

Body mass index is not a predictor of biochemical recurrence after radical prostatectomy in Dutch men diagnosed with prostate cancer

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Abstract

Purpose To determine the effect of body mass index (BMI) on clinical and pathological characteristics at time of diagnosis and on risk of biochemical recurrence after radical prostatectomy among Dutch men diagnosed with prostate cancer.

Methods In total, 1,116 prostate cancer patients with known BMI, diagnosed between 2003 and 2006, were identified from the population-based cancer registry held by the Comprehensive Cancer Centre East, The Netherlands. Of

these, 504 patients underwent a radical prostatectomy. Patients were categorized as normal weight (BMI < 25 kg/m²), overweight (BMI 25–30 kg/m²), or obese (BMI ≥ 30 kg/m²). Multivariable proportional hazards regression models, adjusted for age, pre-diagnostic PSA levels, and pathological characteristics were used to evaluate BMI as a prognostic factor for biochemical recurrence after radical prostatectomy.

Results Overall, clinical and biopsy characteristics did not significantly differ among BMI groups. Pathological characteristics after radical prostatectomy did not significantly differ among BMI groups, except for tumor stage, which was highest in obese patients ($P = 0.017$). For patients treated with radical prostatectomy, 5-year risk (95% Confidence Intervals) of biochemical recurrence was 30% (23–37%) for normal weight, 32% (25–39%) for overweight, and 25% (9–41%) for obese patients (log rank $P = 0.810$). BMI was not an independent prognostic factor for biochemical recurrence in multivariable proportional hazards regression analyses (HR 0.99 per kg/m², 95% CI: 0.93–1.06).

Conclusions Compared with non-obese men, pathological tumor stage tended to be higher in obese men. Clinical relevance of this finding is unclear, because BMI was not an independent predictor of biochemical recurrence after radical prostatectomy.

Keywords Obesity · Body mass index · Prostate cancer · Radical prostatectomy · Biochemical recurrence · Prognosis

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Introduction

It has been hypothesized that obesity is a risk factor for the development and progression of prostate cancer (PC), although results are inconsistent. Most studies focusing on

body size and PC were conducted in the United States, where a rapidly growing epidemic of obesity is reported with over 66% of adult Americans being overweight or obese [1]. In Europe, incidence of overweight and obesity is also increasing substantially [2]. Whether body size predisposes to adverse PC characteristics or outcome in European men is a matter of debate. Only few European studies examined effects of BMI on adverse pathological findings after biopsy or radical prostatectomy (RP) [3–6]. Gallina and colleagues suggested that high-grade PC at RP might be more prevalent among obese men; however, adding BMI to the multivariable model failed to increase predictive accuracy for high-grade PC [6]. Other studies did not find an association for BMI and tumor grade or stage, extracapsular extension, seminal vesicle invasion, lymph node involvement or positive surgical margins either [3–5]. Results for PC outcome are inconclusive as well. One study from Germany reported BMI as independent predictor of biochemical recurrence (BCR) after RP, although it did not improve predictive accuracy [7], while we and others did not find any effect of BMI on BCR rates after RP [5, 8] or brachytherapy [9].

Since results are conflicting and the epidemic of obesity is growing, additional evidence on the effects of body size on PC risk and prognosis in Europe are needed. Aim of the present study was to determine effects of BMI on clinical and pathological findings at time of diagnosis and on risk of BCR after RP among Dutch men with PC.

Subjects and methods

Patients diagnosed with PC were identified from the population-based cancer registry held by the Comprehensive Cancer Centre East (CCCE), The Netherlands. From 2003 to 2006, 1,668 patients with PC were identified in this region. Only patients with known BMI data were included in our analyses ($n = 1,116$). For all patients, clinical data were collected retrospectively by review of the clinical charts. Part of the patients ($n = 951$), who were diagnosed before the age of 76, participated in the POLYGENE project [10] and filled out a postal questionnaire as part of it. Self-reported weight and length were collected either from the POLYGENE questionnaire ($n = 943$) or from the clinical charts ($n = 173$) and were used to calculate BMI. For 278 patients, BMI was available from the questionnaire as well as from the charts (Spearman $r = 0.81$, $P < 0.001$). For these patients, BMI from the questionnaire was used in the analyses. BMI categories were defined according to the WHO criteria: BMI < 25 kg/m² (normal weight), BMI 25–30 kg/m² (overweight), and BMI ≥ 30 kg/m² (obesity). The institutional review board approved the study, and all participants of the POLYGENE project provided written informed consent.

Primary treatments were categorized as radical prostatectomy (RP) with or without neoadjuvant androgen-deprivation therapy (ADT), radiotherapy (RT, including external beam radiation and brachytherapy) with or without ADT, active surveillance (AS), androgen-deprivation therapy (ADT), and others (such as cryotherapy and chemotherapy). In total, 517 patients who underwent RP as primary therapy were identified. Patients treated with neoadjuvant ADT ($n = 13$) were excluded, leaving 504 patients for analysis. BMI was evaluated as prognostic factor for BCR, which is defined as two consecutive PSA levels ≥ 0.2 ng/ml. For these analyses, 11 patients were excluded, because data on post-operative PSA levels or BCR status were missing. After RP, patients were generally seen after 6 weeks, 3, 6, 9, and 12 months and then every 6 months, according to the national guidelines for PC follow-up [11]. RP specimens were processed according to protocols from the institutes where patients were submitted to. Gleason grade was presented as the sum of two main Gleason scores. Clinical and pathological stages were classified according to the 2002 TNM classification based on the American Joint Committee on Cancer guidelines (AJCC) [12].

We used Kruskal–Wallis tests to assess the association between BMI categories and continuous clinical and pathological variables, while Chi-square tests were applied to categorical variables. Risk of BCR was calculated with the Kaplan–Meier method, using the log-rank test to compare BMI groups. Univariable and multivariable proportional hazards regression analyses adjusted for age, prediagnostic PSA levels, and pathological variables (Gleason score at RP, pathological stage, surgical margin status, and lymph node status) were performed to evaluate whether BMI is a prognostic factor for BCR after RP. The significance level was set at $P < 0.05$, and all P values were two tailed. Statistical Package of Social Sciences (SPSS, version 16.0, Chicago, Illinois) was used for all analyses.

Results

Patient characteristics are shown in Table 1. Among all PC patients included in the analyses ($n = 1,116$), median age at diagnosis was 66.3 (inter-quartile range: 61.2–70.5) years. Median BMI was 25.3 (IQR: 23.9–27.0) kg/m², with 47% of this population being overweight and 7% obese. Overall, no statistically significant differences for clinical or pathological findings were observed among the BMI groups. Although not statistically significant, obese patients were somewhat less likely to be referred for RP compared to normal weight and overweight patients (38% versus 46% and 48%, respectively).

Table 2 shows characteristics of patients with PC who underwent RP. Median age and BMI of patients treated

Table 1 Demographic, clinical, and pathological characteristics of Dutch patients diagnosed with prostate cancer according to BMI categories

	Total group	BMI < 25 kg/m ²	BMI 25–30 kg/m ²	BMI ≥ 30 kg/m ²	<i>P</i> value
Number of patients (%)	1,116 (100%)	510 (46%)	530 (47%)	76 (7%)	–
Age at diagnosis (years)	66.3 (61.2–70.5)	66.1 (61.5–71.0)	66.2 (61.0–70.2)	65.1 (61.1–69.6)	0.753
BMI (kg/m ²)	25.3 (23.9–27.0)	23.7 (22.9–24.4)	26.6 (25.8–27.8)	31.6 (30.7–33.6)	–
BMI at age 18 (kg/m ²) ^a	22.2 (21.0–23.7)	21.5 (20.2–22.6)	23.0 (21.8–24.2)	24.4 (23.1–28.1)	–
Height (cm)	177 (172–182)	178 (173–183)	176 (172–180)	175 (172–179)	–
Weight (kg)	80 (74–85)	75 (70–80)	83 (80–90)	100 (92–104)	–
Smoking (%)					
Never	170 (15%)	86 (17%)	74 (14%)	10 (13%)	0.035
Former	641 (57%)	285 (56%)	321 (61%)	35 (46%)	
Current	136 (12%)	80 (16%)	50 (9%)	6 (8%)	
Family history of prostate cancer (%)					
Yes	228 (20%)	101 (20%)	117 (22%)	10 (13%)	0.285
No	736 (66%)	357 (70%)	336 (63%)	43 (57%)	
Prediagnostic PSA level (ng/ml) ^b	10 (6–20)	9 (6–20)	10 (7–21)	10 (7–27)	0.187
Gleason score biopsy (%)					
<7	689 (62%)	331 (65%)	316 (60%)	42 (55%)	0.128
7	226 (20%)	88 (17%)	120 (23%)	18 (24%)	
>7	120 (11%)	49 (10%)	61 (12%)	10 (13%)	
Clinical stage (cTNM) (%)					
cT1	447 (40%)	200 (39%)	224 (42%)	23 (30%)	0.229
cT2	418 (38%)	196 (38%)	194 (37%)	28 (37%)	
cT3 or cT4	233 (21%)	107 (21%)	104 (20%)	22 (29%)	
Primary treatment (%)					
Active surveillance (AS)	121 (11%)	58 (11%)	57 (11%)	6 (8%)	0.585
RP without ADT	504 (45%)	230 (45%)	245 (46%)	29 (38%)	
RP with ADT	13 (1%)	4 (1%)	9 (2%)	–	
RT without ADT	115 (10%)	60 (12%)	46 (9%)	9 (12%)	
RT with ADT	210 (19%)	94 (19%)	100 (18%)	16 (21%)	
ADT	138 (12%)	58 (11%)	66 (12%)	14 (18%)	
Others	10 (1%)	5 (1%)	4 (1%)	1 (1%)	

Data presented as median (IQR) or number (%)

Percentages may not add up to 100% because of missing values

ADT androgen-deprivation therapy, AS active surveillance, BMI body mass index, cTNM clinical tumor-node-metastasis, PSA prostate specific antigen, RP radical prostatectomy, RT radiotherapy

^a Missing *n* = 243

^b Missing *n* = 12

with RP were 63.3 (IQR: 58.8–67.1) years and 25.3 (IQR: 23.7–26.9) kg/m². Pathological characteristics after RP did not significantly differ between BMI groups, except for tumor (pT) stage which was somewhat higher in obese patients (*P* = 0.017). Furthermore, obese patients tended to have higher prediagnostic PSA levels compared to overweight and normal weight patients (*P* = 0.004). BMI presented as a continuous variable, however, was only weakly correlated with prediagnostic PSA levels (Spearman *r* = 0.13, *P* = 0.004). Median follow-up of patients treated with RP was 40.3 (IQR: 19.5–53.1) months. In total, 142

patients developed BCR after RP. The 5-year risk (95% CI) of BCR was 30% (23–37%), 32% (25–39%), and 25% (9–41%) for normal weight, overweight, and obese patients, respectively (log rank *P* = 0.810) (Fig. 1).

As presented in Table 3, BMI was not a significant prognostic factor for BCR after RP in univariable (HR 1.02 per kg/m², 95% CI: 0.97–1.07) or multivariable (HR 0.99 per kg/m², 95% CI: 0.93–1.06) analyses after adjustment for age, prediagnostic PSA, Gleason score at RP, positive surgical margins, positive lymph nodes, and pathological stage. Higher Gleason score, pathological stage, and positive

Table 2 Demographic, clinical, and pathological characteristics of Dutch patients with prostate cancer treated with radical prostatectomy (RP)

	Total group	BMI < 25 kg/m ²	BMI 25–30 kg/m ²	BMI ≥ 30 kg/m ²	<i>P</i> value
Number of patients (%)	504 (100%)	230 (46%)	245 (49%)	29 (6%)	–
Age at RP (years)	63.3 (58.8–67.1)	63.4 (58.7–66.7)	63.2 (58.8–67.4)	63.0 (59.3–67.8)	0.961
BMI (kg/m ²)	25.3 (23.7–26.9)	23.7 (22.9–24.4)	26.6 (25.8–27.7)	31.3 (30.5–34.3)	–
Prediagnostic PSA (ng/ml) ^a	8 (6–12)	7 (5–10)	8 (6–13)	8 (5–12)	0.004
Follow-up (months)	40.3 (19.5–53.1)	40.9 (24.7–53.8)	39.4 (17.0–52.4)	40.6 (17.1–57.0)	0.502
Surgery (%)					
Open	284 (56%)	123 (53%)	145 (59%)	16 (55%)	0.251
Laparoscopic	195 (39%)	99 (43%)	88 (36%)	8 (28%)	
Missing	25 (5%)	8 (3%)	12 (5%)	5 (17%)	
PSA nadir < 0.2 ng/ml (%)					
Yes	461 (91%)	213 (93%)	221 (90%)	27 (93%)	0.853
No	36 (7%)	15 (7%)	19 (8%)	2 (7%)	
Missing	7 (1%)	2 (1%)	5 (2%)	0	
Biochemical recurrence (%)					
Yes ^b	142 (28%)	65 (28%)	70 (29%)	7 (24%)	0.874
No	351 (70%)	163 (71%)	167 (68%)	21 (72%)	
Missing	11 (2%)	2 (1%)	8 (3%)	1 (3%)	
Gleason score RP (%)					
<7	348 (69%)	165 (72%)	162 (66%)	21 (72%)	0.148
7	111 (22%)	44 (19%)	60 (24%)	7 (24%)	
>7	30 (6%)	10 (4%)	20 (8%)	0	
Missing	15 (3%)	11 (5%)	3 (1%)	1 (3%)	
Pathological stage (pTNM) (%)					
pT2	349 (69%)	170 (74%)	165 (67%)	14 (48%)	0.017
pT3 or pT4	143 (28%)	54 (23%)	76 (31%)	13 (45%)	
Missing	12 (2%)	6 (3%)	4 (2%)	2 (7%)	
Surgical margins (%)					
Positive	211 (42%)	93 (40%)	102 (42%)	16 (55%)	0.341
Negative	270 (54%)	125 (54%)	133 (54%)	12 (41%)	
Missing	23 (5%)	12 (5%)	10 (4%)	1 (3%)	
Extracapsular extension (%)					
Yes	175 (35%)	72 (31%)	89 (36%)	14 (48%)	0.204
No	221 (44%)	102 (44%)	110 (45%)	9 (31%)	
Missing	108 (21%)	56 (24%)	46 (19%)	6 (21%)	
Invasion seminal vesicles (%)					
Yes	45 (9%)	15 (7%)	25 (10%)	5 (17%)	0.068
No	446 (88%)	211 (92%)	214 (87%)	21 (72%)	
Missing	13 (3%)	4 (2%)	6 (2%)	3 (10%)	
Lymph node dissection (%)	230 (46%)	83 (36%)	131 (53%)	16 (55%)	0.001
Positive lymph nodes (%)	17 (3%)	6 (3%)	9 (4%)	2 (7%)	0.726

Data presented as median (IQR) or numbers (%)

BMI body mass index, *PSA* prostate specific antigen, *pTNM* pathological tumor-node-metastasis, *RP* radical prostatectomy

^a Missing *n* = 5

^b Including 36 patients who did not reach post-operative PSA levels <0.2 ng/ml

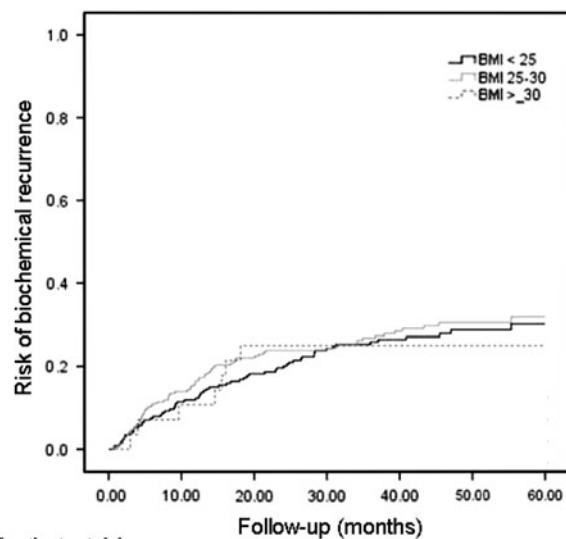


Fig. 1 The 5-year risk of biochemical recurrence in normal weight, overweight, and obese prostate cancer patients treated with radical prostatectomy ($n = 493$). Log rank $P = 0.810$

surgical margins were all statistically significant predictors of risk of BCR after RP.

Discussion and conclusion

In the present study among Dutch men diagnosed with PC, BMI was weakly associated with higher pathological tumor (pT) stage and higher pre-diagnostic PSA levels in patients treated with RP. Gleason score, pathological stage, and positive surgical margins were independent predictors of BCR, whereas BMI did not add any prognostic value in multivariable proportional hazards regression analyses.

Our findings are consistent with other European studies which did not find a prognostic effect of BMI in patients treated with RP [5, 8]. Only one study reported a trend toward statistical significance for BMI as independent prognostic factor for BCR [7]. Addition of BMI to a multivariable model, however, did not significantly increase predictive accuracy [7]. Whereas most European studies so far were not able to find an association between BMI and any clinical or pathological characteristics, several studies from the United States did report BMI as predictor of BCR and adverse pathological findings after RP [13–15]. These inconsistent results might be explained by the lower rates of obesity and severe obesity in Europe compared to the United States [1, 2].

A remarkable observation in this study is the weak positive association between BMI and pre-diagnostic PSA levels

among RP patients, which was not observed in the overall study population. Several studies observed an inverse association between BMI and pre-diagnostic PSA levels [16, 17]. Based on the theory of hemodilution, it has been hypothesized that obese patients have larger plasma or serum volumes, which may lead to lower PSA concentrations [16]. It has also been suggested that lower PSA levels in obese patients might result from decreased androgenic activity [18]. Our results indicated a weak correlation between BMI and PSA levels and were limited to a small subpopulation of patients treated with RP; therefore, we cannot rule out that our result was a chance finding.

Another finding of our study was the association between BMI and pathological tumor (pT) stage among RP patients, suggesting that advanced-staged tumors were more common among obese patients. As reviewed by others, obesity might indeed play a role in PC aggressiveness, i.e. high stage, high grade, and increased risk of recurrence or mortality [19]. It has been hypothesized that both non-biological and biological mechanisms can be responsible for the association between tumor aggressiveness and body size. Firstly, it might be more difficult to detect (early) PC in obese men, due to lower PSA levels [16, 17] and difficult digital rectal examinations [19]. Secondly, difficulties related to treatment might be responsible for an aggressive type of PC in obese men. Pathological findings related to technical aspects of surgery like positive surgical margins, however, would be more likely to be affected than tumor grade or stage. Finally, alterations in levels of steroid hormones, adipokines, and inflammatory mediators might also drive PC toward a more aggressive form in obese men [19, 20].

Evidence is growing that differentiation between total adiposity and distribution of adipose tissue is relevant in the studies related to obesity and PC. Recent studies suggested that measures of body fat distribution might be better predictors of PC risk and prognosis when compared to BMI [21, 22]. Fat distribution measurements usually distinct subcutaneous fat from visceral fat depots or simply indicate the location of adipose tissue. Skin fold measurements, waist circumference, and waist-to-hip ratios are frequently used estimates for the amount and location of adipose tissue. Magnetic resonance imaging (MRI) and computed tomography (CT) are considered more reliable methods for assessing subcutaneous and visceral fat content [23]. Von Hafe et al. [22] examined the relation between abdominal visceral fat accumulation, as measured by CT, and PC incidence within a case-control study. They found that visceral fat area and visceral to subcutaneous fat ratio were strongly associated with increased PC risk (crude OR 4.6, 95% CI: 2.6–8.2 and OR 6.0, 95% CI: 2.3–11.0, respectively). Unfortunately, we did not have data on any measures of fat distribution. Other potential limitations of our study might

Table 3 Univariable and multivariable proportional hazards regression models predicting biochemical recurrence after radical prostatectomy (RP)

	<i>n</i>	Univariable			Multivariable (<i>n</i> = 444) ^{a,b}		
		HR	95% CI	<i>P</i> values	Adjusted HR	95% CI	<i>P</i> values
BMI (kg/m ²)	493	1.02	0.97–1.07	0.525	0.99	0.93–1.06	0.732
BMI	493						
<25 kg/m ²		1.00	–	–			
25–30 kg/m ²		1.08	0.77–1.51	0.658			
≥30 kg/m ²		0.90	0.41–1.96	0.789			
Age at RP (years)	493	1.05	1.02–1.08	0.003	1.02	0.98–1.05	0.396
Surgery	472						
Open		1.00	–	–			
Laparoscopic		1.15	0.81–1.62	0.429			
Year of RP	493	1.07	0.90–1.27	0.441			
Prediagnostic PSA level (ng/ml)	489	1.03	1.01–1.05	0.002	1.00	0.98–1.02	0.866
Prediagnostic PSA level	489						
<4 ng/ml		1.00	–	–			
4–10 ng/ml		3.02	0.95–9.58	0.061			
≥10 ng/ml		4.99	1.57–15.89	0.006			
Gleason score at RP	478						
<7		1.00	–	–	1.00	–	–
7		2.55	1.77–3.68	<0.001	1.71	1.13–2.60	0.012
>7		4.39	2.64–7.31	<0.001	2.55	1.43–4.52	0.001
Pathological stage (pTNM)	483						
pT2		1.00	–	–	1.00	1.00	–
pT3 or pT4		2.50	1.79–3.50	<0.001	1.68	1.13–2.49	0.010
Extracapsular extension	386	2.41	1.62–3.58	<0.001			
Positive surgical margins	470	4.33	2.94–6.38	<0.001	2.85	1.87–4.35	<0.001
Invasion seminal vesicles	480	2.58	1.64–4.04	<0.001			
Positive lymph nodes ^c	489	2.93	1.54–5.58	0.001	1.57	0.80–3.07	0.186

BMI body mass index, PSA prostate specific antigen, pTNM pathological tumor-node-metastasis, RP radical prostatectomy

^a Variables in the multivariable model are adjusted for each other

^b Replacing pathological stage by extracapsular extension and seminal vesicles invasion in the multivariable model resulted in adjusted hazards ratios (95% CI) of 1.45 (0.92–2.28, *P* = 0.106) for extracapsular extension and 1.06 (0.59–1.91, *P* = 0.845) for seminal vesicles invasion, while the adjusted hazards ratios for the remaining variables hardly changed

^c The reference category is: no lymph node dissection performed or no positive lymph nodes

be its retrospective data collection, self-reported BMI, relatively short follow-up (median 40.3 months), and small number of patients, especially in the obese group. Results therefore need to be interpreted with some caution. We cannot exclude the possibility that the relatively large number of missing values for BMI might have been a source of selection bias, although the observation that patients with missing BMI did not have more advanced tumor characteristics compared to the patients with evaluable BMI in our RP cohort (data not shown) argues against this. The absence of an association between BMI and BCR might also be explained by treatment-related selection. If obese patients tend to have more advanced tumor characteristics at diagnosis, and therefore have other types of treatment

(e.g. ADT), while mainly normal weight, low-risk patients will have surgery, a possible association between BMI and BCR could be missed. Our aim was, however, to study the association between BMI and BCR in an average population-based RP cohort. We conclude from our results that in this cohort, BMI does not have any prognostic value for risk of BCR. Whether BMI is associated with risk of recurrence in other treatment groups should be verified in the future studies.

In summary, BMI did not affect clinical or pathological characteristics of PC patients at time of diagnosis. Compared with non-obese men, pathological stage tended to be higher in obese men treated with RP. Clinical relevance of these findings with respect to risk of BCR, however, needs

to be further elucidated, since BMI itself was not an independent predictor of BCR after RP.

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Conflict of interest The authors declare that they have no conflict of interest.

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