02, 1.23)	1.14 (1.03, 1.25)
	Obese	2,931 (709)	1.15 (1.03, 1.29)	1.24 (1.10, 1.39)
			p-trend = 0.016	p-trend < 0.001
Race	Caucasian	13,372 (3,044)	Reference	Reference
	African-American	1,381 (378)	1.28 (1.13, 1.45)	1.38 (1.20, 1.57)
	Other	829 (206)	1.12 (0.95, 1.32)	1.19 (1.01, 1.42)
Clinical Tumor Stage	T1	11,341 (2,512)	Reference	Reference
	T2a	2,889 (726)	1.18 (1.07, 1.30)	1.58 (1.43, 1.75)
	T2b	1,084 (302)	1.36 (1.18, 1.56)	1.95 (1.68, 2.28)
	T2c	204 (70)	1.84 (1.37, 2.46)	2.27 (1.65, 3.13)
	T3	64 (18)	1.38 (0.80, 2.38)	2.34 (1.28, 4.30)
Biopsy Gleason Sum			0.44 (0.40, 0.47)	0.31 (0.28, 0.34)
Pre-surgery PSA, log ₂			1.47 (1.40, 1.53)	1.61 (1.54, 1.69)
Age at Surgery			1.03 (1.02, 1.03)	1.04 (1.03, 1.04)
Year of Surgery			0.98 (0.97, 0.98)	1.02 (1.01, 1.03)

*Adjusted for all presented variables.

Upgrade in Gleason Sum			
Variable	Caucasian (n=13,372) n (# outcome)	OR (95% CI)	African-American (n=1,381) n (# outcome) OR (95% CI)
BMI Category			
Normal	3,569 (762)	Reference	231 (64) Reference
Overweight	7,362 (1,704)	1.13 (1.03, 1.25)	779 (211) 0.90 (0.64, 1.28)
Obese	2,441 (578)	1.26 (1.10, 1.43) p-trend = 0.001	371 (103) 1.01 (0.69, 1.49) p-trend = 0.770
Clinical Tumor Stage			
T1	9,599 (2,053)	Reference	1,103 (304) Reference
T2a	2,550 (638)	1.65 (1.48, 1.84)	201 (50) 0.99 (0.69, 1.44)
T2b	983 (274)	2.06 (1.75, 2.42)	59 (17) 1.08 (0.57, 2.09)
T2c	182 (62)	2.34 (1.67, 3.29)	17 (7) 3.09 (1.05, 9.04)
T3	58 (17)	2.46 (1.31, 4.62)	1 (0) omitted
Biopsy Gleason Sum		0.31 (0.28, 0.35)	0.24 (0.18, 0.33)
Pre-surgery PSA, log2		1.62 (1.54, 1.70)	1.52 (1.31, 1.76)
Age at Surgery		1.03 (1.03, 1.04)	1.04 (1.02, 1.06)
Year of Surgery		1.02 (1.01, 1.03)	1.00 (0.97, 1.02)

*Adjusted for all presented variables.

Upgrade in Gleason Sum Group (n=14,871)			
Variable	n (# upgrade)	Univariable OR (95% CI)	Multivariable* OR (95% CI)
BMI Category			
Normal	3,919 (948)	Reference	Reference
Overweight	8,198 (2,177)	1.13 (1.04, 1.24)	1.11 (1.01, 1.21)
Obese	2,754 (765)	1.21 (1.08, 1.35)	1.19 (1.06, 1.33)
		p-trend = 0.001	p-trend = 0.004
Race			
Caucasian	12,821 (3,241)	Reference	Reference
African-American	1,283 (426)	1.47 (1.30, 1.66)	1.41 (1.24, 1.61)
Other	767 (223)	1.21 (1.03, 1.42)	1.18 (1.00, 1.39)
Clinical Tumor Stage			
T1	10,988 (2,670)	Reference	Reference
T2a	2,706 (787)	1.28 (1.16, 1.40)	1.52 (1.37, 1.68)
T2b	953 (345)	1.77 (1.54, 2.03)	1.91 (1.64, 2.21)
T2c	177 (68)	1.94 (1.43, 2.64)	1.84 (1.34, 2.52)
T3	47 (20)	2.31 (1.29, 4.12)	2.28 (1.24, 4.21)
Biopsy Gleason Sum			
		1.29 (1.19, 1.40)	0.92 (0.84, 1.00)
Pre-surgery PSA, log ₂		1.62 (1.55, 1.69)	1.63 (1.56, 1.71)
Age at Surgery		1.04 (1.03, 1.04)	1.03 (1.03, 1.04)
Year of Surgery		1.01 (1.00, 1.02)	1.03 (1.02, 1.03)

*Adjusted for all presented variables.

Upgrade in Gleason Sum Groups				
Variable	Caucasian (n=12,821)		African-American (n=1,282)	
	n (# outcome)	OR (95% CI)	n (# outcome)	OR (95% CI)
BMI Category				
Normal	3,450 (806)	Reference	211 (73)	Reference
Overweight	7,069 (1,819)	1.12 (1.02, 1.24)	731 (233)	0.87 (0.62, 1.21)
Obese	2,302 (616)	1.20 (1.06, 1.37)	341 (120)	1.06 (0.73, 1.53)
		p-trend = 0.004		p-trend = 0.479
Clinical Tumor Stage				
T1	9,348 (2,162)	Reference	1,035 (342)	Reference
T2a	2,402 (686)	1.58 (1.42, 1.75)	186 (59)	1.00 (0.70, 1.41)
T2b	868 (314)	2.02 (1.73, 2.36)	49 (19)	1.12 (0.61, 2.07)
T2c	160 (61)	1.89 (1.35, 2.64)	12 (6)	2.10 (0.65, 6.74)
T3	43 (18)	2.18 (1.15, 4.14)	1 (0)	omitted
Biopsy Gleason Sum		0.93 (0.85, 1.03)		0.75 (0.57, 0.99)
Pre-surgery PSA, log2		1.65 (1.57, 1.74)		1.44 (1.25, 1.66)
Age at Surgery		1.03 (1.03, 1.04)		1.05 (1.03, 1.07)
Year of Surgery		1.03 (1.02, 1.03)		1.01 (0.99, 1.04)

*Adjusted for all presented variables.

Table 6. Multivariable-adjusted association* between BMI and change in Gleason sum in Caucasian men, 1993-2014, Johns Hopkins Hospital.						
Change in Gleason sum among Caucasian men (n=14,494)						
Variable	n	#	Downgrading (n=1,122) OR (95% CI)	Upgrading 1 level (n=2,713) # OR (95% CI)	Upgrading 2 or more levels (n=331) # OR (95% CI)	
BMI Category						
Normal	3,850	281	Reference	Reference	73	Reference
Overweight	8,022	660	1.13 (0.96, 1.33)	1,517 1.12 (1.01, 1.24)	187	1.29 (0.98, 1.71)
Obese	2,622	181	0.82 (0.66, 1.02)	507 1.22 (1.07, 1.40)	71	1.60 (1.14, 2.25)
			p-trend = 0.093	p-trend = 0.003		p-trend = 0.006
Tumor Stage					209	Reference
T1	10,361	762	Reference	Reference	61	1.61 (1.19, 2.17)
T2a	2,798	248	0.84 (0.71, 0.99)	577 1.65 (1.47, 1.85)	49	3.49 (2.48, 4.92)
T2b	1,068	85	0.44 (0.33, 0.58)	225 1.90 (1.60, 2.26)	9	2.95 (1.44, 6.04)
T2c	203	21	0.64 (0.38, 1.09)	53 2.21 (1.55, 3.15)	3	3.34 (0.97, 11.49)
T3	64	6	0.16 (0.06, 0.46)	14 2.32 (1.19, 4.52)		
Biopsy Gleason Sum			4.67 (4.24, 5.13)	0.29 (0.26, 0.33)		0.34 (0.27, 0.43)
Pre-surgery PSA, log2			0.81 (0.76, 0.88)	1.56 (1.48, 1.65)		2.10 (1.84, 2.39)
Age at Surgery			1.01 (1.00, 1.02)	1.03 (1.03, 1.04)		1.05 (1.03, 1.07)
Year of Surgery			0.96 (0.94, 0.97)	1.02 (1.01, 1.03)		1.03 (1.01, 1.05)

*From a multinomial logistic regression model and adjusted for all presented variables.

Table 7. Multivariable-adjusted association* between BMI and change in Gleason sum in African-American men, 1993-2014, Johns Hopkins Hospital.

Change in Gleason sum among African American men (n=1,523)						
Variable	n	Downgrading (n=142)		Upgrading 1 level (n=347)		Upgrading 2 or more levels (n=31)
		#	OR (95% CI)	#	OR (95% CI)	# OR (95% CI)
BMI Category	266	35	Reference	60	Reference	4 Reference
Normal	848	69	0.56 (0.34, 0.91)	192	0.84 (0.59, 1.21)	19 1.28 (0.43, 3.86)
Overweight	409	38	0.62 (0.35, 1.08)	95	0.98 (0.66, 1.45)	8 1.24 (0.36, 4.22)
Obese			p-trend = 0.179		p-trend = 0.817	p-trend = 0.826
Tumor Stage	1,214	111	Reference	281	Reference	23 Reference
T1	233	22	0.77 (0.44, 1.35)	45	0.98 (0.66, 1.43)	5 1.36 (0.49, 3.73)
T2a	67	8	0.79 (0.33, 1.91)	15	1.04 (0.52, 2.04)	2 1.55 (0.33, 7.15)
T2b	18	1	0.51 (0.06, 4.46)	6	2.79 (0.91, 8.54)	1 4.28 (0.49, 37.64)
T2c	1	0	omitted	0	omitted	0 omitted
T3			4.76 (3.64, 6.24)		0.21 (0.15, 0.29)	0.35 (0.16, 0.77)
Biopsy Gleason Sum			0.83 (0.66, 1.04)		1.48 (1.27, 1.73)	2.13 (1.43, 3.18)
Pre-surgery PSA, log2			0.99 (0.96, 1.02)		1.04 (1.02, 1.06)	1.05 (1.00, 1.11)
Age at Surgery			0.95 (0.91, 0.98)		0.99 (0.97, 1.02)	1.03 (0.96, 1.1)
Year of Surgery						

*From a multinomial logistic regression model and adjusted for all presented variables.

Table 8. Multivariable-adjusted association* between BMI and change in Gleason sum in Caucasian men with biopsy Gleason 6 disease, 1993-2014, Johns Hopkins Hospital.						
Change from Gleason sum 6 among Caucasian men (n=9,977)						
Variable		n	Downgrading (n=181)		Upgrading (n=2,437)	
			#	OR (95% CI)	#	OR (95% CI)
BMI Category	Normal	2,707	55	Reference	614	Reference
	Overweight	5,555	111	1.13 (0.81, 1.57)	1,379	1.11 (0.99, 1.24)
	Obese	1,715	15	0.56 (0.31, 1.00)	444	1.19 (1.03, 1.38)
			p-trend = 0.126		p-trend = 0.016	
Clinical Tumor Stage	T1	7,676	137	Reference	1,739	Reference
	T2a	1,691	34	0.85 (0.57, 1.26)	473	1.74 (1.53, 1.97)
	T2b	493	6	0.43 (0.18, 0.98)	175	2.25 (1.83, 2.76)
	T2c	94	4	1.53 (0.53, 4.38)	40	2.68 (1.73, 4.16)
	T3	23	0	zero #	10	2.96 (1.22, 7.19)
Pre-surgery PSA, log2			0.90 (0.77, 1.05)		1.77 (1.67, 1.88)	
Age at Surgery			1.01 (0.99, 1.03)		1.04 (1.03, 1.05)	
Year of Surgery			0.84 (0.81, 0.87)		1.04 (1.03, 1.05)	

*From a multinomial logistic regression model and adjusted for all presented variables.

Table 9. Multivariable-adjusted association* between BMI and change in Gleason sum in African-American men with biopsy Gleason 6 disease, 1993-2014, Johns Hopkins Hospital.						
Change from Gleason sum 6 among African American men (n=920)						
Variable		n	Downgrading (n=8)		Upgrading (n=314)	
			#	OR (95% CI)	#	OR (95% CI)
BMI Category	Normal	152	1	Reference	53	Reference
	Overweight	527	6	2.19 (0.25, 19.52)	171	1.18 (0.57, 1.26)
	Obese	241	1	0.79 (0.05, 13.23)	90	1.15 (0.74, 1.79)
			p-trend = 0.756		p-trend = 0.286	
Clinical Tumor Stage	T1	769	7	Reference	259	Reference
	T2a	120	1	0.59 (0.07, 5.04)	40	1.10 (0.71, 1.70)
	T2b	25	0	zero #	11	1.48 (0.63, 3.47)
	T2c	6	0	zero #	4	3.92 (0.68, 22.69)
	T3	0	0	omitted	0	omitted
Pre-surgery PSA, log2			0.89 (0.43, 1.86)		1.77 (1.48, 2.12)	
Age at Surgery			1.13 (1.00, 1.27)		1.05 (1.02, 1.07)	
Year of Surgery			0.84 (0.72, 0.98)		1.03 (1.00, 1.06)	

*From a multinomial logistic regression model and adjusted for all presented variables.

Table 10. Multivariable-adjusted association* between BMI and upgrading in Caucasian and African-American men with clinical tumor stage \leq T2a and PSA<10 ng/mL, 1993-2014, Johns Hopkins Hospital.				
Upgrading from Gleason sum 6 among Caucasian men with \leqT2a and PSA<10 ng/mL (n=8,366)				
Variable		n	Upgrading (n=1,817) # OR (95% CI)	
BMI Category	Normal	2,276	464	Reference
	Overweight	4,662	1,020	1.06 (0.93, 1.20)
	Obese	1,428	333	1.19 (1.01, 1.41)
				p-trend = 0.035
Clinical Tumor Stage	T1	6,856	1,447	Reference
	T2a	1,510	370	1.57 (1.37, 1.80)
Pre-surgery PSA				1.20 (1.16, 1.23)
Age at Surgery				1.04 (1.03, 1.05)
Year of Surgery				1.05 (1.04, 1.06)
Upgrading from Gleason sum 6 among African American men with \leqT2a and PSA<10 ng/mL (n=763)				
Variable		n	Upgrading (n=233) # OR (95% CI)	
BMI Category	Normal	124	37	Reference
	Overweight	438	128	0.91 (0.58, 1.42)
	Obese	201	68	1.22 (0.74, 2.00)
				p-trend = 0.265
Clinical Tumor Stage	T1	663	204	Reference
	T2a	100	29	0.99 (0.61, 1.61)
Pre-surgery PSA				1.21 (1.12, 1.32)
Age at Surgery				1.04 (1.02, 1.06)
Year of Surgery				1.03 (1.00, 1.06)

*Adjusted for all presented variables

Table 11. Multivariable-adjusted association* between BMI and upgrading in Caucasian and African-American men with biopsy Gleason sum 6 disease, clinical tumor stage \leq T2a, and PSA<10 ng/mL, 1993-2014, Johns Hopkins Hospital.				
Upgrading from Gleason sum 6 among Caucasian men with \leq T2a and PSA<10ng/mL (n=8,366)				
Variable		n	Upgrading (n=1,817) # OR (95% CI)	
BMI Category**	Not obese	6,938	1,484	Reference
	Obese	1,428	333	1.15 (1.00, 1.32)
Clinical Tumor Stage	T1	6,856	1,447	Reference
	T2a	1,510	370	1.57 (1.37, 1.80)
Pre-surgery PSA				1.20 (1.16, 1.23)
Age at Surgery				1.04 (1.03, 1.05)
Year of Surgery				1.05 (1.04, 1.06)
Upgrading from Gleason sum 6 among African American men with \leq T2a and PSA<10ng/mL (n=763)				
Variable		n	Upgrading (n=233) # OR (95% CI)	
BMI Category**	Not Obese	562	165	Reference
	Obese	201	68	1.31 (0.92, 1.87)
Clinical Tumor Stage	T1	663	204	Reference
	T2a	100	29	0.99 (0.61, 1.61)
Pre-surgery PSA				1.21 (1.12, 1.31)
Age at Surgery				1.04 (1.02, 1.06)
Year of Surgery				1.03 (0.99, 1.06)

*Adjusted for all presented variables

**Due to smaller sample size BMI categories normal and overweight were combined.

FIGURES

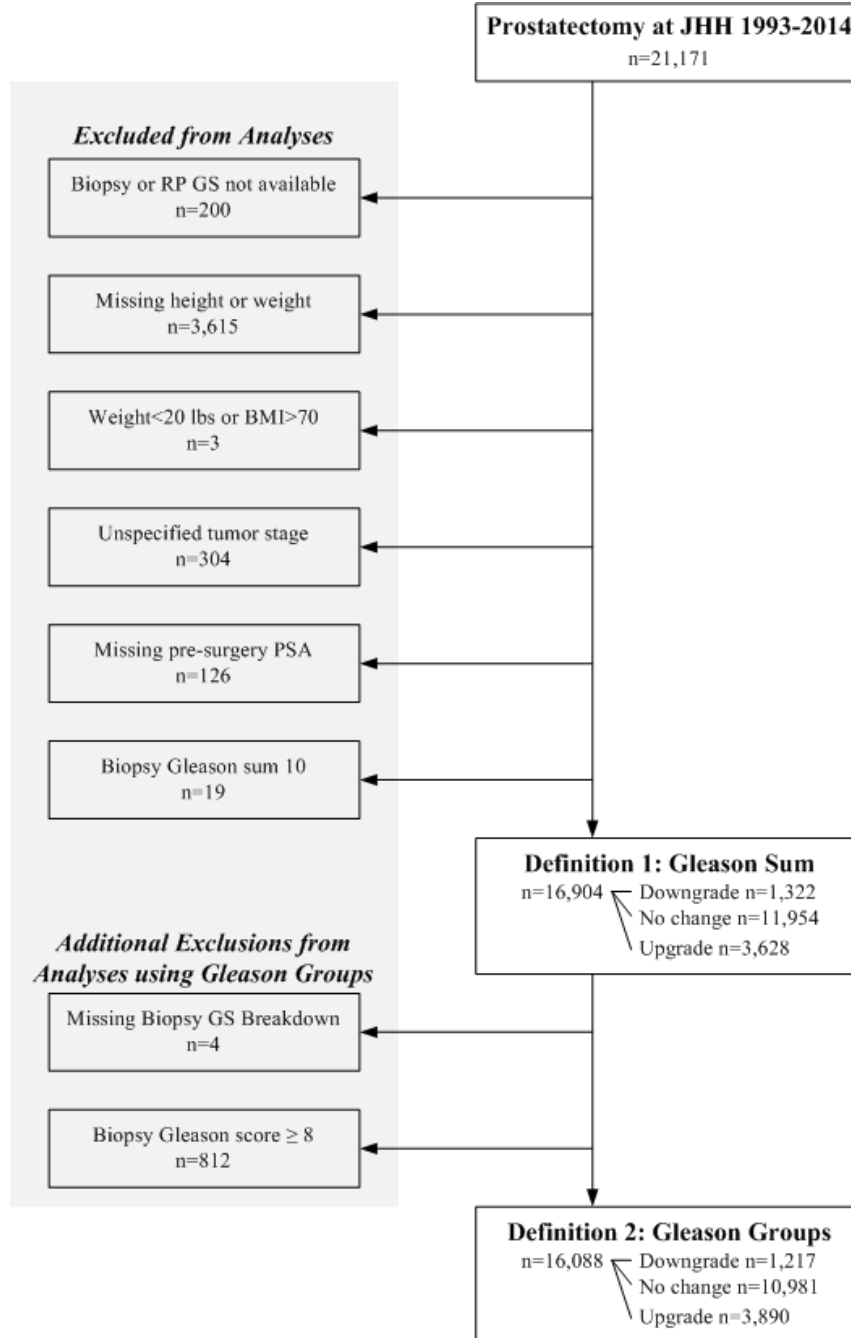


Figure 1. Inclusion and exclusion of subjects in analyses, 1993-2014, Johns Hopkins Hospital.

Abbreviations: JHH, Johns Hopkins Hospital; RP, radical prostatectomy; GS, Gleason sum; lbs, pounds; BMI, body mass index; PSA, prostate-specific antigen.

This figure shows the numbers and reasons for exclusion from analyses using each definition of Gleason sum upgrading.

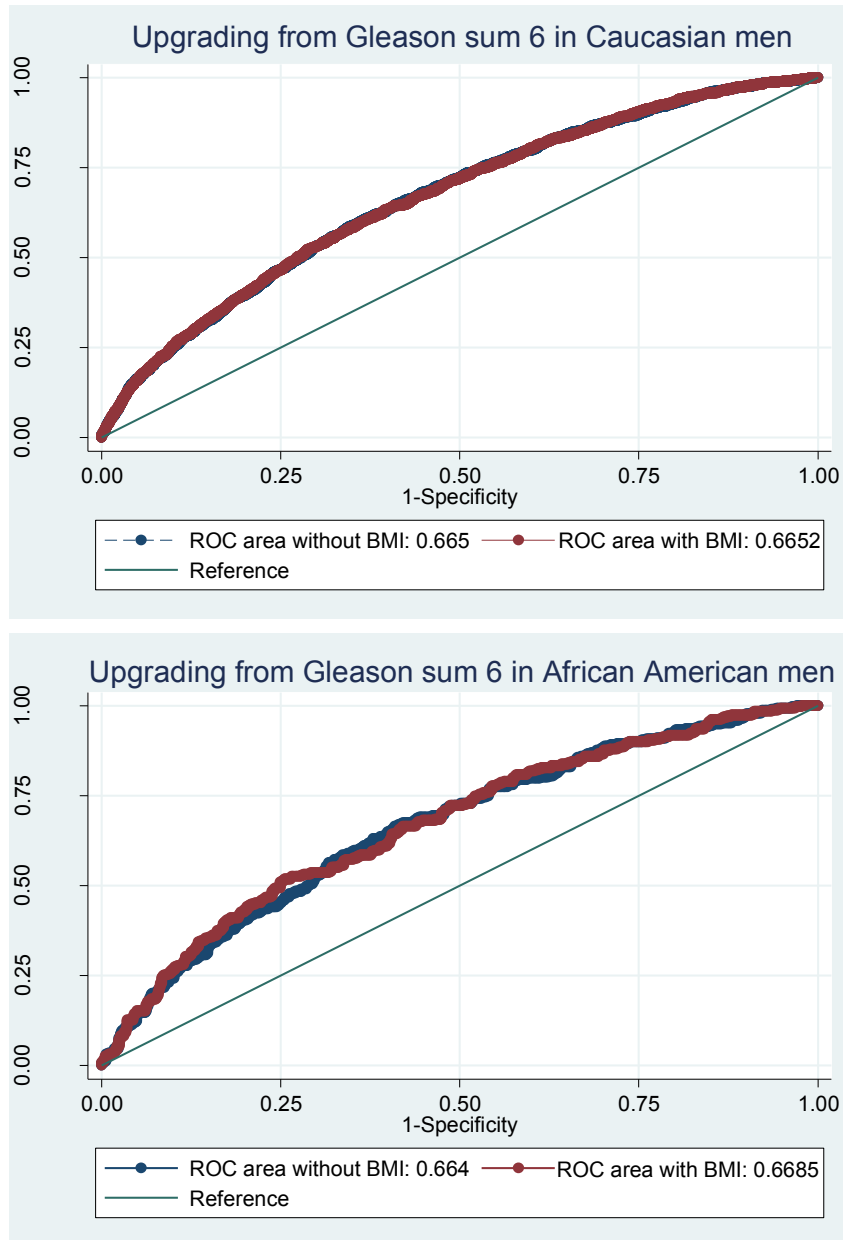


Figure 2. Receiver operating characteristic curves for men with Gleason sum 6 prostate cancer in Caucasian and African American men, 1993-2014, Johns Hopkins Hospital. Models including age, year of surgery, pre-surgery PSA, and clinical tumor stage, with and without BMI are compared. Areas under each curve are displayed in the legend.

APPENDIX

The percentage of obese men in the sample increased from 9.9% in 1993 to 26.7% in 2014 (Figure 3, next page). A complementary decrease was observed in the proportion of men with BMI less than 25 from 34% to 23% over the same period. Trends over time were also observed in the proportion of men with Gleason 6 prostate cancer, which appears to increase in the sample over the first 5 years to 80%, then decrease to less than 50% more recently. Since 2000, only 17 men have had prostatectomies for prostate cancers graded with a combined Gleason sum of 5 or less within the sample. As such, the proportions of men with Gleason 7 or higher prostate cancers increased gradually over the course of study. Over time, the proportion of men with T1 disease in the sample has increased as by definition these cancers are not felt during DRE or seen with ultrasound. As expected, the percentages of men with T2 or T3 prostate cancers have decreased over the period during which PSA screening has become popular. Lastly in Figure 3, there have been no stark changes in median PSA but the variability appears to be lower from 2001 to 2014.

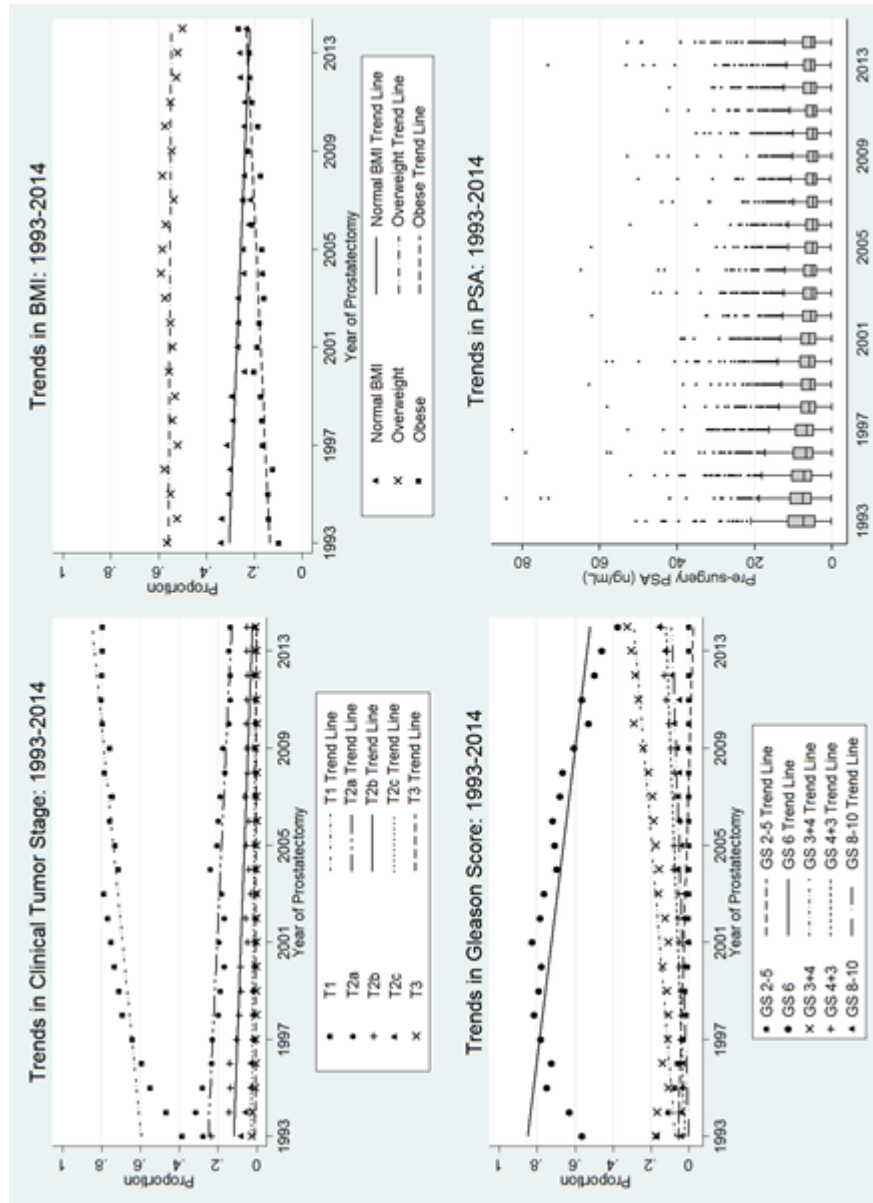


Figure 3. Trends in the proportions of selected characteristics over time, 1993-2014, Johns Hopkins Hospital.

The proportion of men of normal weight decreases over time, as does those diagnosed with Gleason sum 6 prostate cancer. The proportion of men with stage T1 disease increases after the advent of PSA screening while mean PSA appears stable over time.

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