OPEN ACCESS

GAVIN PUBLISHERS

Journal of Oncology Research and Therapy

Zhang Q, et al. J Oncol Res Ther: JONT-171.

DOI: 10.29011/2574-710X. 000071

Research Article

Impact of Metabolic Syndrome on Prostate Cancer Diagnosis and Grade in Chinese Patients Undergoing Prostate Biopsy

Qian Zhang[1], Xingbin Wu[2], Binyuan Yan[3], Qiji Li[4], Shubin Peng[5], Shaoxu Wu[6], Jun Li[3*]

[1]Department of Rehabilitation Medicine, Seventh Affiliated Hospital, Sun Yat-sen University Shenzhen, People's Republic of China

[1]Department of Rehabilitation Medicine, Guangzhou First People's Hospital, Guangzhou Medical University, Guangzhou, People's Republic of China

[2]Xiacun Community Health Service Center, Shenzhen Hospital, University of Chinese Academy of Sciences, Shenzhen, People's Republic of China

[3]Department of Urology, Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, People's Republic of China

[4]Department of Orthopedic, Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, People's Republic of China

[5]Department of Urology, Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, People's Republic of China

[6]Department of Urology, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, People's Republic of China

[3]Department of Urology, Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, People's Republic of China

[*]**Corresponding author:** Jun Li, Department of Urology, Seventh Affiliated Hospital, Sun Yat-sen University, 628 Zhenyuan Road, Shenzhen, 518107, People's Republic of China. Tel: +86-15017555405. Email: lijunsysu@163.com

Citation: Zhang Q, Wu X, Yan B, Li Q, Peng S, Wu S, Li J. (2019) Impact of Metabolic Syndrome on Prostate Cancer Diagnosis and Grade in Chinese Patients Undergoing Prostate Biopsy. J Oncol Res Ther: JONT-171. DOI: 10.29011/2574-710X. 000071

Received Date: 17 December, 2018; **Accepted Date:** 02 January, 2019; **Published Date:** 10 January, 2019

Abstract

Objective: Biologic rationale exists for the association between Metabolic Syndrome (MS) and prostate cancer. However, epidemiologic studies have been conflicting. This study aimed to evaluate the association between MS and prostate cancer diagnosis and grade in Chinese patients undergoing prostate biopsy.

Methods: An observational study was conducted of 890 men who underwent prostate biopsy from two Chinese clinical centers. MS was defined according to the Adult Treatment Panel III criteria. Clinicopathological factors including age, PSA, DRE, prostate volume, Body Mass Index (BMI), waist circumference, blood pressure, fasting blood sugar level, lipid profiles, and MS were considered for analysis.

Results: 890 patients were enrolled with a median age and PSA of 67.5 years and 14.44 ng/ml respectively. 247 patients (27.75%) had MS and 404 patients (45.39%) were diagnosed with prostate cancer. Age, PSA, prostate volume, DRE, BMI and MS were significant predictors for prostate cancer detection. Out of 404 patients with prostate cancer, 200 (49.5%) had Gleason score≥4+3, which include 79(39.5%) had MS. PSA, BMI, and MS were significantly associated with an increased risk of high-grade prostate cancer.

Conclusion: Presence of MS was associated with a significantly increased risk of diagnosis of overall and high-grade prostate cancer. However, these results need to be evaluated in large-scale prospective cohorts.

Keywords: Gleason Score; Prostate Cancer; Metabolic Syndrome; Prostate Biopsy

Introduction

Prostate cancer remains the most common non-skin cancer and is the second leading cause of cancer-related deaths among men in developed countries [1]. Although the pathogenesis of prostate cancer has multiple causes, the only established risk factors are age, race and family history. Since prostate cancer incidence rates in Asian men are 10 to 15 times lower than those observed in western countries but appear to be increasing rapidly as this region has gradually begun embracing the western lifestyle, which include excess calorie intake and sedentary living habits. Large epidemiological studies suggest that lifestyle factors may contribute to the etiology and progression of the disease [2]. Metabolic Syndrome (MS) is cluster of risk factors for cardiovascular and metabolic complications, including visceral obesity, hypertension, dyslipidemia and hyperglycemia, each of which have been implicated in prostate cancer carcinogenesis.

Current clinical research on MS and prostate cancer is still discordant and has failed to determine the real impact of MS and/or of its individual component, on prostate cancer incidence and progression. Most of the cohort studies of overall prostate cancer incidence on European populations have demonstrated a positive association [3,4]; However, similar studies performed on American populations revealed null [5] or even inverse [6] associations. Furthermore, some studies did not find an association between MS and prostate cancer detection but found an association with high-grade prostate cancer [7] or low-grade prostate cancer [8]. Given the inconsistency of existing information, as well as tumor heterogeneity in patients of different ethnic backgrounds, the aim of this research was to investigate whether there is a relationship between MS and prostate cancer in a Chinese population who underwent a trans rectal ultrasound-guided prostate biopsy.

Material and Methods

Study Subjects

This retrospective study included 890 consecutive patients from two Chinese clinical centers: The Department of Urology at the Sun Yat-sen Memorial Hospital of Sun Yat-sen University from January 2013 to April 2018, and the Department of Urology at the Third Affiliated Hospital of Sun Yat-sen University from January 2013 to April 2018. Indications for prostate biopsy were as follows: Serum PSA>4 ng/ml，or ultrasound or MRI found suspicious nodules, or clinical digital rectal examination identified hard nodules. We excluded patients who had a history of prostate cancer or prostatic surgery and patients taking 5-alpha reductase inhibitors from the study. All patients were hospitalized, underwent routine hospitalization tests and coagulation index detection. Prophylactic antibiotics were taken from 48 hrs. before the prostate biopsy until 72 hrs. after the biopsy. A fleets enema was administrated 1-2 hrs. before the biopsy. Trans rectal ultrasound-guided prostate biopsy was performed by using an ultrasound instrument (Mindary Bio-Medical Electronics Co. Ltd., Shenzhen city, China) equipped with a 6-MHz bi-convex probe. An automated biopsy gun (Bard Biopsy Systems, Tempe, AZ, USA) and16-gauge biopsy needle (Bard Biopsy Systems) were used in the present study. Each patient underwent a systemic 12-core biopsy plus an additional core from each suspicious area detected by TRUS. Pathological information included the diagnosis of Benign Prostatic Hyperplasia (BPH), acute or chronic prostatitis, chronic inflammatory atrophy, atypical small acinar proliferation, High Grade Intraepithelial Neoplasia (HGPIN) and prostate cancer with Gleason score.

Prostate cancer grade was assigned using the Epstein 5-grade system where low-grade disease was defined as Grade Group (GG) 1 to 2 (Gleason score≤3+4) and high-grade prostate cancer as GG 3 to 5 (Gleason score≥4+3).

All patients received a physical examination including measurement of height, weight, and waist circumference measurement before the prostate biopsy. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Additionally, resting blood pressure was recorded by auscultator methods. Fasting serum samples were analyzed for High-Density Lipoprotein (HDL), cholesterol, triglyceride, blood glucose, PSA. The study protocol was approved by the Institutional Research Review Board of Sun Yat-sen University (Ethical Application Ref: su2018-e1015) and written informed consent was acquired from all participants.

Exposure measures

Metabolic syndrome was defined according to the National Cholesterol Education Program Adult Treatment Panel Ⅲ (NCEP-ATP Ⅲ) criterial [9], which requires that at least three of five of the following standards are met: (1) high fasting blood glucose level: ≥110 mg/dl (6.1 mmol/L); (2) hypertriglyceridemia: ≥150 mg/dl (1.7 mmol/L); (3) reduced HDL cholesterol: <40 mg/dl (1.0 mmol/L) in men and <50 mg/dl (1.3 mmol/L) in women; (4) high blood pressure: ≥130/85 mmHg or use of anti-hypertensive drugs; (5) abdominal obesity: abdomen circumference >90 cm in men or >80 cm in women according to the 2000 World Health Organization criterial for abdominal obesity in the Western Pacific region.

Statistical analysis

SPSS 20.0 software (IBM Corporation, Armonk, NY, USA) was used for statistical analyses. Evaluation of data distribution showed a normal distribution of the study data set. Differences between groups of patients in medians for quantitative variables were tested by an unpaired t-test, and differences in categorical variables were compared using Chi-squared tests. The unconditional logistic regression analysis was carried out using data from patients for whom complete data were available. By use of multiple logistic regression with the enter method, the statistically significant variables as assessed in the univariate analysis were entered and investigated as predictors of prostate cancer presence versus absence and in a separate model comparing predictors of high-grade versus low-grade prostate cancer among men with cancer on biopsy. The logistic regression analysis was performed to estimate Odds Ratio (ORs) and 95% Confidence Intervals (CI). Two-sided $P<0.05$ were considered statistically significant.

Results

A total of 890 patients underwent trans rectal ultrasound-guided prostate biopsy in the study period. The patients' mean age was 67.5±7.9 years, their mean PSA was 14.44±9.87 ng/ml, their mean prostate volume 53.25±23.31 ml, their mean waist circumference was 86.13±6.24 cm, their mean weight was 65.03±10.09 kg and mean BMI was 23.21±3.16 kg/m^2. Of the 890

men, 247(27.75%) patients had MS according to the Adult Treatment Panel III criteria. No significant difference was observed for age and prostate volume between the groups with and without MS. Patients with MS had higher values of PSA, BMI, waist circumference, blood pressure, fasting blood glucose, and triglyceride, and presented with a lower HDL-cholesterol level, than did patients without MS (Table 1).

Patient's characteristics	Overall	No MS	MS	P-value[a]
Patients (%)	890	643(72.25)	247(27.75)	
Age, years	67.5±7.9	67.5±8.05	67.3±7.51	0.646
PSA, ng/ml	14.44±9.87	13.96±9.7	15.68±10.22	0.02
Prostate volume, ml	53.25±23.31	54.34±23.71	51.32±21.54	0.621
BMI, kg/m^2	23.21±3.16	22.47±2.78	25.14±3.29	0
Waist circumference, cm	86.13±6.24	82.69±9.44	92.98±8.55	0
Glycemia, mg/dl	5.57±1.39	5.23±0.89	6.44±1.96	0
Trygliceridemia, mg/dl	1.49±0.98	1.25±0.65	2.09±1.36	0
Cholesterol HDL, mg/dl	1.15±0.3	1.22±0.29	0.96±0.23	0
Systolic blood pressure, mmHg	135.14±19.03	132.72±18.88	141.45±17.99	0
Diastolic blood pressure, mmHg	78.21±10.28	77.09±9.73	81.12±11.1	0
MS: Metabolic Syndrome; PSA: Prostate-Specific Antigen; BMI: Body Mass Index; HDL: High-Density Lipoprotein. a: Student's t-test.				

Table 1: Patient's characteristics according to the presence or absence of Metabolic Syndrome.

Histological evaluation of biopsy cores showed prostate cancer in 404 (45.39%) patients and a diagnosis of benign prostatic hyperplasia/chronic prostatitis (390 patients, 43.82%) or HGPIN (96 patients, 10.79%) in the remaining 486 patients (54.61%). Patients diagnosed with prostate cancer had higher age and PSA, with a lower prostate volume, and more likely to be overweight and hyperglycemia than did patients without prostate cancer (Table 2). Among the 404 patients with prostate cancer, 130 (32.18%) had MS. At the same time, among the patients without prostate cancer, 117 (24.07%) had MS. There exists a significant difference in MS was observed between patients with cancer and without cancer (P=0.007).

Patient's characteristics	No cancer (486 patients)	Cancer (404 patients)	P-value[a]
Age, years	66.77±8.3	79.29±11.32	0
PSA, ng/ml	11.95±7.56	17.43±11.39	0
Prostate volume, ml	57.34±23.71	41.32±21.54	0
BMI, kg/m^2	22.53±2.98	24.03±3.18	0
Waist circumference, cm	85.61±7.39	88.56±7.27	0.003
Glycemia, mg/dl	5.47±1.38	5.68±1.4	0.021
Trygliceridemia, mg/dl	1.47±0.89	1.51±1.08	0.555
Cholesterol HDL, mg/dl	1.16±0.29	1.14±0.3	0.198
Systolic blood pressure, mmHg	134±19.26	136.52±18.68	0.054
Diastolic blood pressure, mmHg	78.21±10.34	78.21±10.22	0.998
MS, %	117 (24.07)	130 (32.18)	0.007[b]
MS, metabolic syndrome; PSA, prostate-specific antigen; BMI, body mass index; HDL, high-density lipoprotein. a: Student's t-test. b: Chi-squared test.			

Table 2: Patient's characteristics according to prostate biopsy diagnosis.

Out of 404 patients with prostate cancer, 204 (50.5%) patients had a Gleason score ≤3+4 and 200(49.5%) patients had a Gleason score ≥4+3. Obviously, higher PSA and BMI, waist circumference was seen in patients with high-grade disease compared to those with low-grade disease (Table 3). In addition, the presence of MS was also significantly common in high-grade prostate cancer patients (P=0.002).

Patient's characteristics	Low-grade (204 patients)	High-grade (200 patients)	P-value[a]
Age, years	68.60±6.91	67.94±7.72	0.36
PSA, ng/ml	14.78±9.52	20.14±12.48	0
Prostate volume, ml	52.69±20.52	53.98±24.66	0.648
BMI, kg/m^2	23.2±3.28	24.88±2.84	0
Waist circumference, cm	87.79±8.24	89.51±9.27	0.023
Glycemia, mg/dl	5.62±1.24	5.75±1.54	0.351
Trygliceridemia, mg/dl	1.41±1.15	1.6±1	0.076
Cholesterol HDL, mg/dl	1.12±0.33	1.15±0.28	0.421
Systolic blood pressure, mmHg	136.56±17.38	136.48±19.97	0.964
Diastolic blood pressure, mmHg	77.33±9.68	79.1±10.69	0.082
MS, %	51(25)	79(39.5)	0.002[b]

MS: Metabolic Syndrome; PSA: Prostate-Specific Antigen; BMI: Body Mass Index; HDL: High-Density Lipoprotein.
a: Student's t-test.
b: Chi-squared test.

Table 3: Patient's characteristics according to biopsy Gleason score in prostate cancer patients.

In the logistic regression analysis, the variables considered for entry into the multivariate analysis for predicting prostate cancer detection included age, PSA, DRE, prostate volume, BMI, waist circumference, and MS. While variables considered for entry into the separate model for predictors of high-grade versus low-grade prostate cancer included PSA, DRE, BMI, waist circumference, and MS. (data not shown) As seen in (Table 4), the multivariate analysis showed age, PSA, positive DRE, prostate volume, BMI, and MS were independent parameters associated with a higher risk of cancer on biopsy. In addition, the significant predictors of high-grade prostate cancer were PSA, BMI, and MS. In summary, the presence of MS was significantly associated with not only an increased prostate cancer risk (OR,1.814; P=0.003) but also a higher risk of high-grade disease (OR,1.844; P=0.005).

Prostate cancer detection	OR	95% CI	P-value[a]
Age	1.02	1.005-1.043	0.011
PSA	1.06	1.040-1.073	0
DRE	2.87	1.822-4.507	0
Prostate volume	0.98	0.975-0.995	0.004
BMI	1.13	1.077-1.194	0
Waist circumference	1.57	0.933-2.636	0.092
MS	1.81	1.233-2.669	0.003
Biopsy Gleason score≥4+3			
DRE	1.38	0.956-1.994	0.083
BMI	1.18	1.091-1.275	0.018
Waist circumference	1.56	0.887-2.739	0.123
MS	1.84	1.201-2.832	0.005

MS: Metabolic Syndrome; PSA: Prostate-Specific Antigen; BMI: Body Mass Index; HDL: High-Density Lipoprotein.
a: logistic regression analysis.

Table 4: Logistic regression analysis for predicting prostate cancer detection or a high Gleason score among men with prostate cancer on biopsy.

Discussion

Metabolic syndrome is characterized by a cluster of abnormal biochemical factors, epidemiological data show that MS is an increasingly important public health issue. Among American adults, the prevalence of MS increases with age, reaching 18.3% in people aged 20-39 and 46.7% in those 60 or older [10]. In mainland China, its overall prevalence is 19.2% for males and 27.0% for females; this rate is also higher in older age groups [11]. MS is related to cardiovascular disease or type 2 diabetes; however, the relationship between MS and malignancy is unclear. Recent studies have proven a relationship between MS and increased risk of cancers, including hepatocellular carcinoma, pancreatic cancer, gastric cancer, colorectal cancer and breast cancer. In addition, MS and its components are likewise associated with tumor progression in some cancers [12,13]. Changes in neoplastic metabolism, DNA oxidation damage or repair malfunction, chronic inflammation and Insulin-like Growth Factor 1 (IGF-1) may contribute to the relationship between MS and malignant cancer [14].

The relationship between MS and prostate cancer has also been examined, but a consensus has not been reached. In 2004, Laukkanen, et al. [4]. proposed MS as a composite factor associated with prostate cancer risk for the first time, in that prospective population-based study, men with MS were two fold more likely to develop prostate cancer than those without MS. In 2012, Esposito et al. performed a systematic review and meta-analysis on 14 data sets, demonstrating the lack of association between MS and risk of prostate cancer (RR (95% CI: 1.09 (0.88-1.34), P=0.438) [15]. Interestingly, in that paper, a remarkable difference among European (RR (95% CI: 1.28 (0.89-1.87), P=0.083), Asian (RR (95% CI: 0.98 (0.71-1.36), P=0.932), American populations (RR (95% CI: 0.79 (0.69-0.91), P=0.001) was clearly presented. In addition, several other cohort's studies of prostate cancer incidence in European populations have showed a significant positive association [3,4,16], while analogous studies performed on American cohorts revealed no [17] or a negative association[18].These discrepancies might be caused by different ethnical backgrounds and MS definitions. Compared with people in developed countries, the Chinese population has different environments and lifestyle modification.

In fact, in our study, we evaluated the relationship between MS and prostate cancer in Chinese patients who underwent trans rectal ultrasound-guided prostate biopsy. Our results showed that the presence of MS significantly increase both prostate cancer diagnosis risk and an increased risk of high-grade disease defined by Gleason score ≥4+3 in patients with prostate cancer on biopsy. Similar to our results, a positive association between MS and higher Gleason score was reported by several research groups [7,19]. However, no significant relationship was found between MS and Gleason score in studies by Han, et al. [20]. and Beebe-Dimmer, et al. [21] Interestingly, Jeon, et al. [8] showed that MS was associated with a significantly decreased risk of high-grade prostate cancer. Clearly, further research using large-scale populations is needed.

Furthermore, we investigated the relationship between individual component of MS and prostate cancer. The multivariate analysis showed that BMI was independently associated with an increased risk of prostate cancer or high-grade prostate cancer, which were partly consistent with several other studies [22,23]. This phenomenon might result from an inverse linear relationship between total testosterone and BMI. A previous study observed an inverse association of serum testosterone with visceral fat mass and the degree of hypogonadism was positively associated with degree of obesity in males [24].

The exact method by which MS influences prostate cancer remains uncertain. Several mechanisms are most commonly proposed to help explain the association: based on insulin resistance, the activation of the insulin/Insulin-like Growth Factor (IGF) pathway has been implicated in prostate cancer carcinogenesis though positive effects on cellular proliferation and anti-apoptosis [25]. Beyond changes in insulin, obesity is also linked with decreased androgen levels, those who have low testosterone tend toward a more aggressive phenotype [26]. Furthermore, chronic inflammation is seen with MS and results in release of several cytokines that can promote tumor growth [27]. Finally, altered levels of circulating adipokines are also associated with prostate cancer risk and progression [28]. Thus, further studies are warranted to explore the complex molecular mechanisms by which MS is linked to prostate cancer.

There are limitations to our study. First, the data were analyzed retrospectively, which carries an intrinsic selection bias. Second, we were lack of some important information, such as prostatectomy Gleason score, family history, and medication usage, including anti-diabetes, aspirin, and statins, which limited the statistical power and generalizability of our results. Third, given evidence that obesity is associated with a lower PSA, it is possible that obese men have a reduced chance of undergoing biopsy compared with other men, leading to delayed diagnosis and more advanced disease at diagnosis [29]. Finally, all the data were based on a limited number of patients enrolled from only Chinese men and thus the results cannot be generalized to other ethnic populations. Further prospective studies in large patient groups and with long-term follow-up as well as basic research are needed.

Conclusions

The results of our study suggest that MS is highly prevalent in a prostate biopsy population. Age, PSA, positive DRE, prostate volume, BMI, and MS were significant predictors for

prostate cancer diagnosis. Furthermore, PSA, BMI, and MS were significantly associated with an increased risk of high-grade prostate cancer. Therefore, the presence of MS was significantly associated with not only an increased prostate cancer risk but also a higher risk of high-grade disease. Further studies in a large patient population across multiple institutions and countries are needed to clarify which exact factors involved in the MS are responsible for the observed increase in prostate cancer and how these effects are mediated at a molecular level.

Acknowledgements

This study was funded by the grant from the National Natural Science Foundation of China (81802681)

Declaration of interest: The authors declare no conflict of interest.

References

1. Siegel RL, Miller KD, Jemal A (2015) Cancer statistics, 2015. CA Cancer J Clin 65: 5-29.
2. Pelser C, Mondul AM, Hollenbeck AR, Park Y (2013) Dietary fat, fatty acids, and risk of prostate cancer in the NIH.AARP diet and health study. Cancer Epidemiol Biomarkers Prev 22: 697-707.
3. Lund Haheim L, Wisloff TF, Holme I, Nafstad P (2006) Metabolic syndrome predicts prostate cancer in a cohort of middle-aged Norwegian men followed for 27 years. Am J Epidemiol 164: 769-774.
4. Laukkanen JA, Laaksonen DE, Niskanen L, Pukkala E, Hakkarainen A, et al. (2004) Metabolic syndrome and the risk of prostate cancer in Finnish men: a population-based study. Cancer Epidemiol Biomarkers Prev 13: 1646-1650.
5. Wallner LP, Morgenstern H, McGree ME, Jacobson DJ, St. Sauver JL, et al. (2011) The effects of metabolic conditions on prostate cancer incidence over 15 years of follow-up: results from the Olmsted County Study. BJU Int 107: 929-935.
6. Tande AJ, Platz EA, Folsom AR (2006) The metabolic syndrome is associated with reduced risk of prostate cancer. Am J Epidemiol 164: 1094-1102.
7. Morote J, Ropero J, Planas J, Bastarós JM, Delgado G, et al. (2013) Metabolic syndrome increases the risk of aggressive prostate cancer detection. BJU Int 111: 1031-1036.
8. Jeon KP, Jeong TY, Lee SY, Hwang SW, Shin JH, et al. (2012) Prostate Cancer in Patients with Metabolic Syndrome Is Associated with Low Grade Gleason Score When Diagnosed on Biopsy. Korean J Urol 53: 593-597.
9. Cholesterol N, Program E (2002) Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 106: 3143-3421.
10. Aguilar M, Bhuket T, Torres SB, Liu B, Wong RJ (2015) Prevalence of the metabolic syndrome in the United States, 2003-2012. JAMA 313: 1973-1974.
11. Li R, Li W, Lun Z, Zhang H, Sun Z, et al. (2016) Prevalence of metabolic syndrome in Mainland China: a meta-analysis of published studies. BMC Public Health 16: 296.
12. Park J, Morley TS, Kim M, Clegg DJ, Scherer PE (2014) Obesity and cancer - mechanisms underlying tumor progression and recurrence. Nat Rev Endocrinol 10: 455-465.
13. Tal S, Melzer E, Chsherbakov T, Malnick S (2014) Metabolic syndrome is associated with increased prevalence of advanced colorectal polyps. J Nutr Health Aging 18: 22-25.
14. Hauner D, Hauner H (2014) Metabolic syndrome and breast cancer: is there a link? Breast Care (Basel) 9: 277-281.
15. Esposito K, Chiodini P, Colao A, Lenzi A, Giugliano D (2012) Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care 35: 2402-2411.
16. Martin RM, Vatten L, Gunnell D, Romundstad P, Nilsen TI (2009) Components of the metabolic syndrome and risk of prostate cancer: the HUNT 2 cohort, Norway. Cancer Causes Control 20: 1181-1192.
17. Wallner LP, Morgenstern H, McGree ME, Sarma AV (2011) The effects of metabolic conditions on prostate cancer incidence over 15 years of follow-up: results from the Olmsted County Study. BJU Int 107: 929-935.
18. Tande AJ, Platz EA. Folsom AR (2006) The metabolic syndrome is associated with reduced risk of prostate cancer. Am J Epidemiol 164: 1094-1102.
19. De Nunzio C, Simone G, Brassetti A, Mastroianni R, Collura D, et al. (2016) Metabolic syndrome is associated with advanced prostate cancer in patients treated with radical retropubic prostatectomy: results from a multicenter prospective study. BMC Cancer 16: 407.
20. Han BK, Choi WS, Yu JH, Han JH, Chang IH, et al. (2007) The characteristics of prostate cancer with metabolic syndrome in Korean men. Korean J Urol 48: 585.
21. Beebe-Dimmer JL, Nock NL, Neslund-Dudas C, Rundle A, Bock CH, et al. (2009) Racial differences in risk of prostate cancer associated with metabolic syndrome. Urology 74: 185-190.
22. Qu YY, Dai B, Kong YY, Chang K, Ye DW, et al. (2013) Influence of obesity on localized prostate cancer patients treated with radical prostatectomy. Asian J Androl 15: 747-752.
23. Allott EH, Masko EM, Freedland SJ (2013) Obesity and prostate cancer: weighing the evidence. Eur Urol 63: 800-809.
24. McGrowder DA, Jackson LA, Crawford TV (2012) Prostate cancer and metabolic syndrome: is there a link? Asian Pac J Cancer Prev 13: 1-13.
25. Pollak M (2008) Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev Cancer. 2008; 8: 915-928.
26. Schnoeller T, Jentzmik F, Rinnab L, Cronauer MV, Damjanoski I, et al. (2013) Circulating free testosterone is an independent predictor of advanced disease in patients with clinically localized prostate cancer. World J Urol 31: 253-259.
27. DeNardo DG, Andreu P, Coussens LM (2010) Interactions between lymphocytes and myeloid cells regulate pro- versus anti-tumor immunity. Cancer Metastasis Rev 29: 309-316.

28. Zhang Q, Sun LJ, Qi J, Yang ZG, Huang T (2014) Influence of adipocytokines and periprostatic adiposity measurement parameters on prostate cancer aggressiveness. Asian Pac J Cancer Prev 15: 1879-1883.

29. Freedland SJ, Platz EA, Presti JC, Aronson WJ, Amling CL, et al. (2006) Obesity, serum prostate specific antigen and prostate size: implications for prostate cancer detection. J Urol 175: 500-504.