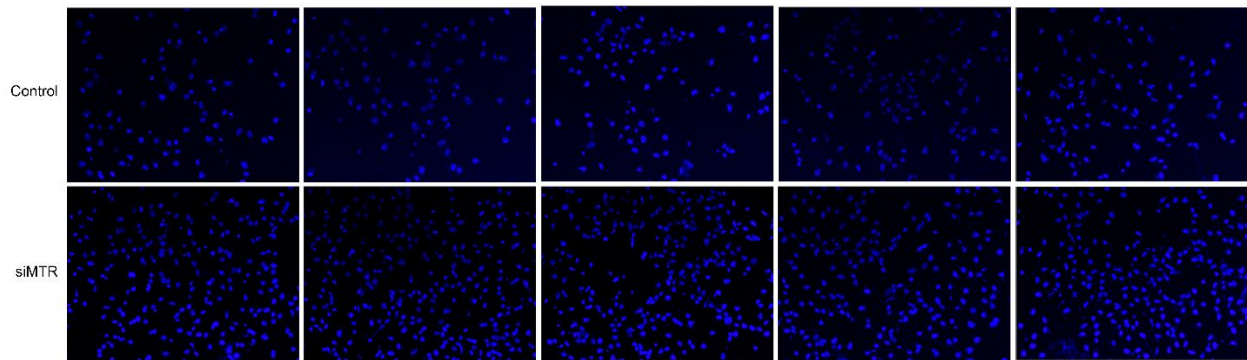


## Supplementary file

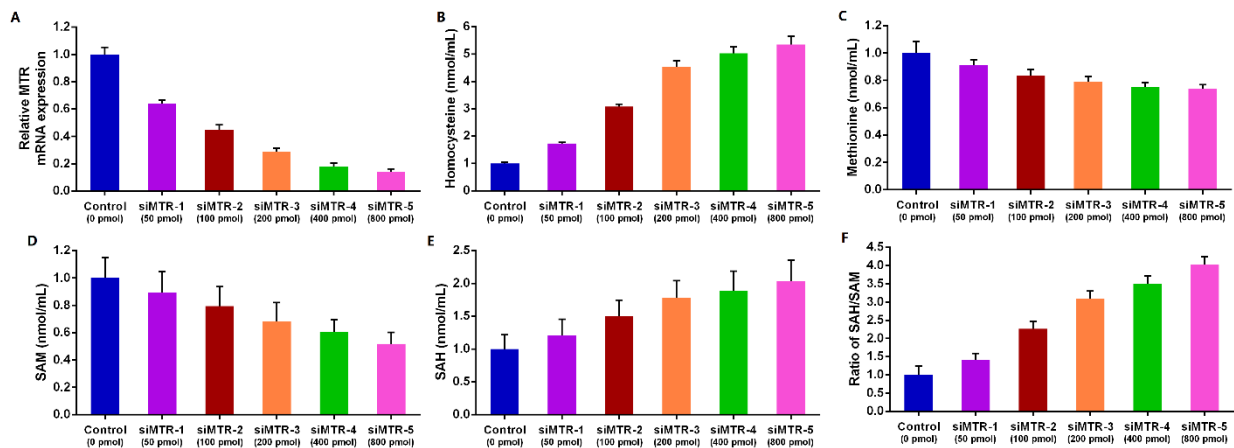
### **Functional variants of the 5-methyltetrahydrofolate-homocysteine methyltransferase gene significantly increase susceptibility to prostate cancer: Results from an ethnic Han Chinese population**

**Running title: Functional variants of *MTR* increase susceptibility to PCa**

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**Supplementary Figure 1. Down-regulation of *MTR* significantly increased PCa cell invasion.** Down-regulation of *MTR* significantly increased the number of invading PC3 cells. Each experiment was performed in triplicate and five random microscopic fields were evaluated for each insert.



**Supplementary Figure 2. Down-regulation of *MTR* contributes to elevated cellular homocysteine and SAH levels, reduced methionine and SAM levels, and increased SAH/SAM ratio in LNCaP cells.** (A) Knockdown efficiency of gradient *MTR* siRNA was measured using quantitative real-time polymerase chain reaction. (B) Cellular homocysteine concentration after transfection with gradient *MTR* siRNA. (C) Cellular methionine level after transfected with gradient *MTR* siRNA. (D) Cellular SAM level after transfection with gradient *MTR* siRNA. (E) Cellular SAH level after transfection with gradient *MTR* siRNA. (F) Ratio of SAH/SAM after transfection with gradient *MTR* siRNA. Each value represents the mean  $\pm$  SD of three independent experiments, and each experiment was performed in triplicate.

**Supplementary Table 1.** The linkage disequilibrium structure of *MTR* gene variants

Variants	D' statistic			Variants	R <sup>2</sup> statistic		
	rs28372871	rs1131450	rs1805087		rs28372871	rs1131450	rs1805087
rs28372871	.	0.265	0.646	rs28372871	.	0.022	0.046
rs1131450	.	.	0.235	rs1131450	.	.	0.002
rs1805087	.	.	.	rs1805087	.	.	.

**Supplementary Table 2.** The linkage disequilibrium structure of *MTRR* gene variants

Variants	D' statistic		Variants	R <sup>2</sup> statistic	
	rs326119	rs1801394		rs326119	rs1801394
rs326119	.	0.929	rs326119	.	0.137
rs1801394	.	.	rs1801394	.	.

**Supplementary Table 3.** Stratified analysis for associations between genetic polymorphisms in homocysteine removal genes and PCa risk by dominant genetic model in Han Chinese men

Variables	rs28372871		Adjusted OR <sup>a</sup> (95% CI)	<i>P</i>	<i>P</i> <sup>hom</sup>	rs1131450		Adjusted OR <sup>a</sup> (95% CI)	<i>P</i>	<i>P</i> <sup>hom</sup>	rs1805087		Adjusted OR <sup>a</sup> (95% CI)	<i>P</i>	<i>P</i> <sup>hom</sup>
	(cases/controls)					(cases/controls)					(cases/controls)				
	TT	TG/GG	GG	GA/AA	AA	AG/GG									
Age (yr), median															
≤68	248/376	767/929	1.18 (0.95-1.48)	0.140	0.660	580/813	435/492	<b>1.27 (1.04-1.56)</b>	<b>0.018</b>	0.967	830/1085	185/220	1.08 (0.83-1.40)	0.580	0.507
>68	201/203	601/518	1.23 (0.92-1.65)	0.160		465/454	337/267	1.19 (0.92-1.56)	0.190		651/607	151/114	1.26 (0.90-1.78)	0.180	
BMI (kg/m <sup>2</sup> )															
<25	347/423	961/1040	1.12 (0.93-1.34)	0.230	0.069	779/916	529/547	1.10 (0.93-1.30)	0.250	0.052	1064/1223	244/240	1.16 (0.94-1.43)	0.180	0.753
≥25	102/156	407/407	<b>1.54 (1.12-2.12)</b>	<b>0.007</b>		266/351	243/212	<b>1.48 (1.13-1.94)</b>	<b>0.005</b>		417/469	92/94	1.08 (0.75-1.54)	0.680	
Hypertension															
No	274/344	780/857	1.11 (0.90-1.37)	0.320	0.291	599/748	455/453	1.17 (0.97-1.42)	0.100	0.768	859/1001	195/200	1.10 (0.86-1.41)	0.460	0.869
Yes	175/235	588/590	1.27 (0.98-1.64)	0.072		446/519	317/306	1.13 (0.89-1.43)	0.310		622/691	141/134	1.27 (0.94-1.71)	0.120	
Diabetes mellitus															
No	406/524	1230/1302	<b>1.21 (1.03-1.43)</b>	<b>0.024</b>	0.995	946/1140	960/686	1.15 (0.99-1.34)	0.064	0.474	1330/1523	306/303	1.15 (0.95-1.40)	0.160	0.217
Yes	43/55	138/145	1.29 (0.73-2.27)	0.380		99/127	82/73	1.47 (0.90-2.41)	0.130		151/169	30/31	1.34 (0.69-2.60)	0.390	
Cardiovascular disease															
No	415/525	1245/1317	1.18 (1.00-1.39)	0.053	0.387	953/1155	707/687	<b>1.19 (1.02-1.38)</b>	<b>0.026</b>	0.586	1353/1549	307/293	1.19 (0.98-1.44)	0.087	0.144
Yes	34/54	123/130	1.51 (0.81-2.82)	0.190		92/112	65/72	1.09 (0.63-1.87)	0.760		128/143	29/41	0.79 (0.41-1.56)	0.500	
Gleason score															
≤7	331/579	881/1447	1.05 (0.88-1.26)	0.570	<b>0.002</b>	736/1267	476/759	1.01 (0.86-1.20)	0.870	<b>0.001</b>	985/1692	227/334	1.17 (0.95-1.44)	0.150	0.758
≥8	118/579	487/1447	<b>1.64 (1.27-2.13)</b>	<b>0.0001</b>		309/1267	296/759	<b>1.64 (1.32-2.03)</b>	<b>&lt;0.0001</b>		496/1692	109/334	1.17 (0.89-1.56)	0.270	
Extracapsular extension															
No	357/579	874/1447	0.94 (0.79-1.12)	0.500	<b>&lt;0.0001</b>	773/1267	458/759	0.92 (0.78-1.08)	0.320	<b>&lt;0.001</b>	1002/1692	229/334	1.16 (0.94-1.43)	0.170	0.883
Yes	92/579	494/1447	<b>2.27 (1.71-3.01)</b>	<b>&lt;0.0001</b>		272/1267	314/759	<b>2.01 (1.62-2.51)</b>	<b>7×10<sup>-4</sup></b>		479/1692	107/334	1.26 (0.95-1.68)	0.120	
Seminal vesicle invasion															
No	383/579	1008/1447	1.02 (0.86-1.21)	0.790	<b>&lt;0.0001</b>	844/1267	547/759	1.02 (0.88-1.20)	0.760	<b>&lt;0.001</b>	1133/1692	258/334	1.18 (0.97-1.44)	0.100	0.924
Yes	66/579	360/1447	<b>2.41 (1.72-3.36)</b>	<b>&lt;0.001</b>		201/1267	225/759	<b>1.99 (1.54-2.56)</b>	<b>&lt;0.0001</b>		348/1692	78/334	1.24 (0.89-1.73)	0.200	

**Supplementary Table 3 Continued.** Stratified analysis for associations between genetic polymorphisms in homocysteine removal genes and PCa risk by dominant genetic model in Han Chinese men

Positive surgical margin															
No	358/579	1107/1447	<b>1.22 (1.03-1.45)</b>	<b>0.006</b>	0.623	847/1267	618/759	<b>1.16 (1.00-1.36)</b>	<b>0.005</b>	0.639	1197/1692	268/334	1.10 (0.90-1.33)	0.360	0.698
Yes	91/579	261/1447	1.11 (0.81-1.53)	0.510		198/1267	154/759	1.24 (0.93-1.66)	0.140		284/1692	68/334	<b>1.69 (1.17-2.45)</b>	<b>0.006</b>	
Lymph node involvement															
No	424/579	1239/1447	1.16 (0.98-1.36)	0.076	<b>0.016</b>	971/1267	692/759	1.13 (0.98-1.31)	0.100	<b>0.021</b>	1343/1692	320/334	<b>1.21 (1.00-1.46)</b>	<b>0.045</b>	<b>0.011</b>
Yes	25/579	129/1447	<b>1.99 (1.18-3.34)</b>	<b>0.006</b>		74/1267	80/759	<b>1.89 (1.26-2.84)</b>	<b>0.002</b>		138/1692	16/334	0.67 (0.36-1.24)	0.190	
Variables	rs326119		Adjusted OR <sup>a</sup>	<i>P</i>	<i>P</i> <sup>hom</sup>	rs1801394		Adjusted OR <sup>a</sup>	<i>P</i>	<i>P</i> <sup>hom</sup>	rs2850144		Adjusted OR <sup>a</sup>	<i>P</i>	<i>P</i> <sup>hom</sup>
	(cases/controls)					(cases/controls)					(cases/controls)				
	AA	AC/CC	(95% CI)	AA	AG/GG	CC	CG/GG	(95% CI)							
Age (yr), median															
≤68	497/625	518/680	0.96 (0.81-1.13)	0.610	0.179	556/719	459/586	1.01 (0.86-1.19)	0.880	0.866	430/546	585/759	0.98 (0.83-1.16)	0.800	0.751
>68	399/319	403/402	0.78 (0.61-1.02)	0.067		429/392	373/329	0.97 (0.75-1.26)	0.840		344/298	458/423	0.92 (0.71-1.20)	0.540	
BMI (kg/m <sup>2</sup> )															
<25	646/670	662/793	0.86 (0.73-1.02)	0.078	0.382	710/809	598/654	1.01 (0.86-1.19)	0.910	0.696	555/614	753/849	0.99 (0.84-1.17)	0.920	0.630
≥25	250/274	259/289	1.00 (0.77-1.32)	0.980		275/302	234/261	0.92 (0.70-1.20)	0.540		219/230	290/333	0.94 (0.72-1.23)	0.660	
Hypertension															
No	527/542	527/659	<b>0.80 (0.67-0.97)</b>	<b>0.022</b>	0.110	554/672	500/529	1.14 (0.94-1.37)	0.180	0.041	436/514	618/687	1.12 (0.93-1.35)	0.240	0.077
Yes	369/402	394/423	1.02 (0.81-1.29)	0.840		431/439	332/386	0.80 (0.64-1.01)	0.060		338/330	425/495	0.82 (0.65-1.03)	0.094	
Diabetes mellitus															
No	803/852	833/974	0.91 (0.79-1.06)	0.230	0.584	893/1013	743/813	0.99 (0.85-1.14)	0.840	0.614	699/773	937/1053	1.02 (0.88-1.18)	0.810	0.290
Yes	93/92	88/108	0.72 (0.43-1.18)	0.190		92/98	89/102	0.89 (0.55-1.44)	0.630		75/71	106/129	0.71 (0.43-1.17)	0.180	
Cardiovascular disease															
No	819/843	841/999	0.87 (0.75-1.01)	0.070	0.098	900/1015	760/827	0.99 (0.86-1.15)	0.920	0.615	705/768	955/1074	0.99 (0.85-1.15)	0.880	0.740
Yes	77/101	80/83	1.72 (1.00-2.95)	0.050		85/96	72/88	0.77 (0.45-1.34)	0.360		69/76	88/108	1.06(0.62-1.81)	0.820	
Gleason score															
≤7	611/944	601/1082	0.84 (0.72-0.99)	0.039	0.262	645/1111	567/915	1.01 (0.86-1.19)	0.930	0.309	525/844	687/1182	0.96 (0.82-1.14)	0.660	0.458
≥8	285/944	320/1082	1.00 (0.81-1.24)	1.000		340/1111	265/915	0.92 (0.74-1.15)	0.470		249/844	356/1182	1.00 (0.80-1.24)	0.980	

**Supplementary Table 3 Continued.** Stratified analysis for associations between genetic polymorphisms in homocysteine removal genes and PCa risk by dominant genetic model in Han Chinese men

Extracapsular extension															
No	613/944	618/1082	0.87 (0.74-1.02)	0.089	0.612	654/1111	577/915	0.98 (0.84-1.16)	0.850	0.255	511/844	720/1182	1.04 (0.89-1.23)	0.600	0.251
Yes	283/944	303/1082	0.94 (0.76-1.17)	0.600		331/1111	255/915	0.93 (0.74-1.16)	0.500		263/844	323/1182	0.80 (0.65-1.00)	0.052	
Seminal vesicle invasion															
No	688/944	703/1082	0.89 (0.76-1.03)	0.120	0.842	738/1111	653/915	0.99 (0.85-1.16)	0.910	0.120	585/844	806/1182	1.00 (0.86-1.17)	0.990	0.464
Yes	208/944	218/1082	0.95 (0.74-1.22)	0.680		247/1111	179/915	0.86 (0.67-1.12)	0.260		189/844	237/1182	0.86 (0.67-1.11)	0.240	
Positive surgical margin															
No	722/944	743/1082	0.90 (0.78-1.05)	0.180	0.965	780/1111	685/915	1.01 (0.87-1.17)	0.940	0.135	622/844	843/1182	0.99 (0.85-1.15)	0.870	0.827
Yes	174/944	178/1082	0.82 (0.62-1.08)	0.160		205/1111	147/915	0.88 (0.66-1.17)	0.360		152/844	200/1182	0.93 (0.70-1.24)	0.630	
Lymph node involvement															
No	827/944	836/1082	0.88 (0.77-1.02)	0.094	0.274	898/1111	765/915	0.98 (0.85-1.13)	0.780	0.578	704/844	959/1182	0.99 (0.85-1.14)	0.840	0.483
Yes	69/944	85/1082	1.01 (0.68-1.50)	0.960		87/1111	67/915	0.96 (0.65-1.43)	0.860		70/844	84/1182	0.84 (0.56-1.26)	0.400	

OR, odds ratio; 95%CI, 95% confidence interval.

<sup>a</sup>Adjusted for age, BMI, hypertension, diabetes mellitus, and cardiovascular disease in multivariate logistic regression models.

<sup>hom</sup>*P* value for homogeneity test using the  $\chi^2$ -based Q-test.

**Supplementary Table 4.** Stratified analysis for associations between genetic polymorphisms in homocysteine removal genes and PCa risk by log-additive genetic model in Han Chinese men

Variables	rs28372871		rs1131450		rs1805087	
	Adjusted OR <sup>a</sup> (95% CI)	<i>P</i>	Adjusted OR <sup>a</sup> (95% CI)	<i>P</i>	Adjusted OR <sup>a</sup> (95% CI)	<i>P</i>
Age (yr), median						
≤68	1.14 (0.99-1.32)	0.061	<b>1.28 (1.08-1.52)</b>	<b>0.005</b>	1.05 (0.83-1.34)	0.680
>68	<b>1.23 (1.02-1.49)</b>	<b>0.027</b>	1.20 (0.96-1.50)	0.110	1.30 (0.95-1.78)	0.100
BMI (kg/m <sup>2</sup> )						
<25	1.13 (1.00-1.27)	0.045	1.13 (0.98-1.30)	0.093	1.17 (0.96-1.43)	0.120
≥25	<b>1.37 (1.12-1.66)</b>	<b>0.002</b>	<b>1.43 (1.13-1.79)</b>	<b>0.002</b>	1.08 (0.77-1.51)	0.650
Hypertension						
No	1.09 (0.96-1.25)	0.190	1.18 (1.00-1.39)	0.044	1.09 (0.86-1.37)	0.480
Yes	<b>1.26 (1.07-1.48)</b>	<b>0.006</b>	1.15 (0.94-1.39)	0.170	1.32 (1.00-1.74)	0.050
Diabetes mellitus						
No	<b>1.20 (1.08-1.33)</b>	<b>7×10<sup>-4</sup></b>	<b>1.17 (1.03-1.33)</b>	<b>0.016</b>	1.15 (0.96-1.38)	0.120
Yes	1.05 (0.74-1.49)	0.800	1.46 (0.98-2.19)	0.063	1.38 (0.75-2.55)	0.300
Cardiovascular disease						
No	1.15 (1.03-1.27)	0.011	<b>1.22 (1.07-1.38)</b>	<b>0.002</b>	1.16 (0.97-1.39)	0.100
Yes	1.62 (1.11-2.38)	0.012	0.93 (0.60-1.45)	0.750	1.04 (0.58-1.87)	0.890
Gleason score						
≤7	1.07 (0.95-1.20)	0.280	1.02 (0.89-1.18)	0.770	1.15 (0.94-1.40)	0.170
≥8	<b>1.47 (1.26-1.71)</b>	<b>&lt;0.0001</b>	<b>1.63 (1.37-1.95)</b>	<b>&lt;0.0001</b>	1.23 (0.96-1.58)	0.110
Extracapsular extension						
No	0.98 (0.88-1.10)	0.780	0.96 (0.84-1.11)	0.590	1.16 (0.95-1.40)	0.140
Yes	<b>1.81 (1.54-2.14)</b>	<b>&lt;0.0001</b>	<b>1.84 (1.53-2.21)</b>	<b>&lt;0.0001</b>	1.29 (0.99-1.68)	0.066
Seminal vesicle invasion						
No	1.05 (0.94-1.17)	0.410	1.04 (0.91-1.19)	0.550	1.19 (0.99-1.43)	0.064
Yes	<b>1.86 (1.54-2.25)</b>	<b>&lt;0.001</b>	<b>1.89 (1.53-2.32)</b>	<b>&lt;0.0001</b>	1.23 (0.90-1.68)	0.190
Positive surgical margin						
No	<b>1.19 (1.07-1.32)</b>	<b>0.002</b>	<b>1.17 (1.03-1.33)</b>	<b>0.014</b>	1.10 (0.92-1.32)	0.290
Yes	1.15 (0.93-1.40)	0.190	1.26 (0.99-1.61)	0.060	1.67 (1.19-2.35)	0.004



**Supplementary Table 4 Continued.** Stratified analysis for associations between genetic polymorphisms in homocysteine removal genes and PCa risk by log-additive genetic model in Han Chinese men

Lymph node involvement						
No	1.14 (1.03-1.27)	0.011	<b>1.14 (1.01-1.29)</b>	<b>0.035</b>	<b>1.21 (1.02-1.44)</b>	<b>0.027</b>
Yes	<b>1.67 (1.25-2.23)</b>	<b>4×10<sup>-4</sup></b>	<b>1.83 (1.32-2.54)</b>	<b>3×10<sup>-4</sup></b>	0.72 (0.40-1.28)	0.250
Variables	rs326119		rs1801394		rs2850144	
	Adjusted OR <sup>a</sup> (95% CI)	<i>P</i>	Adjusted OR <sup>a</sup> (95% CI)	<i>P</i>	Adjusted OR <sup>a</sup> (95% CI)	<i>P</i>
Age (yr), median						
≤68	0.96 (0.85-1.09)	0.530	1.01 (0.88-1.14)	0.930	0.99 (0.87-1.11)	0.820
>68	0.83 (0.68-1.02)	0.070	0.99 (0.81-1.22)	0.950	0.94 (0.78-1.13)	0.490
BMI (kg/m <sup>2</sup> )						
<25	0.90 (0.79-1.02)	0.089	1.02 (0.89-1.16)	0.790	0.98 (0.87-1.10)	0.710
≥25	0.98 (0.80-1.21)	0.860	0.89 (0.72-1.10)	0.290	0.99 (0.82-1.19)	0.910
Hypertension						
No	<b>0.84 (0.73-0.96)</b>	<b>0.013</b>	1.11 (0.96-1.29)	0.160	1.05 (0.92-1.20)	0.490
Yes	1.07 (0.90-1.28)	0.460	0.83 (0.69-1.00)	0.044	0.89 (0.75-1.05)	0.170
Diabetes mellitus						
No	0.93 (0.83-1.04)	0.230	0.99 (0.88-1.11)	0.840	0.99 (0.89-1.10)	0.890
Yes	0.68 (0.44-1.04)	0.071	0.85 (0.57-1.28)	0.440	0.95 (0.66-1.36)	0.770
Cardiovascular disease						
No	0.89 (0.80-1.00)	0.049	0.99 (0.88-1.12)	0.920	0.99 (0.89-1.11)	0.910
Yes	<b>1.59 (1.03-2.44)</b>	<b>0.033</b>	0.76 (0.49-1.18)	0.210	1.07 (0.74-1.55)	0.720
Gleason score						
≤7	0.90 (0.79-1.02)	0.094	1.00 (0.88-1.14)	0.960	0.96 (0.85-1.08)	0.460
≥8	0.96 (0.81-1.13)	0.590	0.93 (0.78-1.10)	0.400	1.02 (0.88-1.19)	0.790
Extracapsular extension						
No	0.89 (0.78-1.00)	0.058	0.98 (0.86-1.11)	0.700	1.01 (0.90-1.14)	0.860
Yes	0.99 (0.84-1.17)	0.890	0.95 (0.80-1.14)	0.600	0.89 (0.76-1.04)	0.130

**Supplementary Table 4 Continued.** Stratified analysis for associations between genetic polymorphisms in homocysteine removal genes and PCa risk by log-additive genetic model in Han Chinese men

Seminal vesicle invasion						
No	0.91 (0.81-1.02)	0.110	0.98 (0.87-1.11)	0.750	0.99 (0.88-1.10)	0.810
Yes	0.97 (0.80-1.17)	0.750	0.92 (0.75-1.13)	0.420	0.92 (0.77-1.11)	0.380
Positive surgical margin						
No	0.91 (0.81-1.02)	0.110	0.98 (0.87-1.11)	0.780	0.99 (0.89-1.10)	0.820
Yes	0.91 (0.73-1.13)	0.400	0.95 (0.75-1.20)	0.680	0.94 (0.76-1.15)	0.540
Lymph node involvement						
No	0.90 (0.81-1.01)	0.070	0.97 (0.87-1.09)	0.620	0.99 (0.89-1.10)	0.820
Yes	1.05 (0.78-1.41)	0.740	1.05 (0.77-1.44)	0.740	0.91 (0.68-1.21)	0.520

OR, odds ratio; 95%CI, 95% confidence interval.

<sup>a</sup>Adjusted for age, BMI, hypertension, diabetes mellitus, and cardiovascular disease in multivariant logistic regression models.

**Supplementary Table 5. Genotypes of surveyed SNPs in cell lines**

Cell lines	rs28372871	rs1131450	rs1805087	rs326119	rs1801394	rs2850144
LNCaP	TT	GG	AA	AA	AA	CC
PC3	TT	GG	AA	AA	AA	CC

**Supplementary Table 6. DNA sequence of all used primer pairs**

Primer Name	Sequence (5'→3')	Purpose
rs28372871-F	AACGCCTACTACAACCCTAAAA	PCR
rs28372871-R	AGTTCTGCGCTCAATCTATCC	PCR
rs1131450-F	CATGCCATTCTCCTGCCTCA	PCR
rs1131450-R	TGCCCACTTGTTCCA ACTCC	PCR
rs1805087-F	TTTCAGTGTTCCTCAGCTGTTAGAT	PCR
rs1805087-R	AAACTAGGATCATAAAAAACAGTCACATT	PCR
rs326119-F	GCCTTTGGCTTTGGTGTCC	PCR
rs326119-R	TTCCGCAAGAGATAAGCAGTAGT	PCR
rs1801394-F	GGAAACACAGATTCAAGCCCAA	PCR
rs1801394-R	CCCAACCAA AATTCTTCAAAGC	PCR
rs2850144-F	CAGGCTGGCTGAAGGCTCT	PCR
rs2850144-R	CGCAGAACAGTCGCCTTG	PCR
rs28372871-typing	CGGCTGCGAGGAGCTCG	Genotyping
rs1131450-typing	AAATTAGCCGGGTGTGGTGG	Genotyping
rs1805087-typing	CACTTACCTTGAGAGACTCATAATGG	Genotyping
rs326119-typing	GTTTCATTCACCGAAAGCCAAG	Genotyping
rs1801394-typing	AAAGGCCATCGCAGAAGAAAT	Genotyping
rs2850144-typing	CGGCCCGCGCAGCTCCGCCG	Genotyping
MTR-promter -F	ATGGCGACGCGTCGCCATCTCATTCCCTCCCTTCTTT	Construct
MTR-promter -R	ACTGGAAGATCTTCCAGTCCTTGGTGTCTGGCCTAGCAG	Construct
MTR-UTR -F	CACA ACTCGAGCAGA ACTCCCTTTGGCAA AAGGCAT	Construct
MTR-UTR -R	AAGGATCCCTTCATTTGTTCTCCCTTGCTTCT	Construct
MTR-mRNA-F	CGCAACCCGAAGGTCTGAA	RT-qPCR
MTR-mRNA-R	TTCTTCGTTTAGCTTCTCCCG	RT-qPCR
GAPDH-mRNA-F	GAAGGTGAAGGTCTGGAGTC	RT-qPCR
GAPDH-mRNA-R	GAAGATGGTGATGGGATTTC	RT-qPCR