Title

Abstract 880: Obesity predicts prostate cancer-specific mortality after radical prostatectomy: Results from the SEARCH database

Journal

Cancer Research, 75(15_Supplement)

ISSN

0008-5472

Authors

Vidal, Adriana C
Howard, Lauren E
Cooperberg, Matthew R
et al.

Publication Date

2015-08-01

DOI

10.1158/1538-7445.am2015-880

Peer reviewed

Published in final edited form as:
BJU Int. 2012 August ; 110(4): 492–498. doi:10.1111/j.1464-410X.2011.10754.x.

Obesity is associated with castration-resistant disease and metastasis in men treated with androgen deprivation therapy after radical prostatectomy: results from the SEARCH database

Christopher J. Keto, **William J. Aronson**[*], **Martha K. Terris**[†], **Joseph C. Presti**[‡], **Christopher J. Kane**[§], **Christopher L. Amling**[¶], and **Stephen J. Freedland**

Duke University School of Medicine and Veterans Affairs Medical Center, Durham, NC

[*]University of California at Los Angeles Medical Center and Veterans Affairs Medical Center, Los Angeles

[‡]Stanford University Medical Center and Veterans Affairs Medical Center, Palo Alto

[§]University of California at San Diego, San Diego, CA

[†]Medical College of Georgia and Veterans Affairs Medical Center, Augusta, GA

[¶]Oregon Health and Science University, Portland, OR, USA

Abstract

OBJECTIVE—

- To investigate whether obesity predicts poor outcomes in men starting androgen deprivation therapy (ADT) before metastasis, since previous studies found worse outcomes after surgery and radiation for obese men.

METHODS—

- A retrospective review was carried out of 287 men in the SEARCH database treated with radical prostatectomy between 1988 and 2009.
- Body mass index (BMI) was categorized to <25, 25–29.9 and ≥30 kg/m2.
- Proportional hazards models were used to test the association between BMI and time to castration-resistant prostate cancer (PC), metastases and PC-specific mortality adjusting for demographic and clinicopathological data.

RESULTS—

- During a median 73-month follow-up after radical prostatectomy, 403 men (14%) received early ADT.
- Among 287 men with complete data, median BMI was 28.3 kg/m2.
- Median follow-up from the start of ADT was 52 months during which 44 men developed castration-resistant PC, 34 developed metastases and 24 died from PC.

Correspondence: Stephen J. Freedland, MD, Division of Urology, DUMC, Box 2626, Duke University School of Medicine, Durham, NC 27710, USA. steve.freedland@duke.edu.

CONFLICT OF INTEREST
None declared.

- In multivariate analysis, higher BMI was associated with a trend for greater risk of progression to castration-resistant PC ($P = 0.063$), a more than threefold increased risk of developing metastases ($P = 0.027$) and a trend toward worse PC-specific mortality ($P = 0.119$).
- Prognostic biomarkers did not differ between BMI groups.

CONCLUSIONS—

- Among men treated with early ADT, our results suggest that obese men may have increased risk of PC progression.
- These data support the general hypothesis that obesity is associated with aggressive PC, although validation of these findings and further study of the mechanisms linking obesity and poor PC outcomes are required.

Keywords

obesity; prostate cancer; androgen deprivation therapy; castration-resistant prostate cancer; metastases

INTRODUCTION

In the USA obesity prevalence is 32% for adult men [1], while in Europe obesity ranges from 13–24% for men and women [2]. Some studies found higher adult body mass index (BMI) was associated with increased prostate cancer (PC) risk [3,4] whereas others found no increased risk [5]. Multiple recent large studies suggest higher BMI is associated with lower diagnosis risk, although a higher risk of high grade PC [6,7]. Furthermore, several studies found that obese men undergoing radical prostatectomy (RP) have higher rates of biochemical recurrence [8,9]. Finally, among men with PC, obesity is correlated with higher PC-specific mortality (PCSM) [10,11].

While the impact of obesity on primary treatment outcomes has been studied including previous studies by our group [8,12], no study has examined the influence of obesity on outcomes after secondary treatment. Beyond the general association between obesity and aggressive PC, there is reason to think that obese men undergoing androgen deprivation therapy (ADT) in particular may have poor outcomes. One small study found obese men on continuous leuprolide had higher post-ADT free and total testosterone levels than normal weight men [13]. Recent evidence suggests higher testosterone levels on ADT may correlate with poor cancer-specific outcomes [14,15]. We hypothesized that obese men treated with ADT are more likely to progress to castration-resistant PC (CRPC), develop metastases and die of PC. To test this, we investigated whether obesity predicted PC-specific outcomes in men treated with early ADT after RP.

METHODS

STUDY POPULATION

After obtaining institutional review board approval from each institution, data from men who underwent RP from 1988 to 2009 at five Veterans Affairs Hospitals in the USA (West Los Angeles, CA, Palo Alto, CA, Augusta, GA, Asheville, NC, and Durham, NC) were combined into the SEARCH database [16]. Men treated with preoperative ADT or radiotherapy were excluded. We identified 403 men treated with ADT in the SEARCH database prior to the onset of metastases (i.e. early ADT). Of these 403 men, we excluded men with missing data for BMI at the time of ADT ($n = 87$), pre-ADT PSA ($n = 31$), extracapsular extension ($n = 13$), Gleason score ($n = 7$), seminal vesicle invasion ($n = 11$)

and margin status ($n = 11$), resulting in 287 eligible men treated with continuous ADT after RP.

Height and weight were obtained from progress notes within 1 year prior to ADT. BMI was categorized as <25 kg/m^2, normal; 25–29.9 kg/m^2, overweight; and ≥30 kg/m^2, obese. CRPC was defined using the two Prostate Cancer Working Group criteria: a 25% PSA increase from the ADT PSA nadir *and* a PSA increase ≥2 ng/mL [17]. Metastases were determined by review of radiology reports and clinical notes. Pre-ADT PSA was defined as the PSA closest to but prior to starting ADT (up to 1 year prior). PCSM was defined as death in any patient with metastases showing progression following ADT. Pre-ADT PSA doubling time (PSADT) was calculated using PSA values according to the Prostate Specific Antigen Working Group criteria [18]. All men were required to have three values or more ≥0.2 ng/mL with at least 1 month separating each value. To calculate PSADT, we divided the natural log of 2 by the slope of the linear regression line of the natural log of PSA over 2 years of time prior to starting ADT. The PSA nadir during ADT was defined as the lowest PSA measurement during ADT.

STATISTICAL ANALYSIS

We compared baseline characteristics across BMI categories using the chi-squared test for categorical data and the Kruskal –Wallis test for continuous variables. Proportional hazards models were used to test whether obesity independently predicted progression to CRPC, metastases or PCSM. ADT start was used as time zero. We adjusted for calendar year of ADT, surgical centre, race (black vs non-black), age at ADT start, pathological Gleason (2–6, 3 + 4 and ≥4 + 3), extracapsular extension, seminal vesicle invasion, margin status, lymph node metastases (yes, no, not performed) and absolute PSA at ADT (continuous, logarithmically transformed). PSA nadir on ADT was not included as this information is unavailable when initiating ADT and we sought to assess whether obesity influences outcomes *after* ADT. We did not adjust for pre-ADT PSADT as this information was missing for 132 men. All analyses were performed using Stata, version 11.0 (Stata Corp, College Station, TX, USA), and $P < 0.05$ was considered significant.

RESULTS

Median follow-up after RP was 73 months and median follow-up after ADT was 52 months (interquartile range 31–83 months). Of the 287 men, 44 progressed to CRPC, 34 developed metastases and 24 died from PC. A total of 67 men (23%) were normal weight, 120 (42%) were overweight and 100 (35%) were obese (Table 1). Median BMI at ADT start was 28.3 kg/m^2. There were no significant differences across BMI groups in age, race or pathological features. Also, obese and overweight men vs normal weight men had similar values for pre-ADT PSA ($P = 0.163$), pre-ADT PSADT ($P = 0.428$) and PSA nadir on ADT ($P = 0.06$). Overweight and obese men had higher Gleason grade tumours ($P = 0.007$).

Five-year non-PC survival after starting ADT did not differ by BMI (Fig. 1, log-rank $P = 0.540$). In unadjusted analysis, higher BMI was associated with greater risk of CRPC (Fig. 2, log-rank $P = 0.017$). On multivariate analysis, higher BMI remained associated with a trend for greater risk of progression to CRPC ($P = 0.063$), although this was not significant (Table 2). Overweight and obese men were more than threefold more likely to progress to CRPC than normal weight men (Table 2). Additionally, seminal vesicle invasion (hazard ratio [HR] 2.79, $P = 0.002$) and higher pre-ADT PSA (HR 2.33, $P < 0.001$) independently predicted progression to CRPC (Table 2). No other clinicopathological characteristics were related to CRPC.

In unadjusted (Fig. 3, log-rank $P = 0.041$) and adjusted analyses (Table 3, $P = 0.027$), higher BMI was significantly related to greater risk of metastases. Overweight and obese men were more than threefold and fivefold more likely to develop metastases than normal weight men. Seminal vesicle invasion (HR = 2.39, $P = 0.025$) and higher pre-ADT PSA (HR = 2.24, $P < 0.001$) also independently predicted metastases. Metastases were not significantly associated with other clinicopathological features.

In unadjusted analysis, higher BMI was associated with greater risk of PCSM (Fig. 4, log-rank $P = 0.023$). On multivariate analysis, higher BMI remained associated with greater risk of PCSM, although the number of PC deaths was modest ($n = 24$), and this did not reach significance (Table 4, $P = 0.119$). The only significant independent predictors of PCSM were seminal vesicle invasion (HR = 2.54, $P = 0.041$) and higher pre-ADT PSA (HR = 1.82, $P = 0.025$). No other clinicopathological features significantly predicted PCSM.

DISCUSSION

Many studies found that obesity was associated with more aggressive PC and worse PC-specific outcomes [6–11,19], although some studies did not find this association [20]. Whether obesity specifically increases the progression risk after starting ADT has not been addressed. We hypothesized that obese men treated with early ADT after RP would be more likely to progress to CRPC, metastases and PCSM. To test this hypothesis, we analysed the risk of PC-specific outcomes after initiating ADT in the SEARCH cohort. We found obese men had significantly increased risk of CRPC, metastases and PCSM on unadjusted analyses. On multivariate analyses, obesity remained associated with CRPC, metastases and PCSM, although the association with CRPC and PCSM approached, but did not reach, significance. Moreover, all-cause mortality was unrelated to BMI, suggesting obesity was explicitly associated with poor cancer-specific outcomes. These findings suggest that obese men receiving early ADT after RP represent a high risk group and should be considered for clinical trials.

Obesity is associated with a decreased risk of PC diagnosis, but in contrast is associated with larger tumours and high grade disease [6,7]. Moreover, obese men treated with RP are more likely to have PSA recurrence [8,9,19]. Several studies of men treated with primary external radiotherapy found obesity predicted increased risk for recurrence and metastases [11,21]. Moreover, multiple studies found obese men have increased PCSM [10,11]. What remained unexamined to date is the association between obesity and outcomes after ADT. In line with the above studies showing obesity is associated with aggressive PC in general, we found obese men treated with early ADT after RP had higher risks of CRPC, metastases and PCSM.

There are several reasons why we hypothesized obese men would have worse outcomes. First, ADT may be inadequate in obese men due to an increased volume of drug distribution resulting in lower blood/tissue concentrations, which may be insufficient to fully suppress testosterone secretion and result in inadequate castration relative to a normal weight man. A previous study found obese men treated with continuous leuprolide have higher testosterone at 24 and 48 weeks vs normal weight men [13]. Other studies showed men with higher post-ADT testosterone levels have worse PC-specific outcomes [14,15]. Second, perhaps tumours in obese men are primed for ADT resistance. Given obesity is associated with lower testosterone levels prior to ADT, it is plausible that these tumours are selected to be more aggressive and grow in this low testosterone environment and thus are less affected by ADT. Multiple studies found men with low testosterone at presentation have more aggressive PC [22,23]. Third, alternative growth factors associated with obesity, like insulin, IGF-1 and leptin, have all been associated with PC [20]. Specifically, leptin produced by adipocytes

stimulates growth of androgen-independent, but not androgen-sensitive, PC cells *in vitro* [20]. IGF-1 also stimulates the growth of both androgen-independent and androgen-sensitive cells [20].

When evaluating PC outcomes, it is always important to think in terms of competing risks. As such, it is noteworthy that, on a population level among otherwise 'healthy' individuals, men with a BMI of ~27 kg/m^2 have better overall survival than normal weight individuals [24]. In our cohort of US veterans, median BMI at ADT start was 28.3 kg/m^2. Thus, the classically defined normal weight group (i.e. BMI < 25 kg/m^2) was abnormal for our cohort. We were concerned that in this cohort of older men ' normal' weight may be associated with significant pre-existing comorbidities and possibly shortened overall survival and thus that these men were not living long enough to experience adverse PC outcomes due to increased mortality from competing risks. However, in our cohort, non-PC survival was independent of BMI (log-rank = 0.540) implying that all BMI groups had equal non-PC survival and equal opportunity for PC progression (Fig. 1). Smith *et al.* previously also showed similar all-cause mortality across BMI groups [11]. Thus, this cannot explain the poor cancer-specific outcomes among obese men.

Pre-ADT PSA, pre-ADT PSADT and PSA nadir during ADT are well-known prognostic variables [25]. Interestingly, all these were similar across BMI groups suggesting that, although on the surface obese men may not appear to harbour more aggressive disease, they experience more rapid progression. Alternatively, due to obesity-related haemodilution [26,27], PSA values (and PSA kinetics) in obese men may underestimate disease burden (and aggressiveness). Regardless of why, these findings support the hypothesis that obesity is associated with post-ADT progression.

Beyond obesity, we found absolute PSA level at ADT start and seminal vesicle invasion significantly predicted progression. These findings agree with other studies which found pre-ADT PSA level [25] and seminal vesicle invasion [28] predicted worse PC-specific outcomes. Although PSA nadir during ADT is known to be prognostic [25], we did not include it in our models because it is unavailable until *after* ADT and thus cannot be used at ADT *start* to predict outcome. We did not use PSADT in our models either because many men did not have enough PSA data to calculate PSADT, although PSADT did not differ by BMI group and thus inclusion of this would probably not have influenced our results [18].

Ultimately, if confirmed in larger studies, our results can help guide clinicians in risk stratification of men undergoing ADT based upon BMI. Counselling obese men considering ADT should include discussion about lifestyle changes like weight loss, exercise and dietary modification. Although it is unknown if these measures modify the risk of PC-specific outcomes in obese men, they are known to reduce the risk of heart disease and are unlikely to be harmful [29,30]. Moreover, these high risk men should be considered for additional PC therapies such as anti-androgens or clinical trials and should be counselled appropriately. Future studies to improve PC outcomes in obese men undergoing ADT should focus on elucidating the effects of lifestyle changes when starting ADT, additional diagnostic testing and/or more rigorous ADT. For example, perhaps testosterone should be measured after a set time period in obese men after starting ADT, even if PSA is stable. If the testosterone is not below a certain cut-point, then perhaps additional hormonal therapy such as anti-androgens or CYP17 inhibitors (i.e. ketoconazole or, in the future, abiraterone) should be added. Alternatively, as ADT in the Veterans Affairs system is almost always with the LHRH agonist goserelin (exact data unavailable), whether better results would be obtained with an LHRH antagonist, which shows better progression-free survival, is unknown [31].

Our study was retrospective and only included men from the Veterans Affairs system; whether these results are generalizable is unclear. Height and weight were not obtained in a standardized manner and are subject to human error in measurement. Testosterone levels were not available in all men to confirm castration. Thus, ‘ CRPC’ may be better described as ‘ADT-resistant’. We only studied men who underwent RP; whether these observations apply to men undergoing other treatments is unknown. Although obesity and poor PC outcomes are associated, the mechanisms responsible remain unknown. Data related to treatments post-ADT (i.e. chemotherapy) were unavailable, although no treatment after ADT to date extends survival by more than several months and thus probably did not influence our results. ADT is well known to induce weight gain and metabolic changes. How these changes influence PC progression is an important topic, but one which is beyond the scope of this paper. Furthermore, such information about changes after starting ADT is not available at the time of starting ADT and the goal of this paper was to test whether obesity at the time of ADT influenced outcomes. One of our outcomes was ‘metastases’ defined typically by a positive bone scan. Probably, these men had micrometastatic disease prior to the bone scan becoming positive. However, the fact that obesity was suggestively correlated with other endpoints such as CRPC and PCSM provides further support for the hypothesis that obesity is linked with PC progression. Finally, our study had a modest sample size and a small number of PC-specific events. Further study using larger populations with longer follow-up are necessary to validate these findings and investigate potential mechanisms underlying the link between obesity and post-ADT progression.

Our data support the hypothesis that obese men are at increased risk of progression to CRPC, metastases and PCSM. On unadjusted analysis these were statistically significant; however, not all reached statistical significance on multivariate analysis. These differences were seen despite similarity in important prognostic variables (pre-ADT PSA, pre-ADT PSADT and PSA nadir during ADT). Future validation studies are required. However, if confirmed, these data suggest that obese men starting ADT should be counselled regarding lifestyle modifications to promote weight reduction, the potential need for additional PC therapies and consideration of clinical trials.

Acknowledgments

FUNDING

Funding was from the Department of Veterans Affairs, the Department of Defense, Prostate Cancer Research Program (CJK, SJF), NIH R01CA100938 (WJA), NIH Specialized Programs of Research Excellence Grant P50 CA92131-01A1 (WJA), Georgia Cancer Coalition (MKT) and the American Urological Association Foundation/ Astellas Rising Star in Urology Award (SJF). Views and opinions of and endorsements by the author(s) do not reflect those of the US Army or the Department of Defense.

Abbreviations

BMI	body mass index
PC	prostate cancer
RP	radical prostatectomy
PCSM	PC-specific mortality
ADT	androgen deprivation therapy
CRPC	castration-resistant PC
PSADT	PSA doubling time

HR hazard ratio

References

1. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. JAMA. 2010; 303:235–41. [PubMed: 20071471]
2. Peytremann-Bridevaux I, Faeh D, Santos-Eggimann B. Prevalence of overweight and obesity in rural and urban settings of 10 European countries. Prev Med. 2007; 44:442–6. [PubMed: 17258803]
3. Engeland A, Tretli S, Bjorge T. Height, body mass index, and prostate cancer: a follow-up of 950 000 Norwegian men. Br J Cancer. 2003; 89:1237–42. [PubMed: 14520453]
4. Andersson SO, Wolk A, Bergstrom R, et al. Body size and prostate cancer: a 20-year follow-up study among 135 006 Swedish construction workers. J Natl Cancer Inst. 1997; 89:385–9. [PubMed: 9060961]
5. Schuurman AG, Goldbohm RA, Dorant E, van den Brandt PA. Anthropometry in relation to prostate cancer risk in the Netherlands Cohort Study. Am J Epidemiol. 2000; 151:541–9. [PubMed: 10733035]
6. Rodriguez C, Freedland SJ, Deka A, et al. Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev. 2007; 16:63–9. [PubMed: 17179486]
7. Gong Z, Neuhouser ML, Goodman PJ, et al. Obesity, diabetes, and risk of prostate cancer: results from the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev. 2006; 15:1977–83. [PubMed: 17035408]
8. Freedland SJ, Aronson WJ, Kane CJ, et al. Impact of obesity on biochemical control after radical prostatectomy for clinically localized prostate cancer: a report by the Shared Equal Access Regional Cancer Hospital database study group. J Clin Oncol. 2004; 22:446–53. [PubMed: 14691122]
9. Amling CL, Riffenburgh RH, Sun L, et al. Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. J Clin Oncol. 2004; 22:439–45. [PubMed: 14691120]
10. Ma J, Li H, Giovannucci E, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. Lancet Oncol. 2008; 9:1039–47. [PubMed: 18835745]
11. Smith MR, Bae K, Efstathiou JA, et al. Diabetes and mortality in men with locally advanced prostate cancer: RTOG 92-02. J Clin Oncol. 2008; 26:4333–9. [PubMed: 18779620]
12. Freedland SJ, Banez LL, Sun LL, Fitzsimons NJ, Moul JW. Obese men have higher-grade and larger tumors: an analysis of the Duke Prostate Center database. Prostate Cancer Prostatic Dis. 2009; 12:259–63. [PubMed: 19581922]
13. Smith MR. Obesity and sex steroids during gonadotropin-releasing hormone agonist treatment for prostate cancer. Clin Cancer Res. 2007; 13:241–5. [PubMed: 17200361]
14. Morote J, Orsola A, Planas J, et al. Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. J Urol. 2007; 178:1290–5. [PubMed: 17698136]
15. Perachino M, Cavalli V, Bravi F. Testosterone levels in patients with metastatic prostate cancer treated with luteinizing hormone-releasing hormone therapy: prognostic significance? BJU Int. 2010; 105:648–51. [PubMed: 19747358]
16. Banez LL, Loftis RM, Freedland SJ, et al. The influence of hepatic function on prostate cancer outcomes after radical prostatectomy. Prostate Cancer Prostatic Dis. 2010; 13:173–7. [PubMed: 20195294]
17. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008; 26:1148–59. [PubMed: 18309951]
18. Arlen PM, Bianco F, Dahut WL, et al. Prostate Specific Antigen Working Group guidelines on prostate specific antigen doubling time. J Urol. 2008; 179:2181–6. [PubMed: 18423743]

19. Bassett WW, Cooperberg MR, Sadetsky N, et al. Impact of obesity on prostate cancer recurrence after radical prostatectomy: data from CaPSURE. Urology. 2005; 66:1060–5. [PubMed: 16286124]
20. Buschemeyer WC 3rd, Freedland SJ. Obesity and prostate cancer: epidemiology and clinical implications. Eur Urol. 2007; 52:331–43. [PubMed: 17507151]
21. Strom SS, Kamat AM, Gruschkus SK, et al. Influence of obesity on biochemical and clinical failure after external-beam radiotherapy for localized prostate cancer. Cancer. 2006; 107:631–9. [PubMed: 16802288]
22. Massengill JC, Sun L, Moul JW, et al. Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. J Urol. 2003; 169:1670–5. [PubMed: 12686805]
23. Schatzl G, Madersbacher S, Thurridl T, et al. High-grade prostate cancer is associated with low serum testosterone levels. Prostate. 2001; 47:52–8. [PubMed: 11304729]
24. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA. 2005; 293:1861–7. [PubMed: 15840860]
25. Stewart AJ, Scher HI, Chen MH, et al. Prostate-specific antigen nadir and cancer-specific mortality following hormonal therapy for prostate-specific antigen failure. J Clin Oncol. 2005; 23:6556–60. [PubMed: 16170163]
26. Banez LL, Hamilton RJ, Partin AW, et al. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. JAMA. 2007; 298:2275–80. [PubMed: 18029831]
27. Hekal IA, Ibrahiem EI. Obesity–PSA relationship: a new formula. Prostate Cancer Prostatic Dis. 2010; 13:186–90. [PubMed: 20029402]
28. Swanson GP, Goldman B, Tangen CM, et al. The prognostic impact of seminal vesicle involvement found at prostatectomy and the effects of adjuvant radiation: data from Southwest Oncology Group 8794. J Urol. 2008; 180:2453–8. [PubMed: 18930488]
29. Antonelli JA, Jones LW, Banez LL, et al. Exercise and prostate cancer risk in a cohort of veterans undergoing prostate needle biopsy. J Urol. 2009; 182:2226–31. [PubMed: 19758620]
30. Freedland SJ, Aronson WJ. Dietary intervention strategies to modulate prostate cancer risk and prognosis. Curr Opin Urol. 2009; 19:263–7. [PubMed: 19300265]
31. Tombal B, Miller K, Boccon-Gibod L, et al. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. Eur Urol. 2010; 57:836–42. [PubMed: 19962227]

What's known on the subject? and What does the study add?

The incidence and prevalence of obesity in the USA and Europe is increasing. Higher body mass index is associated with a lower risk of overall prostate cancer diagnosis but also with an increased risk of high grade prostate cancer. Obese men undergoing primary therapy with radical prostatectomy or external beam radiation are more likely to experience a biochemical recurrence after treatment compared with normal weight men. Finally, obesity is associated with increased prostate-cancer-specific mortality. We hypothesized that obese men on androgen deprivation therapy may be at increased risk for prostate cancer progression. Previous studies have shown that obese men have lower levels of testosterone compared with normal weight men. Additionally, one previous study found that obese men have higher levels of testosterone on androgen deprivation therapy. Men with higher levels of testosterone on androgen deprivation therapy are at increased risk of prostate cancer progression.

We found that men with higher body mass index were at increased risk of progression to castration-resistant prostate cancer, development of metastases and prostate-cancer-specific mortality. When we adjusted for various clinicopathological characteristics, obese men were at increased risk of progression to castration-resistant prostate cancer and development of metastases. The results of our study help generate hypotheses for further study regarding the mechanisms between obesity and aggressive prostate cancer.

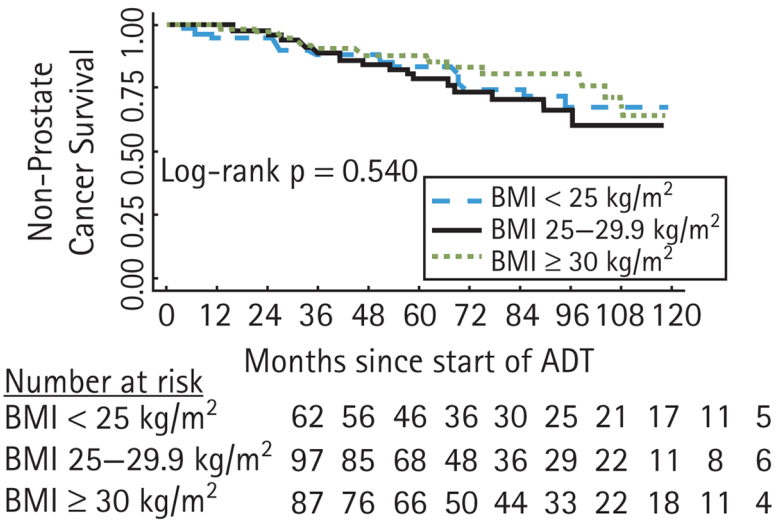

FIG. 1.
Kaplan–Meier plot of non-prostate cancer survival by BMI.

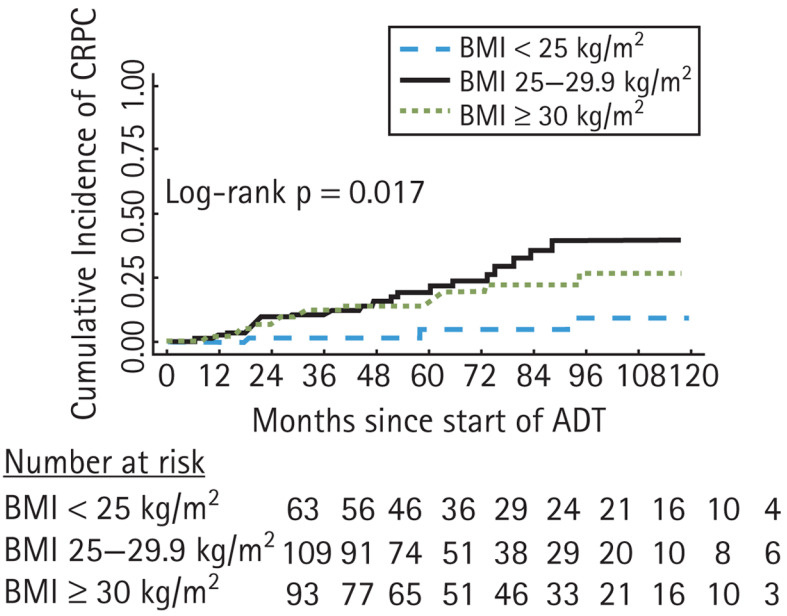

FIG. 2.
Cumulative incidence of progression to CRPC by BMI.

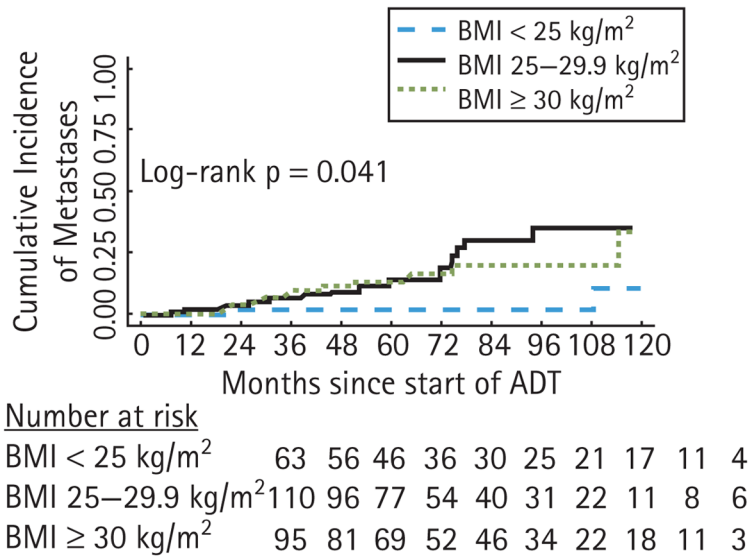

FIG. 3.
Cumulative incidence of development of metastases by BMI.

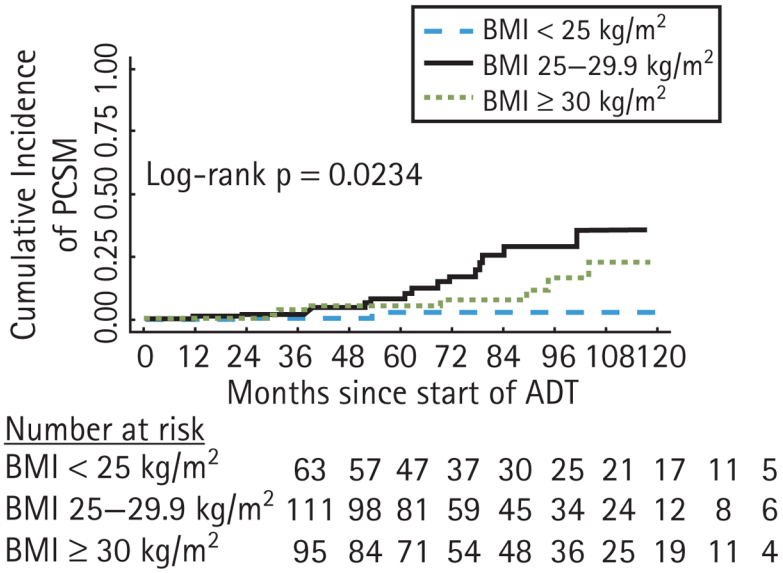

FIG. 4.
Cumulative incidence of PCSM by BMI.

TABLE 1

Baseline characteristics

Characteristic	Normal weight, no. (%)	Overweight, no. (%)	Obese, no. (%)	*P*
Total number of men	67 (23)	120 (42)	100 (35)	
Pathological Gleason score				0.007
2–6	19 (28)	19 (16)	7 (7)	
3 + 4	20 (30)	41 (34)	36 (36)	
≥4 + 3	28 (42)	60 (50)	57 (57)	
Age at ADT (years),				0.143
Median (IQR)	67 (60–75)	65 (60–71)	65 (59–70)	
Year of ADT start,				0.569
Median (IQR)	2003 (2001–2006)	2004 (2001–2007)	2004 (2001–2007)	
Race				0.361
Black	36 (54)	76 (63)	56 (56)	
Non-black	31 (46)	44 (37)	44 (44)	
BMI at ADT, median (IQR)	24 (22–24)	28 (26–29)	33 (32–36)	–
Lymph node metastases	5 (7)	7 (6)	6 (6)	0.956
Positive surgical margins	38 (57)	75 (63)	69 (69)	0.261
Extracapsular extension	27 (40)	57 (48)	44 (44)	0.630
Seminal vesicle invasion	19 (28)	37 (31)	35 (35)	0.641
Pre-ADT PSA (ng/mL),				0.163
Median (IQR)	1.7 (0.6–4.6)	2.2 (0.3–6.8)	1.3 (0.3–3.4)	
PSA nadir on ADT (ng/mL),				0.06
Median (IQR)	0 (0–0.01)	0 (0–0.03)	0 (0–0.01)	
Pre-ADT PSADT (months),				0.428
Median (IQR)	9 (7–17)	8 (4–15)	9 (5–17)	

IQR, interquartile range.

TABLE 2

Multivariate predictors of progression to CRPC

Variable	Hazard ratio	95% CI	*P*
BMI (relative to <25 kg/m^2)			0.063
25–29.9 kg/m^2	3.36	0.96–11.71	
≥30 kg/m^2	3.86	1.08–13.78	
Black race	0.93	0.43–3.23	0.842
Positive surgical margins	0.58	0.29–1.19	0.139
Seminal vesicle invasion	2.79	1.44–5.39	0.002
Extracapsular extension	1.28	0.58–2.84	0.538
Lymph node metastases	0.96	0.29–3.25	0.951
Log pre-ADT PSA	2.33	1.66–3.25	<0.001
Age at ADT start	0.99	0.95 – 1.04	0.683
Year of ADT start	1.08	0.95–1.24	0.211
Pathological Gleason score (relative to 2–6)			
3 + 4	0.94	0.23–3.83	0.932
≥4 + 3	2.64	0.76–9.11	0.126

TABLE 3

Multivariate predictors of progression to metastases

Variable	Hazard ratio	95% CI	*P*
BMI (relative to <25 kg/m^2)			0.027
25–29.9 kg/m^2	3.58	0.77–16.65	
≥30 kg/m^2	5.00	1.04–23.95	
Black race	0.72	0.28–1.86	0.496
Positive surgical margins	0.74	0.31–1.74	0.486
Seminal vesicle invasion	2.39	1.11–5.11	0.025
Extracapsular extension	1.77	0.67–4.64	0.247
Lymph node metastases	1.12	0.28–4.48	0.868
Log pre-ADT PSA	2.24	1.48–3.40	<0.001
Age at ADT start	1.01	0.96 – 1.07	0.661
Year of ADT start	1.00	0.87–1.16	0.959
Pathological Gleason score (relative to 2–6)			
3 + 4	0.16	0.02–1.03	0.054
≥4 + 3	1.52	0.43–5.43	0.517

TABLE 4

Multivariate predictors of PCSM

Variable	Hazard ratio	95% CI	*P*
BMI (relative to <25 kg/m^2)			0.119
25–29.9 kg/m^2	8.21	0.97–69.72	
≥30 kg/m^2	6.59	0.73–59.08	
Black race	1.42	0.44–4.57	0.552
Positive surgical margins	0.40	0.15–1.09	0.074
Seminal vesicle invasion	2.54	1.04–6.20	0.041
Extracapsular extension	1.75	0.55–5.56	0.344
Lymph node metastases	2.53	0.37–17.37	0.346
Log Pre-ADT PSA	1.82	1.08–3.07	0.025
Age at ADT start	1.05	0.97 – 1.13	0.239
Year of ADT start	0.88	0.72–1.08	0.228
Pathological Gleason score (relative to 2–6)			
3 + 4	0.29	0.04–2.06	0.218
≥4 + 3	1.60	0.31–8.23	0.576