Body mass index as a classifier to predict biochemical recurrence after radical prostatectomy in patients with lower prostate-specific antigen levels

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Received October 15, 2016; Accepted January 10, 2017

DOI: 10.3892/mco.2017.1223

Abstract. Prostate cancer, one of the most common malignant tumors among men, is closely associated with obesity and, thus far, several studies have suggested the association between obesity and aggressive pathological characteristics in the United States. However, the effect of obesity on prostate cancer mortality is controversial, and it remains unclear whether obesity contributes to the aggressiveness of prostate cancer in Asian patients. The aim of the present study was to investigate the association between body mass index (BMI) and the clinicopathological characteristics of prostate cancer in 2,003 Japanese patients who underwent radical prostatectomy. There was a significant association between higher BMI and higher Gleason score (GS). The multivariate analysis also revealed that BMI was an independent indicator for GS ≥8 at surgery. Moreover, among patients with lower prostate-specific antigen levels, biochemical recurrence-free survival was significantly worse in those with higher BMI. These results suggest that BMI may be a classifier for predicting adverse pathological findings and biochemical recurrence after radical prostatectomy in Japanese patients.

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Key words: body mass index, obesity, prostate cancer, prostatectomy, prostate-specific antigen

Introduction

Prostate cancer (PCa) is the one of the most common malignant tumors among men in developed countries. Thus far, it has been suggested that diet and other environmental factors may affect the incidence of PCa, as this incidence differs between countries and ethnic populations (1). In fact, migration studies showed an increased incidence of PCa in first-generation immigrants to the United States from Japan (2). These observations suggest that diet may play an important role in the incidence of PCa (3). In addition, several articles have reported various endogenous and exogenous factors that may contribute to PCa (4).

Obesity, which is generally measured by body mass index (BMI), is associated with increased mortality for all cancers combined (5). Obesity has also been suggested to be a risk factor in prostate cancer as well as breast and colon cancer (6,7). However, the association of higher BMI with increased PCa incidence remains controversial (8). Previous studies presented evidence that obesity was associated with an increased risk of diagnosis of larger tumors, more aggressive disease and PCa-related mortality (9,10), whereas other studies reported that obesity was not associated with aggressive pathological characteristics (11,12). As regards biochemical recurrence, it has been reported that obese men are at increased risk of biochemical recurrence (13-17). Recently, obesity has become more prevalent among Asian countries, including Japan. Although obesity in Asian countries is less severe compared with that in western countries, certain studies have suggested an association between BMI and PCa, including pathological characteristics (18,19). However, the effect of obesity on PCa-related mortality has been controversial, and it remains unclear whether obesity contributes to the aggressiveness of PCa in Asian patients (20,21). The aim of the present study was to investigate the association between BMI and the clinicopathological characteristics of PCa, and determine whether obesity increases the risk of biochemical recurrence after radical prostatectomy (RP) in Japanese patients.

Patients and methods

Patients. The subjects included 2003 Japanese patients with PCa who were treated with RP between 2005 and 2014 at Hiroshima University Hospital and affiliated hospitals. None of the patients had a history of preoperative hormonal or radiation therapy. Resection was considered to be curative in all patients based on node-negative pathology and a decrease in the serum level of prostate-specific antigen (PSA) postoperatively. The clinical records of these patients were retrospectively reviewed to investigate clinical information including age, serum PSA level, BMI and pathological characteristics. Staging was based on the 2005 TNM classification (https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf). Gleason score (GS) was assessed according to the International Society of Urological Pathology modified Gleason grading system (22). BMI was calculated as body weight divided by the square of the height (kg/m^2) and was used to categorize patients into two groups according to the classification of obesity of the Japan Society for the Study of Obesity (http://www.jasso.or.jp/data/office/pdf/guideline.pdf). Patients with BMI <25 kg/m^2 were considered as the normoweight group, whereas those with BMI ≥25 kg/m^2 were considered as the overweight group. The associations between the two BMI groups and clinicopathological characteristics were examined. For the evaluation of prognosis, the serum PSA level was measured every 3 months after RP and biochemical recurrence was defined as an increase in the serum PSA level of >0.2 ng/ml over two subsequent measurements.

Statistical analysis. Associations between BMI and clinicopathological characteristics were analyzed using the Chi-squared test. Age (≥70 vs. <70 years) and serum PSA level (≥10 vs. <10 ng/ml) were treated as categorical variables for all analyses. Logistic regression models were used to predict the risk for high-grade (GS ≥8) tumors at RP. Kaplan-Meier survival curves were constructed for the normoweight and overweight groups. Biochemical recurrence-free survival (bRFS) was compared between the normoweight and overweight groups and evaluated for statistical significance using a log-rank test. Univariate and multivariate Cox regression analyses were used to evaluate the associations between clinical covariates and bRFS. Hazard ratio and 95% confidence intervals were estimated with Cox proportional hazard models. All statistical tests were two-sided and a P-value of <0.05 was considered to indicate statistically significant differences. All statistical analyses were performed using JMP v10.0 software (SAS Institute, Cary, NC, USA) and the Kaplan-Meier survival curves were drawn using GraphPad Prizm v6.0 software (GraphPad Software Inc., San Diego, CA, USA).

Results

BMI is associated with higher GS. The median age of the patients was 68 years (range, 45-83 years), the PSA level was 7.50 ng/ml (range, 1-120 ng/ml) and the BMI was 23.50 kg/m^2 (range, 15.9-38.0 kg/m^2). The pathological GS was ≥8 in 537 patients (26.8%), with extraprostatic extension (EPE) and a positive resection margin (RM) observed in 432 (21.6%) and 554 (27.6%) patients, respectively. Based on the BMI distribution, 569 patients (28.4%) comprised the overweight group (BMI ≥25 kg/m^2), and 1,434 patients (71.6%) comprised the normoweight group (BMI <25 kg/m^2). The BMI exhibited a normal distribution. Only 33 patients (1.6%) had a BMI >30 kg/m^2. When comparing the clinicopathological characteristics between the normoweight and overweight groups (Table I), no significant differences were observed in age (≥70 years), PSA (≥10 ng/ml), pathological T stage (≥T3), EPE and RM.

However, the number of patients with pathological GS ≥8 was higher in the overweight group (P=0.0308, Chi-squared test). Logistic regression analysis was next performed to evaluate whether BMI may be a predictor for PCa with higher GS (Table II). The univariate analysis revealed that age (≥70 years), PSA (≥10 ng/ml), GS at biopsy (≥4+3) and BMI (≥25 kg/m^2) were significantly associated with GS ≥8 at RP. In addition, a multivariate analysis including age, PSA, GS at biopsy and BMI also revealed that PSA, GS at biopsy and BMI were independent indicators for GS ≥8 at RP. These results

Table I. Associations between BMI and clinicopathological characteristics of prostate cancer.

Parameters	BMI (kg/m^2) <25, n (%)	BMI (kg/m^2) ≥25, n (%)	P-value
Operative approach			0.2705
RRP	533 (73.6)	191 (26.4)	
RPP	95 (70.9)	39 (29.1)	
LRP	587 (69.4)	259 (30.6)	
RALP	219 (73.2)	80 (26.8)	
Age (years)			0.1379
<70	836 (72.9)	311 (27.1)	
≥70	598 (69.8)	258 (30.1)	
PSA (ng/ml)			0.4603
<10	943 (71.1)	384 (28.9)	
≥10	491 (72.6)	185 (27.4)	
pT stage			0.2943
T2	1,120 (72.6)	432 (27.8)	
T3	314 (69.6)	137 (30.4)	
GS			0.0308
≤7	1,069 (72.9)	397 (27.1)	
≥8	365 (68.0)	172 (32.0)	
EPE			0.2182
EPE0	1,135 (72.3)	436 (27.8)	
EPE1	299 (69.2)	133 (30.8)	
RM			0.1999
RM0	1,049 (72.4)	400 (27.6)	
RM1	385 (69.5)	169 (30.5)	

BMI, body mass index; LRP, laparoscopic radical prostatectomy; RALP, robot-assisted laparoscopic radical prostatectomy; RPP, retroperineal radical prostatectomy; RRP, retropubic radical prostatectomy; GS, Gleason score; EPE, extraprostatic extension; RM, resection margin.

Table II. Univariate and multivariate logistic regression models to predict tumors with GS ≥8.

	Univariate analysis			Multivariate analysis		
Parameters	OR	95% CI	P-value	OR	95% CI	P-value
Age (years)						
<70	1 (Reference)			1 (Reference)		
≥70	1.301	1.067-1.588	0.0095	1.208	0.970-1.506	0.0913
PSA (ng/ml)						
<10	1 (Reference)			1 (Reference)		
≥10	2.698	2.200-3.311	<0.0001	2.180	1.747-2.722	<0.0001
GS (at biopsy)						
≤3+4	1 (Reference)			1 (Reference)		
≥4+3	6.784	5.418-8.544	<0.0001	6.113	4.865-7.724	<0.0001
BMI (kg/m^2)						
<25	1 (Reference)			1 (Reference)		
≥25	1.269	1.022-1.571	0.0308	1.291	1.016-1.638	0.0364

GS, Gleason score; BMI, body mass index; CI, confidence interval; OR, odds ratio; PSA, prostate-specific antigen.

suggest that obesity may be associated with adverse pathological findings of PCa.

BMI is a predictor of the prognosis of PCa at lower PSA levels. The median follow-up period of this study was 34 months (range, 0-108 months). Of the 2003 patients, 396 (19.8%) experienced biochemical recurrence, including 283 of the 1,434 (19.7%) in the normoweight group and 113 of the 569 (19.9%) in the overweight group. Kaplan-Meier analysis was used to evaluate the association of BMI with biochemical recurrence. When evaluated in all 2003 cases, there was no significant difference between bRFS in the normoweight vs. the overweight group (Fig. 1A). In patients with lower PSA levels (<10 ng/ml), the overweight group exhibited a significantly worse prognosis compared with the normoweight group (P=0.0179, log-rank test, Fig. 1B). However, no significant difference was observed in patients with higher PSA levels (>10 ng/ml, Fig. 1C).

Univariate and multivariate Cox proportional hazards analyses were next performed to evaluate the role of BMI as a predictor of bRFS in patients with PSA<10 ng/ml (Table III). The univariate analysis indicated that pathological stage T3, GS ≥8, EPE1, RM1 and BMI >25 kg/m^2 were significantly associated with bRFS, whereas age was not. The multivariate model, which included pT stage, GS, EPE, RM and BMI, revealed that BMI was not an independent predictor of bRFS, whereas pT3, GS ≥8 and RM1 were.

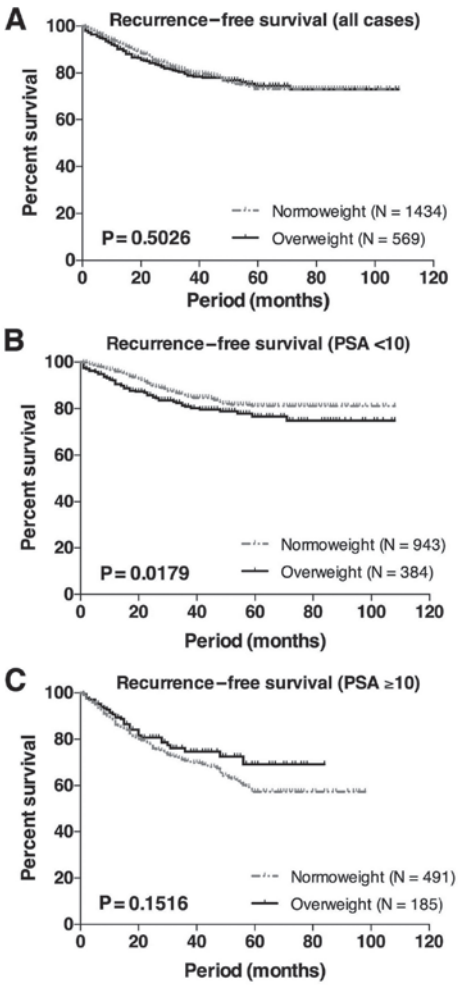

Figure 1. Biochemical recurrence-free survival after radical prostatectomy in (A) 2,003 patients with PCa, (B) 1,327 patients with serum PSA <10 ng/ml and (C) 676 patiens with serum PSA ≥10 ng/ml. Statistical significance was evaluated using the log-rank test. PCa, prostate cancer; PSA, prostate-specific antigen.

Discussion

The association between BMI and the clinicopathological characteristics was investigated in 2003 Japanese patients with PCa who underwent RP. First, it was demonstrated that high BMI was associated with adverse pathological findings. These results, supported those of previous studies showing that obese men in the United States who underwent RP had higher-grade

Table III. Univariate and multivariate Cox proportional hazard models for biochemical recurrence after prostatectomy in patients with PSA <10 ng/ml.

	Univariate analysis			Multivariate analysis		
Parameters	HR	95% CI	P-value	HR	95% CI	P-value
Age (years)			0.1715			0.1768
<70	1 (Reference)			1 (Reference)		
≥70	1.224	0.916-1.631		1.222	0.913-1.631	
pT stage			<0.0001			0.0330
T2	1 (Reference)			1 (Reference)		
T3	3.866	2.872-5.174		2.273	1.070-4.528	
GS			<0.0001			<0.0001
≤7	1 (Reference)			1 (Reference)		
≥8	3.461	2.585-4.617		2.433	1.791-3.291	
EPE			<0.0001			0.9371
EPE0	1 (Reference)			1 (Reference)		
EPE1	3.433	2.541-4.603		0.971	0.489-2.049	
RM			<0.0001			<0.0001
RM0	1 (Reference)			1 (Reference)		
RM1	3.926	2.946-5.235		2.712	1.992-3.693	
BMI (kg/m^2)			0.0309			0.4604
<25	1 (Reference)			1 (Reference)		
≥25	1.400	1.032-1.882		1.122	0.824-1.515	

BMI, body mass index; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; GS, Gleason score; EPE, extraprostatic extension; RM, resection margin.

and larger tumors (8,10,13-17). In Asian patients, the adverse pathological findings of PCa may be attributable to obesity according to previous reports (18,19).

However, other reports have not demonstrated any association of obesity with the clinicopathological characteristics of PCa (20,21). Such conflicting results may be explained by the different distribution of BMI among countries. As the obese (BMI ≥30 kg/m^2) population accounted for only 1-2% of the cases in reports from Asian countries, the cutoff for normal BMI is variably classified as 23.5 or 25.0 kg/m^2. In the present study, a significant association of BMI with GS was observed, whereas such an association was not observed for serum PSA level, pT stage, EPE and RM. These results may suggest that a higher BMI was associated with more aggressive phenotypes of PCa.

Although there was no significant association between BMI and serum PSA level (Table I), the overweight group exhibited a greater risk of biochemical recurrence in patients with lower PSA levels (Fig. 1B). Indeed, previous studies reported that BMI is inversely associated with serum PSA levels (23,24), and a higher BMI is associated with higher plasma volume (25). Thus, the reason why obese men have lower serum PSA concentrations may be explained by the hemodilution theory (26,27). Therefore, it is possible that the serum PSA levels may be modified in the overweight group. However, in the multivariate analysis, BMI was not an independent predictor of biochemical recurrence. Recently, PSA mass, which was associated with visceral adipose tissue, was suggested to be a promising indicator for determining an absolute PSA level (28).

Previous studies have also demonstrated an association between obesity and the aggressiveness of PCa through various molecular mechanisms, including oxidative stress, endocrine activities, or other cytokine activities (29). It is known that adipose tissue secretes certain inflammatory cytokines, referred to as adipocytokines (30). In addition, we previously reported a positive correlation between the aggressiveness of PCa and fibroblast growth factor (FGF)-19, including the endocrine FGF subfamily that circulates in the serum and acts in an endocrine-like manner (31). Further investigations are required to elucidate the associations between BMI or obesity and PSA levels.

The present study had certain limitations. First, the median follow-up period for establishing biochemical recurrence after RP was relatively short. Second, this was a retrospective study that involved patients subjected to RP using different procedures by several surgeons, although the oncological outcomes of retropubic, retroperitoneal, laparoscopic and robot-assisted laparoscopic RP were comparable (32,33). Third, we investigated whether obesity affects pathological findings and biological recurrence after RP using only preoperative BMI, as postoperative BMI values were not available. Although it remains unclear whether weight loss may help improve outcomes among patients already diagnosed with

PCa, further investigations are required to elucidate the role of BMI post-RP.

In summary, the results of the present study, including 2003 Japanese patients who underwent RP for PCa, provide evidence that a higher BMI may be associated with adverse pathological findings. Although BMI was not an independent predictor for bRFS after RP, BMI may be associated with more aggressive characteristics of PCa.

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