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## Metabolic Syndrome Components are Associated with Increased Prostate Cancer Risk

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**Background:** Our study investigated the associations of metabolic syndrome (MS) and metabolic indicators with prostate cancer (PCa) risk in the Chinese Han ethnic population.

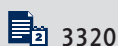
**Material/Methods:** We studied 101 PCa patients (without/with MS) and 120 healthy controls. Clinical data, including waist circumference, BMI, TG, FINS, FBG, and PCa-related indicators, were collected. The correlations between MS and PCa were analyzed.

**Results:** Compared to PCa, PV and Gleason scores increased and PSA levels decreased in PCa with MS group (all  $P < 0.001$ ). PV was positively correlated with BMI, FINS, and HOMA-IR ( $r = 0.459$ ,  $P < 0.001$ ;  $r = 0.421$ ,  $P = 0.001$ ;  $r = 0.490$ ,  $P = 0.003$ , respectively), and was negatively correlated with HDL-C ( $r = -0.378$ ,  $P < 0.001$ ). PSA level in MS patients was negatively correlated with BMI ( $r = -0.125$ ,  $P < 0.001$ ), TG ( $r = -0.256$ ,  $P < 0.001$ ) and FBG ( $r = -0.183$ ,  $P < 0.001$ ). Large PV, high TG, low HDL-C, high LDL-C, and high FBG were associated with an increased risk of PCa ( $P < 0.001$ , OR = 1.10, 95%CI: 1.009–3.304;  $P < 0.001$ , OR = 2.91, 95%CI: 1.612–5.241;  $P < 0.001$ , OR = 7.89, 95%CI: 3.908–15.947;  $P = 0.015$ , OR = 1.87, 95%CI: 1.131–3.077;  $P = 0.004$ , OR = 2.17, 95%CI: 1.280–3.686, respectively). MS-related indicators showed a positive relationship with PCa ( $P < 0.001$ , OR = 1.90, 95%CI: 1.107–10.629).

**Conclusions:** Our study shows that MS and metabolic indicators are associated with an increased risk of PCa, pointing to a novel therapeutic approach for PCa management.

**MeSH Keywords:** **Metabolic Syndrome X • Neoplasm Grading • Prostatic Neoplasms**

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## Background

Prostate cancer (PCa), which is the development of cancer in the male reproductive system, is a chronic disease that exhibits early initiation and slow progression [1]. PCa is the second most commonly diagnosed non-skin malignancy and the sixth leading cause of cancer-related death in males globally. Approximately 1.1 million males were newly diagnosed with PCa and 307 000 PCa-related deaths were recorded in 2012 [2]. PCa may cause no early symptoms, but typical symptoms in later stages including difficulty urinating, blood in urine, pain in the pelvis or back when urinating, or tiredness due to low red blood cell counts [3]. Non-modifiable factors that increase PCa risk include age, race, and family history of prostate disease [4]. Modifiable risk factors of PCa are related to lifestyle factors such as lack of physical activity, higher intake of dietary fat, red meat, refined carbohydrates, or excess calories, all of which are prevalent in most Western countries [5]. The precise underlying molecular and cellular mechanisms of PCa remain unknown; nevertheless, genetic alterations and the role of metabolic disturbances, including obesity, hyperinsulinemia, and insulin resistance, in the pathogenesis of PCa have been demonstrated [6].

Metabolic syndrome (MS) is a disorder of energy utilization and storage resulting from excess dietary calories and sedentary lifestyle, and describes a wide range of metabolic abnormalities [7]. MS is commonly diagnosed by a co-occurrence of 3 out of 5 of the following metabolic abnormalities: abdominal (central) obesity, increased blood pressure (BP), elevated fasting plasma glucose (FPG), high serum triglycerides (TG), and low high-density lipoprotein cholesterol (HDL-C) levels, with insulin resistance as the potential hallmark feature [8]. MS has been on the increase in most populations across the world and has become a major public health problem in many Western countries, including the USA, where 35–41% of adults are diagnosed with some form of MS, with a severe burden of comorbidities [9]. Recently emerging evidence suggests that MS, as an independent etiological factor, is linked to progression of several types of cancers, including breast cancer, endometrial cancer, colorectal cancer, and pancreatic cancer [7,10–12]. In addition, MS has been suggested as a potential risk factor in the pathogenesis of PCa [13]. In order to specifically address this issue, our study investigated the underlying associations of MS and metabolic indicators with PCa development and progression as a new frontier in prevention and treatment of PCa.

## Material and Methods

### Ethics statement

The Ethics Committee of the First Affiliated Hospital, Medical School of Xi'an Jiaotong University approved the study. Written

informed consent was provided by each eligible patient according to the Declaration of Helsinki [14].

### Patients

This study was carried out between May 2013 and May 2014 in a population of male patients (n=147) with pathologically confirmed prostate adenocarcinoma admitted to the First Affiliated Hospital, Medical School of Xi'an Jiaotong University [5]. A total of 101 Chinese Han ethnic male patients (mean age, 73.48±3.50 years; range, 50–99 years) were kept as the case group after removing of those who had other malignancies (n=11), acute or chronic hepatorenal dysfunction (n=3), family history of PCa (n=19), long-term administration of drugs that have effects on blood lipids, blood pressure, or related metabolism (n=8), and non-Chinese Han individuals (n=5). During the same period, 120 age-matched healthy male volunteers (mean age, 74.14±4.44 years) were enrolled as the control group from the Medical Examination Center of the First Affiliated Hospital, Medical School of Xi'an Jiaotong University. Of the controls, 15 out of 190 males who had prostate-specific antigen (PSA) ≥4 ng/ml, 11 males who had dysuria, 10 males who were diagnosed with prostatic hyperplasia by anus touch or B-ultrasound examination, 2 males who had other tumors, 1 male who had acute or chronic hepatorenal dysfunction, 16 males who had family history of PCa, 9 males who had long-term administration of drugs that affect blood lipids, blood pressure, or related metabolism, and 6 males who were non-Chinese Han, were excluded. Statistical analysis showed that all subjects had no addiction to alcohol or heavy cigarette smoking. Several patients reported light alcohol drinking or occasional cigarette smoking according to the definition of heavy alcohol drinking and cigarette smoking [15].

### Clinical data collection

General clinical data of all subjects, including height (cm), weight (kg), waist circumference (cm), and body mass index (BMI,  $BMI = \text{weight} / \text{height}^2$ ), were recorded. After morning fasting for 10 h, elbow venous blood was collected and common clinical laboratory parameters for PCa, including triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting insulin (FINS), glycosylated hemoglobin (HbA1c), free blood glucose (FBG), and serum PSA, were measured and recorded. Next, all subjects were asked to maintain supine position for 15 min, and then a standard mercury sphygmomanometer was used to measure right upper limb BP, including systolic blood pressure (SBP) and diastolic blood pressure (DBP). The homeostasis model assessment for insulin resistance (HOMA-IR) indexes of all subjects was calculated as  $HOMA-IR = FINS \times FBG / 22.5$ . All patients with PCa received transrectal ultrasonography and all controls received transabdominal ultrasonography

to measure prostate volume (PV) twice, and the mean values of 2 measurements were obtained [ $PV=0.52 \times \text{anteroposterior diameter} \times \text{transverse diameter} \times \text{vertical diameter (ml)}$ ]. Gleason scores of all subjects were recorded [16].

### Diagnostic criteria for MS

MS was diagnosed according to the Chinese Adult Dyslipidemia Prevention Guide revised in 2007 ([http://www.360doc.com/content/10/0615/23/494033\\_33307751.shtml](http://www.360doc.com/content/10/0615/23/494033_33307751.shtml)): (1) abdominal obesity, waist circumference  $>90$  cm; (2) TG  $>1.7$  mmol/L; (3) HDL-C  $\leq 1.04$  mmol/L; (4) BP  $\geq 130/85$  mmHg; (5) FBG  $\geq 6.1$  mmol/L, and/or 2-h postprandial blood glucose (ppBG)  $\geq 7.8$  mmol/L, or have a history of diabetes; patients meeting  $\geq 3$  above criteria were diagnosed with MS [17].

### Subgroups of PCa patients

Based on the diagnostic criteria for MS, all 101 enrolled PCa patients were assigned to either the PCa without MS group ( $n=45$ ) or the PCa with MS group ( $n=56$ ). In addition, according to the Chinese Adult Dyslipidemia Prevention Guide (2007), BMI  $\geq 24$  kg/m<sup>2</sup> is defined as overweight, and BMI  $\geq 28$  kg/m<sup>2</sup> as obesity, and all patients were assigned to either the normal weight group, the overweight group, or the obesity group. In the PCa patients with BMI  $\geq 24$  kg/m<sup>2</sup>, waist circumference  $>90$  cm is defined as abdominal obesity; hence, all patients were divided into either the non-abdominal obesity group or the abdominal obesity group according to waist circumference. HDL-C  $\leq 1.04$  mmol/L is defined as low HDL-C; thus, all patients were divided into either the normal HDL-C group or the low HDL-C group. FBG  $\geq 6.1$  mmol/L is defined as abnormal; therefore, all patients were divided into either the normal FBG group or the abnormal FBG group. Furthermore, according to the definition of insulin resistance in Chinese subjects by Weiping Jia ([http://en.cnki.com.cn/Article\\_en/CJFDTOTAL-ZGTL200002000.htm](http://en.cnki.com.cn/Article_en/CJFDTOTAL-ZGTL200002000.htm)), HOMA-IR  $>2.8$  is defined as insulin resistance; therefore, all patients were divided into either the insulin-sensitive group or the insulin-resistant group.

### Statistical analysis

Statistical analysis was conducted using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA). Main statistical indicators were verified by the normality test and the homogeneity of variance test [18]. The statistical indicators that deviated from standard normal distribution were statistically analyzed after natural logarithm transformation was performed. Measurement data are represented as mean  $\pm$  standard deviation (SD). The statistical comparison of the mean values between 2 groups was analyzed using the *t*-test. The statistical comparison of the mean values among multiple groups was analyzed using analysis of variance (ANOVA). Pair-wise comparison of the mean values

was analyzed using the LSD *t*-test. The statistical comparison of the mean values with heterogeneity of variance was also analyzed using *t*-test. Enumeration data are represented as rate or percentage. The statistical comparison of the rates or percentages between 2 groups was analyzed using the  $\chi^2$  test. Correlation analysis was performed utilizing the Pearson correlation analysis and logistic regression analysis [19]. *P* values of  $<0.05$  were regarded as statistically significant.

## Results

### Comparison of clinical characteristics in cases and controls

Table 1 shows the demographic and clinical characteristics of 221 subjects, consisting of 101 PCa patients and 120 healthy controls in a hospital-based population at the time of recruitment. Comparison between the PCa group and the control group demonstrated that the measured values of waist circumference, TG, TC, LDL, FINS, FBG, BMI, HOMA-IR, HbA1c, PV, and PSA were all significantly higher in PCa patients than in controls, with statistical significance (all  $P<0.05$ ). The level of HDL in the PCa group was clearly lower compared to the control group ( $P<0.05$ ). No statistical significance was seen in age, SBP, or DBP between PCa and control groups (all  $P>0.05$ ).

### Comparison of clinical characteristics in PCa patients with/without MS

Comparison of demographic and clinical characteristics between the PCa without MS group and the PCa with MS group is shown in Table 2. We did not detect significant differences in age, SBP, DBP, LDL-C, TC, or 5- $\alpha$  reductase inhibitor between PCa without MS group and PCa with MS group (all  $P>0.05$ ), while significant differences existed in BMI, FBG, HbA1c, HDL-C, TG, FINS, and HOMA-IR between the 2 groups (all  $P<0.05$ ). Compared to the PCa without MS group, PV and Gleason scores in the PCa with MS group were significantly higher (PV:  $51.19 \pm 15.64$  mL vs.  $39.77 \pm 13.67$  mL,  $P<0.001$ ), while serum PSA levels were significantly lower ( $23.32 \pm 1.32$  vs.  $33.51 \pm 3.21$ ,  $P<0.001$ ).

### Association of BMI and waist circumference with PV, PSA and Gleason score

As shown in Table 3, among the 101 patients with PCa, normal BMI ( $18.5$ – $23.9$  kg/m<sup>2</sup>) was detected in 35 patients (34.65%), overweight (BMI= $24$ – $27.9$  kg/m<sup>2</sup>) in 50 patients (49.51%), and obesity (BMI  $\geq 28$  kg/m<sup>2</sup>) in 16 patients (15.84%). The PV and the percentage of PCa patients with Gleason score  $\geq 7$  in the overweight group and obesity group were higher than those in the normal weight group (all  $P<0.05$ ). Serum PSA levels in the overweight group and obesity group tended to be lower

**Table 1.** Comparison of demographic and clinical characteristics between all patients with prostate cancer and healthy controls.

Variable	Prostate cancer group (n=101)	Control group (n=120)	t	P
Age (year)	73.48±3.50	74.14±4.44	1.24	0.218
Waist circumference (cm)	92.46±7.47	82.51±7.49	9.85	<0.001
BMI (kg/m <sup>2</sup> )	25.65±3.71	22.09±3.35	7.43	<0.001
SBP (mmHg)	140.06±7.53	138.14±7.38	1.91	0.058
DBP (mmHg)	78.32±8.44	77.73±7.82	0.54	0.593
FINS (uIU/ml)	8.94±2.69	5.59±1.92	10.49	<0.001
TG (mmol/L)	1.37±0.92	1.07±0.51	2.92	0.004
TC (mmol/L)	4.18±0.76	3.25±0.64	5.13	<0.001
LDL-C (mmol/L)	3.06±0.20	2.35±0.67	11.04	<0.001
HDL-C (mmol/L)	1.10±0.68	1.49±0.75	4.05	<0.001
FBG (mmol/L)	6.20±0.87	5.12±0.71	9.99	<0.001
HbA1C (%)	5.85±0.96	4.78±0.65	9.52	<0.001
HOMA-IR	2.81±1.49	1.05±0.62	11.09	<0.001
PV (mL)	46.06±20.24	30.45±10.33	7.02	<0.001
PSA	30.04±4.32	1.52±2.32	59.52	<0.001

BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FINS – fasting insulin; TG – triglyceride; TC – total cholesterol; LDL-C – low density lipoprotein cholesterol; HDL-C – high density lipoprotein cholesterol; FBG – free blood glucose; HbA1C – glycosylated hemoglobin; HOMA-IR – homeostasis model assessment for insulin resistance; PV – prostate volume.

compared with the normal weight group ( $P<0.05$ ). Comparison between the overweight group and the obesity group demonstrated no significant difference in PV, serum PSA level, or Gleason score (all  $P>0.05$ ). The PCa patients with BMI  $\geq 24$  kg/m<sup>2</sup> (n=66) were divided into the non-abdominal obesity group (n=17, 25.76%, waist circumference  $\leq 90$  cm) and the abdominal obesity group (n=49, 74.24%, waist circumference  $>90$  cm). The comparisons of PV, serum PSA level, and Gleason score between the non-abdominal obesity group and the abdominal obesity group are displayed in Table 4. PV in PCa patients with abdominal obesity was higher than that in non-abdominal obesity patients (51.9±16.51 ml vs. 41.4±11.25 ml,  $P=0.009$ ). No significant difference in serum PSA level or Gleason score was found between the non-abdominal obesity group and the abdominal obesity group (all  $P>0.05$ ).

#### Association of HDL-C with PV, PSA and Gleason score

All PCa patients were divided into the normal HDL-C group (n=64, 63.37%, HDL  $>1.04$  mmol/L) and the low HDL-C group (n=37, 36.63%, HDL  $\leq 1.04$  mmol/L). Comparisons in PV, serum PSA level, and Gleason score between the normal HDL-C group and the low HDL-C group are shown in Table 5, suggesting larger

PV in PCa patients with low HDL-C than in patients with normal HDL-C ( $P=0.002$ ), with no evident difference in serum PSA level or Gleason score between PCa patients with low HDL-C and patients with normal HDL-C (all  $P>0.05$ ).

#### Association of FBG with PV, PSA and Gleason score

As presented in Table 6, among the 101 patients with PCa, normal FBG ( $<6.1$  mmol/L) was found in 37 patients (36.63%) and abnormal FBG ( $\geq 6.1$  mmol/L) was found in 64 patients (63.37%). As compared with the PCa patients in the normal FBG group, PV in the abnormal FBG group increased significantly (50.4±22.56 vs. 41.16±20.80,  $P=0.040$ ) and serum PSA level clearly decreased (26.41±6.59 vs. 29.81±7.69,  $P=0.028$ ). No detectable difference in Gleason score was found between the normal FBG group and the abnormal FBG group ( $P>0.05$ ).

#### Association of PV and PSA with MS related indicators

Correlation analysis of PA and serum PSA level with MS-related indicators, including BMI, waist circumference, FBG, HbA1C, FINS, HDL-C, LDL-C, TG, TC, and HOMA-IR, implied a positive correlation between PV and BMI, FINS and HOMA-IR (BMI:

**Table 2.** Comparison of demographic and clinical characteristics between prostate cancer patients with and without metabolism syndrome.

Variable	Prostate cancer without MS (n=45)	Prostate cancer with MS (n=56)	t	P
Age (year)	72.43±7.16	74.95±7.47	1.68	0.097
Waist circumference (cm)	86.69±9.84	97.98±8.85	5.99	<0.001
BMI (kg/m <sup>2</sup> )	23.70±1.61	27.32±2.25	13.9	<0.001
SBP (mmHg)	137.84±10.34	141.14±9.38	1.01	0.316
DBP (mmHg)	77.13±8.44	79.91±7.79	1.7	0.092
FINS (uIU/ml)	6.46±2.84	12.54±4.19	8.66	<0.001
TG (mmol/L)	1.09±0.66	2.06±0.86	6.41	<0.001
TC (mmol/L)	4.13±0.86	4.27±0.94	0.78	0.437
LDL-C (mmol/L)	2.89±0.79	3.15±0.87	1.57	0.119
HDL-C (mmol/L)	1.22±0.51	0.98±0.33	2.73	0.007
FBG (mmol/L)	5.28±1.37	6.72±1.83	4.52	<0.001
HbA1C (%)	5.43±0.73	6.09±0.92	4.02	<0.001
HOMA-IR	1.60±0.96	3.76±1.78	7.78	<0.001
PV (mL)	39.77±13.67	51.19±15.64	3.91	<0.001
PSA	33.51±3.21	23.32±1.32	19.98	<0.001
Gleason score			11.49	<0.001
<6	28	16		
≥7	17	40		
5-alpha reductase inhibitor use			3.28	0.07
Yes	12	7		
No	33	49		

MS – metabolism syndrome; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; FINS – fasting insulin; TG – triglyceride; TC – total cholesterol; LDL-C – low density lipoprotein cholesterol; HDL-C – high density lipoprotein cholesterol; FBG – free blood glucose; HbA1C – glycosylated hemoglobin; HOMA-IR – homeostasis model assessment for insulin resistance; PV – prostate volume; PSA – prostate specific antigen.

**Table 3.** Comparison of prostate volume, serum prostate specific antigen level and Gleason score in prostate cancer patients among the normal weight group (n=35), overweight group (n=50) and obesity group (n=16).

Indicator	Normal weight group (n=35)	Overweight group (n=50)	Obesity group (n=16)	F	P
PV (ml)	38.1±10.64	49.44±15.83	51.66±16.23	8.02	<0.001
PSA (ng/ml)	31.44±2.02	26.43±2.34	26.18±2.01	61.70	<0.001
Gleason score				6.72	0.035
<6	21	19	4		
≥7	14	31	12		

PV – prostate volume; PSA – prostate specific antigen.



**Table 4.** Comparison of prostate volume, serum prostate specific antigen level and Gleason score in prostate cancer patients between the non-abdominal obesity group (n=17) and the abdominal obesity group (n=49).

Indicator	Non-abdominal obesity group (n=17)	Abdominal obesity group (n=49)	t	P
PV (ml)	41.4±11.25	51.9±16.51	2.91	0.005
PSA (ng/ml)	26.39±2.07	25.67±2.03	1.24	0.225
Gleason score			1.50	0.220
<6	8	15		
≥7	9	34		

PV – prostate volume; PSA – prostate specific antigen.

**Table 5.** Comparison of prostate volume, serum prostate specific antigen level and Gleason score in prostate cancer patients between the normal HDL-C group (n=64) and the low HDL-C group (n=37).

Indicator	Normal HDL-C group (n=64)	Low HDL-C group (n=37)	t	P
PV (ml)	42.04±14.87	52.97±16.92	3.82	0.002
PSA (ng/ml)	28.09±0.66	27.83±0.71	1.82	0.073
Gleason score			0.22	0.641
<6	29	15		
≥7	35	22		

HDL-C – high density lipoprotein cholesterol; PV – prostate volume; PSA – prostate specific antigen.

**Table 6.** Comparison of prostate volume, serum prostate specific antigen level and Gleason score in prostate cancer patients between the normal FBG group (n=37) and the abnormal FBG group (n=64).

Indicator	Normal FBG group (n=37)	Abnormal FBG group (n=64)	t	P
PV (ml)	41.16±20.80	50.4±22.56	2.09	0.040
PSA (ng/ml)	29.81±7.69	26.41±6.59	2.25	0.028
Gleason score			0.002	0.960
<6	16	28		
≥7	21	36		

FBG – free blood glucose; PV – prostate volume; PSA – prostate specific antigen.

r=0.459,  $P<0.001$ ; FINS: r=0.421,  $P=0.001$ ; HOMA-IR: r=0.490,  $P=0.003$ ; respectively) and a negative relationship between PV and HDL-C (r=-0.378,  $P<0.001$ ) (Table 7). In addition, serum PSA level in MS patients was negatively correlated with BMI, TG, and FBG (BMI: r=-0.125,  $P<0.001$ ; TG: r=-0.030,  $P<0.001$ ; FBG: r=-0.183,  $P<0.001$ ; respectively) (Table 8).

#### Logistic regression analysis of MS indicators for PCa risk

The logistic regression analysis was conducted with PCa as the dependent variable, and large PV, high BMI, high TG, low HDL-C, high LDL-C, and high FBG as independent variables, suggesting that large PV, high TG, low HDL-C, high LDL-C, and high FBG were correlated to an increased risk

of PCa (large PV:  $P\leq 0.001$ , OR=1.10, 95%CI=1.009–3.304; high TG:  $P<0.001$ , OR=2.91, 95%CI=1.612–5.241; low HDL-C:  $P<0.001$ , OR=7.89, 95%CI=3.908–15.947; high LDL-C:  $P=0.015$ , OR=1.87, 95%CI=1.131–3.077; high FBG:  $P=0.004$ , OR=2.17, 95%CI=1.280–3.686, respectively) (Table 9).

#### Multivariate logistic regression analysis of the number of MS components for PCa risk

As seen in Table 10, a multivariate non-conditional logistic regression analysis was conducted with the number of the components of the MS as the dependent variable and PCa as the independent variable. The variables were selected with  $\alpha=0.05$ . Results showed that the number of components of

**Table 7.** Correlation analysis of prostate volume with metabolism syndrome related indicators including waist circumference, body mass index, free blood glucose, glycosylated hemoglobin, fasting insulin, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglyceride, total cholesterol, and homeostasis model assessment for insulin resistance in prostate cancer cases (n=101).

	r	P
Waist circumference	0.140	0.164
BMI	0.459	<0.001
FBG	0.091	0.364
HbA1C	0.153	0.127
FINS	0.421	0.001
HDL-C	-0.378	<0.001
LDL-C	0.031	0.757
TG	0.006	0.951
TC	-0.071	0.483
HOMA-IR	0.490	0.003

BMI – body mass index; FBG – free blood glucose; HbA1C – glycosylated hemoglobin; FINS – fasting insulin; HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; TG – triglyceride; TC – total cholesterol; HOMA-IR – homeostasis model assessment for insulin resistance.

**Table 8.** Correlation analysis of serum prostate specific antigen level with metabolism syndrome related indicators including waist circumference, body mass index, free blood glucose, glycosylated hemoglobin, fasting insulin, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglyceride, total cholesterol, and homeostasis model assessment for insulin resistance.

	r	P
Waist circumference	0.030	0.716
BMI	-0.125	< 0.001
FBG	-0.183	< 0.001
HbA1C	0.153	0.127
FINS	0.089	0.376
HDL-C	0.014	0.840
LDL-C	0.038	0.586
TG	-0.256	< 0.001
TC	-0.092	0.264
HOMA-IR	0.250	0.623

BMI – body mass index; FBG – free blood glucose; HbA1C – glycosylated hemoglobin; FINS – fasting insulin; HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; TG – triglyceride; TC total cholesterol; HOMA-IR – homeostasis model assessment for insulin resistance.

**Table 9.** A non-conditional logistic regression analysis with prostate cancer as dependent variable, and large PV, high BMI, high TG, low HDL-C, high LDL-C, and high FBG as independent variables for prostate cancer risk.

Variable	OR <sup>1</sup>	95%CI <sup>1</sup>	OR <sup>2</sup>	95%CI <sup>2</sup>	P
PV >30 ml	1.25	1.019–3.470	1.1	1.009–3.304	<0.001
BMI ≥24 kg/cm <sup>2</sup>	3.5	1.343–9.804	2.51	0.180–9.521	0.066
TG ≥1.7 mmol/L	3.52	1.346–5.729	2.91	1.612–5.241	<0.001
HDL <0.9 mmol/L	8.12	4.015–16.236	7.89	3.908–15.947	<0.001
LDL ≥3.5 mmol/L	1.92	1.023–4.125	1.87	1.131–3.077	0.015
FPG ≥6.1 mmol/L	2.42	1.207–4.804	2.17	1.280–3.686	0.004

OR – odds ratio; CI – confidence interval; <sup>1</sup> univariate non-conditional logistic regression analysis; <sup>2</sup> multivariate non-conditional logistic regression analysis, P test value of multivariate non-conditional logistic regression analysis.

the MS, including waist circumference, BP, FBG, HDL-C, and TG, were related to an increased risk of PCa ( $P<0.001$ , OR=1.90, 95%CI=1.107–10.629). The risk of PCa increased 1.90-fold for each additional component of the MS.

## Discussion

In our present study, the potential role of MS in the diagnosis of PCa was further strengthened by the detailed evidence we gathered in relation to the elevated risk of PCa, as increasing number of MS components became involved. MS components

**Table 10.** A multivariate non-conditional logistic regression analysis with the number of the components of the MS as dependent variable, and PCa as independent variable for prostate cancer risk.

Variable Number of components	Prostate cancer group	Control group	OR	95%CI	P
0	45	81			
1	15	13			
2	13	11			
3	15	10	1.9	1.107–10.629	<0.001
4	8	5			
5	5	0			

OR – odds ratio; CI – confidence interval; MS – metabolic syndrome, the components of the MS including waist circumference, blood pressure, free blood glucose, high-density lipoprotein cholesterol and triglyceride.

analyzed in this study for their association with PCa included abdominal obesity, high TG, high LDL-C, low HDL-C, high FBG, and high BP. Additionally, to the best of our knowledge, this is the first study of the association of MS and its individual components with the risk of PCa in a Chinese Han ethnic population. Waist circumference at diagnosis, the most frequently utilized measurement to evaluate abdominal obesity in MS, was related to an increased PCa risk, which might result from an inverse linear relationship between total testosterone and BMI. A previous study observed an inverse association of serum total and free levels of testosterone with visceral fat mass and the degree of hypogonadism was positively associated with degree of obesity in males [20]. The evidence of the correlation of overweight and obesity at different ages with PCa risk is inconsistent; nevertheless, a positive correlation was consistently observed between obesity and the aggressiveness, progression, and mortality of PCa by Coogan et al. [21]. Furthermore, as shown in the prospective American Cancer Society Cancer Prevention Study II, the risk of PCa was 8% higher in overweight subjects, 20% higher in obese subjects, and 34% higher in severely obese subjects (BMI >35 kg/m<sup>2</sup>) as compared with those with normal weight based on a population of over 400 000 males [22].

We found a large difference in PV between PCa patients and controls, showing that mean PV in PCa patients was significantly higher than in controls. PV has been reported to be positively correlated with obesity [23]. A recent study of 872 men recruited through a health promotion center showed that PV was positively correlated with central obesity as represented by waist circumference, but not with overall obesity as represented by BMI [24]. The underlying explanation of this positive relationship may be that obesity could result in increased estrone and estradiol levels, as well as decreased testosterone and serum globulin levels, leading to prostatic enlargement [25,26]. In addition, the more likely reason in our present study may be that

the differences in modality of PV measurement (transrectal ultrasonography vs. transabdominal ultrasonography) restrict the diagnostic accuracy, which results in sample selection bias.

In addition, high TG, high LDL-C, and low HDL-C are risk factors of PCa, and influence lipid raft signaling to alter the activation of the EGF/AKT pathway in human PCa cells, which may lead to tumor angiogenesis [27]. Therefore, it is reasonable to conclude that high TG, high LDL-C, and low HDL-C are linked to the increased risk of PCa. The link between BP and PCa is compelling because it has been shown that the risk of PCa increases 80% with each 12-mm elevation in DBP in males [28]. Consistent with our results, Pelucchi et al. reported that the risk of PCa was 66% higher in male patients with MS compared to their non-MS counterparts, and that the risk of PCa increased 4-fold when the number of components of MS increased in males with presence of obesity, hypertension, diabetes, and hypercholesterolemia [29]. In addition, Sourbeier et al. also demonstrated that metabolic abnormalities related to obesity, diabetes, hypertension, and hypercholesterolemia are related to the aggressiveness of PCa [13].

Several plausible mechanisms can be considered to explain why MS may increase PCa risk. MS components are associated with a pro-inflammatory state – elevated levels of CRP, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin 8 (IL-8), IL-6, and IL-1 $\beta$  – which are directly linked with PCa risk [30]. Also, high cholesterol levels linked to MS are correlated with increased risk of PCa [31]. Finally, MS conditions can also alter circulating levels of insulin-like growth factor gene 1 (IGF-1), leptin, and adiponectin, all of which are linked to PCa risk [32]. For example, a meta-analysis demonstrated that data from the peer-reviewed literature suggest an association of MS with PCa, although the evidence for a causal relationship remains missing, suggesting that MS could be considered a new domain in basic and clinical research in patients with PCa [1]. In addition,



MS, a cluster of risk factors for cardiovascular disease, including insulin resistance, dyslipidemia, elevated BP, abdominal obesity and proinflammatory states, has been proposed as a risk factor for PCa in the study of Kheterpal et al. [6]. However, Esposito et al. demonstrated that MS is weakly and non-significantly associated with PCa risk, but associations vary with geographic location [33]. Therefore, the controversial nature of existing data should be acknowledged.

The findings of our study indicate that insulin resistance is also a risk factor for PCa, and the underlying biological mechanisms may be related to the IGF pathway [34]. Insulin resistance may increase IGF-1 level through suppressing hepatic secretion of IGF-binding protein-1, and IGF-1 may stimulate cell proliferation and differentiation, at the same time inhibiting cell apoptosis [35]. An earlier study also found higher fasting plasma insulin levels in PCa males who died as compared with those who survived [36].

There are several limitations in our present study. Firstly, the relatively smaller inclusion of subjects and lower number of variables might have an influence on the statistical analysis performance to determine whether there was any correlation between MS and its individual components and the risk of PCa in a Chinese Han ethnic population. Secondly, the study design is similar to a case-control study, which is not as robust as a cohort study, and this might have a negative effect on the optimization of acquisition parameters such as abdominal

obesity, high TG, high LDL-C, low HDL-C, high FBG, and high BP. Thirdly, different PV measurement in PCa patients (transrectal ultrasonography) and controls (transabdominal ultrasonography) influenced the detection of PV, which may restrict the diagnostic accuracy, leading to sample selection bias.

## Conclusions

In summary, the results of our study indicate that MS and metabolic indicators are related to increased risk of PCa, indicating that prevention and treatment of MS might be novel therapeutic approaches for PCa. Further studies in a large patient population across multiple institutions and countries are needed to confirm the results of our study and to better understand the exact factors involved in MS that contribute to the increased risk of PCa and how the effects are mediated at a molecular level.

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## Competing interests

The authors have declared that they have no competing interests.

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