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Original Article

Different effect of obesity and metabolic syndrome on prostate cancer by age group

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Abstract: Substantial evidence supports that metabolic syndrome (MetS) affects the incidence of several cancers, with different effects according to age group. We hypothesized that MetS has an age-specific effect on the occurrence of prostate cancer. We studied a National Health Insurance Service health checkup cohort. A total of 5,370,614 men in the cohort were categorized into three age groups in 2009 (20-39, 40-64, ≥65). Prostate cancer incidence was estimated on a cumulative basis from 2009 to 2018. We tried to identify the correlation of MetS components and prostate cancer by age group using this large retrospective cohort. MetS components included the body mass index (BMI), waist circumference (WC), hypertension, obesity, hyperlipidemia, cardiovascular disease, smoking, drinking, serum glucose, serum total cholesterol, serum triglyceride, serum high-density lipoprotein (HDL)-cholesterol and serum low-density lipoprotein (LDL)-cholesterol. A multivariate Cox proportional hazard model was used for the incidence of prostate cancer according to the MetS component. In the young age (20-39) group, the MetS component was not related to prostate cancer. In the middle-aged (40-64) group, the presence of MetS, WC, HDL cholesterol, and hypertension was significantly associated with an increased prevalence of prostate cancer. In the old age (≥65) group, the presence of MetS, WC, HDL cholesterol, triglycerides, and hypertension were significant factors for the incidence of prostate cancer. This tendency was marked in BMI>30 in the old age group (odds ratio: 1.32; $P<0.0001$). MetS components were age-specifically associated with an increased incidence of prostate cancer. Because the MetS components were related to prostate cancer from middle age to old age, preventing MetS for these age groups is crucial.

Keywords: Obesity, metabolic syndrome, prostatic neoplasms, age groups

Introduction

Prostate cancer is on the rise worldwide and ranks second in the prevalence of male cancer. [1]. The prostate cancer prevalence in South Korea has increased significantly, mainly because of the rise in its incidence. As the incidence and prevalence of prostate cancer increased in Korea, the resulting mortality rate gradually increased [2]. This trend could be explained by the increase in obesity due to Koreans' westernized eating habits, such as increased fat and meat intake. However, the only established risk factors for prostate cancer so far are race, age and family history [3].

Metabolic syndrome (MetS) is a clustering of the following medical conditions: central obesity, hypertension, high fasting blood glucose, high serum triglycerides and low serum high-density lipoprotein (HDL). The incidence of MetS in the cohort of National Health Insurance Service (NHIS) data was approximately 25-40% in South Korea [4]. There have been many studies about the association between MetS and the prevalence of several cancer types [5]. However, the association of obesity, MetS and prostate cancer are uncertain [6-8]. Also, because MetS is composed of several metabolic diseases, it is not established which metabolic component is the risk of prostate cancer [7].

There was a large cohort study of the patients without a prior prostate cancer undergoing prostate biopsy (2003-2013). In this study, no individual MetS component was independently associated with prostate cancer. However, the increase in the number of MetS components was associated with higher grade of prostate cancer (P<0.001), as well as progressively higher odds of prostate cancer outcomes compared with no MetS components [9].

For various cancer types, several lines of evidence have shown that old age patients with MetS are more likely to have cancer than young age patients with MetS [7, 8, 10]. The effect of MetS on prostate cancer incidence by age group has not been confirmed. In the present large population-based study using the Korean NHIS, we tried to validate the hypothesis that MetS has an age-specific impact on the development of prostate cancer. This study was conducted according to the STROBE (STrengthening the Reporting of Observational studies in Epidemiology) reporting checklist.

Methods

Patient cohort

Most of the Korean population of 50 million individuals is covered by the NHIS. We assessed 10,585,844 individuals who had received the KNHIS health checkup in 2009. Those aged younger than 20 years and female individuals were excluded. A total of 5,370,614 individuals were followed until 2018. We determined the prostate cancer patients if they were given a diagnostic name of prostate cancer in this cohort with a 10-year follow-up duration. Smoking history, alcohol consumption, physical activity, income status, comorbidities (diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease), age, body mass index (BMI), waist circumference (WC), blood pressure (systolic, diastolic), fasting blood glucose, total cholesterol, high-density lipoprotein (HDL)-cholesterol, low-density lipoprotein (LDL)-cholesterol, triglyceride and glomerular filtration rate were examined.

Definitions

According to the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) guidelines, abdominal obesity was defined as a waist circumference ≥90 cm in men and ≥85 cm in women. BMI was a person's body weight in kilograms divided by the square of height in meters. Hypertension was defined as a blood pressure ≥140/90 mmHg or at least one claim per year for the prescription of antihypertensive medication under International Classification of Diseases (ICD)-10 codes I10-I13, I15.

We defined MetS based on the joint interim report of the Task Force on Epidemiology and Prevention by the International Diabetes Federation (IDF) Special Committee. According to this criterion, MetS can be diagnosed if it meets three or more of the following five criteria: central obesity (≥90 cm for men and ≥85 cm for women), high blood pressure (systolic ≥130 or diastolic ≥85 mmHg or treatment for previous history of hypertension), hyperglycemia (fasting blood glucose ≥100 mg/dL or previous history of type 2 diabetes), hypertriglyceridemia (triglyceride ≥150 mg/dL or specific treatment for this lipid abnormality), and low HDL cholesterol levels (<40 mg/dL for men, <50 mg/dL for women or specific treatment for this lipid abnormality).

We defined the occurrence of prostate cancer if the patient had a disease code of C61 by the Korean Classification of Diseases, 6th revision. After excluding aged younger than 20 years and men with prostate cancer diagnosed before 2009, 5,370,614 men were followed from 2009 to 2018.

Statistical analysis

We executed the statistical analyses using SAS software (SAS Institute Inc., Cary, NC, USA, version 9.4). We expressed the baseline characteristics of study subjects as means ± standard deviation (SD) for continuous variables and as a percentage of the number of categorical variables according to the existence of MetS. We compared the values using the t-test for continuous variables and the chi-square test for categorical variables. The incidence of prostate cancer was measured by dividing the number of patients by 1,000 person-years. We executed Cox regression to evaluate the association of MetS components with prostate cancer. Adjusting variables were age, smoking status, drinking level, regular exercise, diabetes, hyper-

Table 1. Clinical characteristics according to the presence of metabolic syndrome

	Total (n=5,370,614)	Metabolic syndrome		*P value*
		No (n=3,990,122)	Yes (n=1,380,492)	
Age (years)	44 (35-55)	42 (33-53)	50 (40-60)	<.0001
Cigarette smoking, *n* (%)				<.0001
None	1,628,192 (30.32)	1,231,583 (30.87)	396,609 (28.73)	
Ex-smoker	1,317,621 (24.53)	928,473 (23.27)	389,148 (28.19)	
Current smoker	2,424,801 (45.15)	1,830,066 (45.86)	594,735 (43.08)	
Alcohol consumption, *n* (%)				<.0001
None	1,726,654 (32.15)	1,279,750 (32.07)	446,904 (32.37)	
Mild	2,905,836 (54.11)	2,204,748 (55.26)	701,088 (50.79)	
Heavy	738,124 (13.74)	505,624 (12.67)	232,500 (16.84)	
Physical exercise, *n* (%)	1,063,256 (19.8)	780,250 (19.55)	283,006 (20.5)	<.0001
Low income (20%), *n* (%)	637,946 (11.88)	455,083 (11.41)	182,863 (13.25)	<.0001
Diabetes, *n* (%)	519,310 (9.67)	174,972 (4.39)	344,338 (24.94)	<.0001
Hypertension, *n* (%)	1,401,703 (26.1)	654,045 (16.39)	747,658 (54.16)	<.0001
Dyslipidemia, *n* (%)	825,563 (15.37)	368,767 (9.24)	456,796 (33.09)	<.0001
Chronic kidney disease, *n* (%)	326,381 (6.08)	206,756 (5.18)	119,625 (8.67)	<.0001
Body mass index (kg/m^2)	24.13±3.32	23.44±2.76	26.12±3.95	<.0001
Waist circumference (cm)	83.56±8.27	81.49±7.18	89.55±8.27	<.0001
Systolic BP (mmHg)	124.69±14.14	122.08±13.2	132.23±14.06	<.0001
Diastolic BP (mmHg)	78.05±9.73	76.53±9.17	82.45±9.95	<.0001
Glucose (mM)	99.15±25.88	94.22±19.49	113.41±35.13	<.0001
Glomerular filtration rate	87.95±51.4	89.04±53.76	84.78±43.72	<.0001
Total cholesterol (mM)	194.62±40.9	192.52±37.96	200.71±47.89	<.0001
HDL cholesterol (mM)	53.54±31.49	55.48±31.57	47.92±30.57	<.0001
LDL cholesterol (mM)	118.86±197.52	120.96±214.18	112.77±138.36	<.0001
Triglycerides (mM)	129.13 (129.06-129.19)	111.51 (111.46-111.57)	197.3 (197.12-197.47)	<.0001

BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

tension, dyslipidemia and chronic kidney disease.

Results

Baseline characteristics

The characteristics according to the presence of MetS are summarized in **Table 1**. Among 5,370,614 participants, 1,380,492 (25.7%) were diagnosed with MetS. There was significant difference of the mean age between the group with MetS and the other group without MetS (P<0.001). The proportions of diabetes, hypertension, dyslipidemia and chronic kidney disease were significantly higher in the group with MetS (P<0.001). The men with MetS had significantly higher BMI, WC, blood pressure, fasting blood glucose, total cholesterol, LDL cholesterol and triglyceride levels than those without MetS (P<0.001). The glomerular filtration rate and fasting HDL cholesterol levels were significantly lower in those with MetS (P<0.001) than in those without MetS.

Relationship between obesity and the incidence of prostate cancer by age group

Over the 10-year follow-up duration, 36,958 persons were newly registered as prostate cancer. **Table 2** presented the results of the association between BMI and prostate cancer risk by age group through Cox regression analysis. The young age group (20-39) showed no significant difference according to BMI. However, the middle age group (40-64) and old age group (≥65) showed a positive association with increasing BMI, and BMI over 30 showed a significantly high incidence of prostate cancer, particularly in the old age group. The same results were shown in the analysis of unadjusted models (1) and adjusted models (2 to 4).

Table 2. Multivariate Cox proportional hazard model for the incidence of prostate cancer according to the body mass index by age group

BMI (kg/m^2)	No. of patients	Prostate cancer patients	Duration (days)	Incidence rates per 1000	HR (95% CI)							
					†Model 1	*P value*	‡Model 2	*P value*	§Model 3	*P value*	¶Model 4	*P value*
Total												
<18.5	120,892	765	1,047,548	0.730	1.029 (0.956, 1.107)		0.728 (0.676, 0.783)		0.748 (0.695, 0.805)		0.757 (0.703, 0.814)	
18.5-<23	1,80,6349	11,738	16,411,635	0.715	1 (Ref.)	<.0001	1 (Ref.)	<.0001	1 (Ref.)	<.0001	1 (Ref.)	<.0001
23-<25	1,446,331	10,920	13,243,706	0.825	1.152 (1.122, 1.182)		1.228 (1.196, 1.26)		1.206 (1.174, 1.237)		1.194 (1.163, 1.226)	
25-<30	1,801,172	12,679	16,522,422	0.767	1.072 (1.046, 1.1)		1.279 (1.247, 1.312)		1.249 (1.218, 1.281)		1.227 (1.195, 1.259)	
≥30	195,870	856	1,797,951	0.476	0.667 (0.622, 0.715)		1.301 (1.213, 1.394)		1.276 (1.19, 1.368)		1.24 (1.156, 1.33)	
Age in years (20-39)												
<18.5	50,615	2	470,204	0.004	0.678 (0.164, 2.8)		0.774 (0.187, 3.199)		0.79 (0.191, 3.267)		0.797 (0.193, 3.297)	
18.5-<23	717,850	42	6,681,204	0.006	1 (Ref.)	0.5377	1 (Ref.)	0.8044	1 (Ref.)	0.8192	1 (Ref.)	0.8355
23-<25	489,522	40	4,553,052	0.009	1.401 (0.908, 2.16)		1.232 (0.799, 1.901)		1.223 (0.792, 1.887)		1.21 (0.783, 1.87)	
25-<30	618,582	43	5,742,758	0.007	1.199 (0.784, 1.834)		1.002 (0.655, 1.535)		1 (0.652, 1.533)		0.976 (0.632, 1.507)	
≥30	101,818	8	942,147	0.008	1.367 (0.642, 2.913)		1.277 (0.599, 2.719)		1.282 (0.601, 2.733)		1.216 (0.557, 2.654)	
Age in years (40-64)												
<18.5	45,202	177	402,699	0.440	0.754 (0.649, 0.877)		0.69 (0.593, 0.801)		0.71 (0.611, 0.825)		0.714 (0.614, 0.83)	
18.5-<23	862,597	4,654	7,906,60	0.589	1 (Ref.)	<.0001	1 (Ref.)	<.0001	1 (Ref.)	<.0001	1 (Ref.)	<.0001
23-<25	798,793	5,018	7,357,934	0.682	1.157 (1.112, 1.205)		1.159 (1.113, 1.206)		1.137 (1.093, 1.184)		1.132 (1.087, 1.178)	
25-<30	1,017,839	6,517	9,372,856	0.695	1.181 (1.138, 1.226)		1.218 (1.173, 1.265)		1.187 (1.143, 1.233)		1.177 (1.132, 1.223)	
≥30	84,491	443	775,225	0.571	0.973 (0.883, 1.073)		1.202 (1.091, 1.325)		1.172 (1.063, 1.292)		1.161 (1.052, 1.281)	
Age in years (≥65)												
<18.5	2,5075	586	174644	3.355	0.881 (0.81, 0.958)		0.847 (0.779, 0.922)		0.865 (0.795, 0.941)		0.868 (0.797, 0.944)	
18.5-<23	2,25902	7,042	1823829	3.861	1 (Ref.)	<.0001	1 (Ref.)	<.0001	1 (Ref.)	<.0001	1 (Ref.)	<.0001
23-<25	1,58016	5,862	1332720	4.399	1.135 (1.096, 1.175)		1.16 (1.12, 1.201)		1.143 (1.104, 1.184)		1.14 (1.101, 1.181)	
25-<30	1,64751	6,119	1406808	4.350	1.121 (1.083, 1.16)		1.158 (1.119, 1.199)		1.135 (1.096, 1.175)		1.13 (1.091, 1.171)	
≥30	9561	405	80579	5.026	1.297 (1.174, 1.434)		1.351 (1.222, 1.494)		1.325 (1.199, 1.465)		1.32 (1.193, 1.46)	

†Model 1: Unadjusted. ‡Model 2: Adjusted for age. §Model 3: Adjusted for age, cigarette smoking, alcohol consumption, and physical exercise. ¶Model 4: Adjusted for age, cigarette smoking, alcohol consumption, physical exercise, diabetes, high blood pressure, dyslipidemia, and chronic kidney disease. BMI, body mass index; CI, confidence interval; HR, hazard ratio.

Association of MetS components and prostate cancer by age group

This study showed that MetS components were significantly related with the risk of prostate cancer in all patients by multivariate analysis. However, the young age group showed no statistical relationship with all MetS components by adjusting the models (**Table 3**). The middle age group showed significant risk in the presence of MetS, high waist circumference, low HDL cholesterol, high blood pressure and high glucose level. In the older age group, the presence of MetS, high waist circumference, low HDL cholesterol, high triglyceride and high blood pressure were significantly related to the incidence of prostate cancer (**Table 4**). These results were consistent with the unadjusted Model (1) and adjusted models (2 to 4).

Discussion

In the present study, the study cohort was analyzed from 2009 to 2018. The main findings of this population-based study are as follows: regarding the relationship between obesity and the incidence of prostate cancer, the middle age and old age groups showed a positive association with increasing BMI, whereas the young age group showed no significant difference according to BMI. Using the multivariate analysis, the younger age group showed no statistical relationship with all the MetS components. However, for the middle age and old age groups, many MetS components showed a significant association with the incidence of prostate cancer.

Several hypothesis are known about the association between MetS and cancer incidence [6]. The high association between MetS and Cancer can be explained as a cause of sharing common risk factors such as old age, family history, genetic predisposition, and lack of exercise [11, 12]. The possible mechanisms of cancer development through MetS relate to the abnormal insulin mechanism, inflammatory change, abnormal sex hormone excretion, dysregulated glucose metabolism and dysfunction of the circadian rhythm [12]. In particular, insulin and the insulin-like growth factor system are an important factor in the pathophysiology of MetS [13, 14]. Many studies have shown that insulin resistance may indicate prostate cancer risk among obese subjects [15].

Many lines of evidence exist regarding the relationship between MetS and various cancers. The results from a systemic review and meta-analysis of cohort studies showed that the presence of MetS was associated with liver, colorectal and bladder cancer in men. However, the reported relative risks are small and there was geographic and racial differences. As an example, in U.S. white men population, Mets showed protective effect for prostate cancer [5].

For other cancers, the nationwide cohort study conducted by Y.H. Joo et al. reported the risk of laryngeal cancer was dependent on the MetS components [16]. The combination of fasting blood glucose elevation, triglyceride elevation, and low HDL was associated with a high risk of laryngeal cancer.

KT. Hwang et al. studied the effect of MetS on breast cancer risk through the nationwide data of KNHIS. MetS has increased the risk of all types of breast cancer, and the trend has been particularly pronounced among those over 55 years of age [10].

There is a controversy of the relation between MetS and prostate cancer. From the meta-analysis of 14 articles including 4728 prostate cancer patients, MetS is weakly and non-significantly associated with prostate cancer risk, but associations vary with geography. Among components of the MetS, hypertension and higher waist circumference (>102 cm) are significantly associated with increased risk of prostate cancer [17]. Haggstrom reported that MetS lowered the risk of prostate cancer being diagnosed and did not affect the prognosis [18]. Additionally, other studies have reported a protective effect of obesity [19, 20].

Many other studies have shown that obesity and MetS increased the incidence of prostate cancer. Laukkanen et al. reported that the risk of prostate cancer diagnosis increased as a result of statistical analysis by adjusting various variables in Finnish men with MetS [7]. The association between MetS and the risk of prostate cancer was stronger among overweight and obese men with a BMI ≥27 kg/m^2 than in lighter men [8]. From the meta-analysis of the association between BMI, height, weight, waist circumference and waist-to-hips ratio and the risk of prostate cancer, there was a weak posi-

Table 3. Multivariate Cox analysis for the risk of prostate cancer according to the each metabolic syndrome component in the young age group

	No. of patients	Prostate cancer patients	Duration (days)	Incidence rates per 1000	HR (95% CI)					
					†Model 1	*P value*	‡Model 2	*P value*	§Model 3	*P value*
Age in years (20-39)										
Presence of metabolic syndrome										
No	1,668,368	112	15,516,740	0.007	1 (Ref.)	0.6274	1 (Ref.)	0.597	1 (Ref.)	0.6414
Yes	310,019	23	2,872,625	0.008	1.118 (0.713, 1.75)		0.886 (0.565, 1.389)		0.898 (0.572, 1.411)	
High waist circumference										
No	1,635,734	105	15,211,515	0.007	1 (Ref.)	0.1226	1 (Ref.)	0.313	1 (Ref.)	0.2937
Yes	342,653	30	3,177,850	0.009	1.377 (0.917, 2.065)		1.232 (0.821, 1.85)		1.244 (0.828, 1.868)	
Low HDL cholesterol										
No	1,712,736	120	15,919,220	0.008	1 (Ref.)	0.4273	1 (Ref.)	0.1805	1 (Ref.)	0.187
Yes	265,651	15	2,470,146	0.006	0.805 (0.47, 1.376)		0.693 (0.405, 1.186)		0.696 (0.406, 1.192)	
High triglycerides										
No	1,274,812	75	11,854,606	0.006	1 (Ref.)	0.0305	1 (Ref.)	0.3747	1 (Ref.)	0.3071
Yes	703,575	60	6,534,759	0.009	1.455 (1.036, 2.043)		1.167 (0.83, 1.642)		1.196 (0.848, 1.688)	
High blood pressure										
No	1,243,399	88	11,569,600	0.008	1 (Ref.)	0.6053	1 (Ref.)	0.3198	1 (Ref.)	0.33
Yes	734,988	47	6,819,765	0.007	0.911 (0.639, 1.298)		0.835 (0.586, 1.191)		0.838 (0.587, 1.196)	
High glucose										
No	1,527,677	101	14,212,379	0.007	1 (Ref.)	0.4692	1 (Ref.)	0.7929	1 (Ref.)	0.8158
Yes	450,710	34	4,176,986	0.008	1.154 (0.783, 1.703)		0.949 (0.642, 1.402)		0.955 (0.646, 1.411)	

†Model 1: Unadjusted. ‡Model 2: Adjusted for age. §Model 3: Adjusted for age, cigarette smoking, alcohol consumption, physical exercise. BMI, body mass index; CI, confidence interval; HR, hazard ratio.

Table 4. Multivariate Cox analysis for the risk of prostate cancer according to the each metabolic syndrome component in the middle and old age group

	No. of patients	Prostate cancer patients	Duration (days)	Incidence rates per 1000	HR (95% CI)					
					†Model 1	*P value*	‡Model 2	*P value*	§Model 3	*P value*
Age in years (40-64)										
Presence of metabolic syndrome										
No	1,958,826	10,627	18,039,504	0.589	1 (Ref.)	<.0001	1 (Ref.)	<.0001	1 (Ref.)	0.0001
Yes	850,096	6,182	7,775,811	0.795	1.354 (1.312, 1.397)		1.067 (1.034, 1.101)		1.063 (1.031, 1.098)	

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High waist circumference									
No	2,161,890	12,090	19,876,464	0.608	1 (Ref.)	<.0001	1 (Ref.)	<.0001	1 (Ref.)	<.0001
Yes	647,032	4,719	5,938,851	0.795	1.307 (1.264, 1.352)		1.112 (1.075, 1.15)		1.102 (1.066, 1.14)	
Low HDL cholesterol										
No	2,212,420	12,479	20,353,363	0.613	1 (Ref.)	<.0001	1 (Ref.)	<.0001	1 (Ref.)	<.0001
Yes	5965,02	4,330	5,461,952	0.793	1.294 (1.25, 1.34)		1.086 (1.049, 1.124)		1.088 (1.051, 1.127)	
High triglycerides										
No	1,536,269	9,296	14,119,586	0.658	1 (Ref.)	0.1289	1 (Ref.)	0.6677	1 (Ref.)	0.3454
Yes	1,272,653	7,513	11,695,729	0.642	0.977 (0.947, 1.007)		1.007 (0.977, 1.038)		1.015 (0.984, 1.046)	
High blood pressure										
No	1,342,559	6,368	12,395,306	0.514	1 (Ref.)	<.0001	1 (Ref.)	0.0003	1 (Ref.)	0.0035
Yes	1,466,363	10,441	13,420,009	0.778	1.52 (1.473, 1.568)		1.059 (1.026, 1.093)		1.048 (1.016, 1.082)	
High glucose										
No	1,626,936	9,053	15,008,418	0.603	1 (Ref.)	<.0001	1 (Ref.)	0.0531	1 (Ref.)	0.025
Yes	1,181,986	7,756	10,806,897	0.718	1.194 (1.159, 1.231)		0.97 (0.941, 1)		0.966 (0.937, 0.996)	
Age in years (≥65)										
Presence of metabolic syndrome										
No	362,928	12,144	3,000,532	4.047	1 (Ref.)	<.0001	1 (Ref.)	<.0001	1 (Ref.)	<.0001
Yes	220,377	7,870	1,818,049	4.329	1.071 (1.041, 1.102)		1.079 (1.049, 1.11)		1.071 (1.041, 1.102)	
High waist circumference										
No	423,770	14,070	3,483,744	4.039	1 (Ref.)	<.0001	1 (Ref.)	<.0001	1 (Ref.)	<.0001
Yes	159,535	5,944	1,334,837	4.453	1.101 (1.068, 1.135)		1.107 (1.074, 1.141)		1.097 (1.064, 1.131)	
Low HDL cholesterol										
No	425,539	14,429	3,531,423	4.086	1 (Ref.)	<.0001	1 (Ref.)	<.0001	1 (Ref.)	0.0002
Yes	157,766	5,585	1,287,158	4.400	1.064 (1.032, 1.097)		1.064 (1.032, 1.098)		1.06 (1.027, 1.093)	
High triglycerides										
No	356,397	12,097	2,930,660	4.128	1 (Ref.)	0.2828	1 (Ref.)	0.0325	1 (Ref.)	0.021
Yes	226,908	7,917	1,887,921	4.194	1.016 (0.987, 1.045)		1.031 (1.003, 1.061)		1.034 (1.005, 1.064)	
High blood pressure										
No	163,162	5,398	1,359,798	3.970	1 (Ref.)	<.0001	1 (Ref.)	0.0008	1 (Ref.)	0.0083
Yes	420,143	14,616	3,458,782	4.226	1.066 (1.034, 1.1)		1.055 (1.022, 1.088)		1.043 (1.011, 1.076)	
High glucose										
No	299,239	10,394	2,494,006	4.168	1 (Ref.)	0.7248	1 (Ref.)	0.876	1 (Ref.)	0.7786
Yes	284,066	9,620	2,324,575	4.138	0.995 (0.968, 1.023)		1.002 (0.975, 1.03)		0.996 (0.969, 1.024)	

†Model 1: Unadjusted. ‡Model 2: Adjusted for age. §Model 3: Adjusted for age, cigarette smoking, alcohol consumption, and physical exercise. BMI, body mass index; CI, confidence interval; HR, hazard ratio.

tive correlation between obesity and the prevalence of prostate cancer [21]. Other prospective cohort study investigated the relation of BMI, weight change and the incidence of prostate cancer. The results of this study suggest that obesity is associated with the more aggressive prostate cancer [19].

Meta-analysis of MetS and prostate cancer showed that the incidence of high-grade prostate cancer was statistically different according to the presence of MetS, however, any single metS component was not the determinant of the risk of prostate cancer [22]. From the study of 'Cancer of the Prostate Strategic Urologic Research Endeavour' database, they found that men with overweight and obesity were somewhat more likely to be diagnosed with high-risk prostate cancer [23]. In the meta-analysis, a 15% higher risk of prostate cancer mortality was estimated with each 5 kg/m^2 increase in the body mass index [24].

From the Norwegian cohort study of 16,209 middle age group followed for 27 years, combinations of any two or three Mets components using quartile values of risk factors were predictive of prostate cancer. The results of this long-term prospective cohort study presented a basis for the association of prostate cancer with the components of metS [25].

According to the study of Korea NHIS health checkup cohort, there was significant difference of the incidence of prostate cancer between the patients with MetS and without it over the follow-up period. The presence of MetS significantly increased the risk of prostate cancer by multivariate analysis [7].

Little evidence exists regarding an age-specific effect of MetS on cancer. From the Korean nationwide study of breast cancer, the presence of MetS increased the risk of breast cancers in postmenopausal women but decreased the risk in premenopausal women [11]. In a retrospective cohort study of the Korean NHIS, the effect of MetS on prostate cancer prevalence was significant only in the elderly over 70 years of age. One reason may be that the association MetS and prostate cancer could be more significant with increasing age [8]. In a prospective population-based study Finnish study, there was a significant risk of prostate cancer in the middle-aged men with MetS [7].

The distinctive feature of our study is that it is a population-based observational study concerning the effect of MetS on the incidence of prostate cancer by age group. For men aged ≥40 years, an increasing BMI was significantly associated with the risk of prostate cancer. In particular, for old age, the risk of prostate cancer was significantly higher in men with BMI ≥30 (HR, 1.32; 95% CI, 1.193-1.460). For the middle age and older age groups, many metabolic components were significant factors for prostate cancer using the multivariate Cox proportional hazard model. The presence of metS, high WC, low HDL cholesterol, and hypertension were common risk factors for prostate cancer.

However, for young men aged <40 years, no significant association was found between prostate cancer and BMI or MetS components. Therefore, for men aged older than 40 years, the risk of prostate cancer could be reduced by improving MetS components, such as lifestyle changes and appropriate medical treatment.

For the limitation of this study, the first is that tumor marker, pathology, and staging were not known. The second was selection bias because there was different medical accessibility according to the presence of MetS. Finally, this study was retrospective cohort study. However, this study included more than 5,000,000 men and had a 10-year follow-up duration. Compared to previous studies, the research results are meaningful because they were analyzed for a long period of time for large-scale population. In addition, the advantage of this study is that the significance of the MetS component was confirmed through various adjusted models in statistical analysis by age group.

In conclusion, we found that MetS components could be age-specifically associated with an increased incidence of prostate cancer. Because the MetS components were related to prostate cancer from middle age to old age, preventing MetS in these age groups is crucial.

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Disclosure of conflict of interest

None.

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References

[1] Waters KM, Henderson BE, Stram DO, Wan P, Kolonel LN and Haiman CA. Association of diabetes with prostate cancer risk in the multiethnic cohort. Am J Epidemiol 2009; 169: 937-945.

[2] Han HH, Park JW, Na JC, Chung BH, Kim CS and Ko WJ. Epidemiology of prostate cancer in South Korea. Prostate Int 2015; 3: 99-102.

[3] Chan JM, Holick CN, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ and Giovannucci EL. Diet after diagnosis and the risk of prostate cancer progression, recurrence, and death (United States). Cancer Causes Control 2006; 17: 199-208.

[4] Yoo S, Oh S, Park J, Cho SY, Cho MC, Jeong H and Son H. The impacts of metabolic syndrome and lifestyle on the prevalence of benign prostatic hyperplasia requiring treatment: historical cohort study of 130 454 men. BJU Int 2019; 123: 140-148.

[5] Esposito K, Chiodini P, Colao A, Lenzi A and Giugliano D. Metabolic syndrome and risk of cancer: a systematic review and meta-analysis. Diabetes Care 2012; 35: 2402-2411.

[6] Rhee H, Vela I and Chung E. Metabolic syndrome and prostate cancer: a review of complex interplay amongst various endocrine factors in the pathophysiology and progression of prostate cancer. Horm Cancer 2016; 7: 75-83.

[7] Laukkanen JA, Laaksonen DE, Niskanen L, Pukkala E, Hakkarainen A and Salonen JT. Metabolic syndrome and the risk of prostate cancer in Finnish men: a population-based study. Cancer Epidemiol Biomarkers Prev 2004; 13: 1646-1650.

[8] Yoo S, Oh S, Park J, Cho SY, Cho MC, Son H and Jeong H. Effects of metabolic syndrome on the prevalence of prostate cancer: historical cohort study using the national health insurance service database. J Cancer Res Clin Oncol 2019; 145: 775-780.

[9] Bhindi B, Locke J, Alibhai SMH, Kulkarni GS, Margel DS, Hamilton RJ, Finelli A, Trachtenberg J, Zlotta AR, Toi A, Hersey KM, Evans A, van der Kwast TH and Fleshner NE. Dissecting the association between metabolic syndrome and prostate cancer risk: analysis of a large clinical cohort. Eur Urol 2015; 67: 64-70.

[10] Hwang KT, Han KD, Oh S, Koo BK, Lee SK, Kim J, Seo HJ, Jung J, Kim BH and Hur H. Influence of metabolic syndrome on risk of breast cancer: a study analyzing nationwide data from Korean national health insurance service. Cancer Epidemiol Biomarkers Prev 2020; 29: 2038-2047.

[11] Esposito K, Ciardiello F and Giugliano D. Unhealthy diets: a common soil for the association of metabolic syndrome and cancer. Endocrine 2014; 46: 39-42.

[12] Bellastella G, Scappaticcio L, Esposito K, Giugliano D and Maiorino MI. Metabolic syndrome and cancer: "The common soil hypothesis". Diabetes Res Clin Pract 2018; 143: 389-397.

[13] Braun S, Bitton-Worms K and LeRoith D. The link between the metabolic syndrome and cancer. Int J Biol Sci 2011; 7: 1003-1015.

[14] Mendonca FM, de Sousa FR, Barbosa AL, Martins SC, Araujo RL, Soares R and Abreu C. Metabolic syndrome and risk of cancer: which link? Metabolism 2015; 64: 182-189.

[15] Hsing AW, Gao YT, Chua S Jr, Deng J and Stanczyk FZ. Insulin resistance and prostate cancer risk. J Natl Cancer Inst 2003; 95: 67-71.

[16] Kim SY, Han KD and Joo YH. Metabolic syndrome and incidence of laryngeal cancer: a nationwide cohort study. Sci Rep 2019; 9: 667.

[17] Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Parretta E, Lenzi A and Giugliano D. Effect of metabolic syndrome and its components on prostate cancer risk: meta-analysis. J Endocrinol Invest 2013; 36: 132-139.

[18] Häggström C, Stocks T, Nagel G, Manjer J, Bjørge T, Hallmans G, Engeland A, Ulmer H, Lindkvist B, Selmer R, Concin H, Tretli S, Jonsson H and Stattin P. Prostate cancer, prostate cancer death, and death from other causes, among men with metabolic aberrations. Epidemiology 2014; 25: 823-828.

[19] Rodriguez C, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, Patel AV, Thun MJ and Calle EE. Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev 2007; 16: 63-69.

[20] Wright ME, Chang SC, Schatzkin A, Albanes D, Kipnis V, Mouw T, Hurwitz P, Hollenbeck A and Leitzmann MF. Prospective study of adiposity and weight change in relation to prostate cancer incidence and mortality. Cancer 2007; 109: 675-684.

[21] MacInnis RJ and English DR. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. Cancer Causes Control 2006; 17: 989-1003.
[22] Gacci M, Russo GI, De Nunzio C, Sebastianelli A, Salvi M, Vignozzi L, Tubaro A, Morgia G and Serni S. Meta-analysis of metabolic syndrome and prostate cancer. Prostate Cancer Prostatic Dis 2017; 20: 146-155.
[23] Kane CJ, Bassett WW, Sadetsky N, Silva S, Wallace K, Pasta DJ, Cooperberg MR, Chan JM and Carroll PR. Obesity and prostate cancer clinical risk factors at presentation: data from CaPSURE. J Urol 2005; 173: 732-736.
[24] Cao Y and Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer Prev Res (Phila) 2011; 4: 486-501.
[25] Lund Håheim L, Wisløff TF, Holme I and Nafstad P. Metabolic syndrome predicts prostate cancer in a cohort of middle-aged Norwegian men followed for 27 years. Am J Epidemiol 2006; 164: 769-774.