Associations between obesity, metabolic syndrome, and endometrial cancer risk in East Asian women

Original Article

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Objective: This study investigated the associations between obesity, metabolic syndrome (MetS), the combination of these two components as a metabolic obesity phenotype, and endometrial cancer risk in East Asian women.

Methods: A total of 6,097,686 cancer-free women aged 40–74 years who underwent the National Health Insurance Service health examination between 2009 and 2010 were included. Cancer incidence was identified using the healthcare utilization database. Associations between baseline obesity (body mass index <23 kg/m^2, 23–24.9 kg/m^2, ≥25 kg/m^2), MetS, each component of MetS, MetS stratified by obesity status, combination of obesity and MetS, and endometrial cancer risk were investigated using hazard ratios (HRs).

Results: Obesity, each component of MetS, and MetS increased the endometrial cancer risk. After these factors were mutually adjusted for, the association did not change. When stratified by obesity, MetS and MetS components were not associated with endometrial cancer in normal-weight or overweight women. However, in obese women, MetS and MetS components increased the risk of endometrial cancer (HR=1.29; 95% confidence interval [CI]=1.20–1.39). Compared with normal-weight women without MetS, endometrial cancer risk was not increased in normal-weight women with MetS. Overweight women showed an increased risk of endometrial cancer irrespective of the presence of MetS (HR=1.37 and 1.38, respectively). The HR of obese women with MetS was higher than that of obese women without MetS (HR=2.18 and 1.75).

Conclusion: The association between MetS and endometrial cancer was most prominent in obese women, suggesting that obese women with MetS would be more vulnerable to endometrial cancer.

Keywords: Obesity; Metabolic Syndrome; Endometrial Neoplasms

Synopsis
Obesity, each component of MetS, and MetS increased the endometrial cancer risk. When stratified by obesity, the association between MetS and endometrial cancer was most prominent in obese women, suggesting that obese women with MetS would be more vulnerable to endometrial cancer.

INTRODUCTION

Endometrial cancer is the sixth most common cancer, accounting for 320,000 new cases worldwide in 2012, and the second most common female cancer after breast cancer in developed countries [1]. The incidence rate has largely increased in countries with rapid socioeconomic development, including Asian countries [1]. In South Korea, endometrial cancer is one of the most rapidly increasing gynecological cancers, with an annual incremental increase of 3.5%, despite the general decrement of major gynecological cancers [2].

Risk factors for endometrial cancer include early menarche, late menopause, nulliparity, post-menopausal hormone therapy, and obesity. These risks are mostly related to unopposed estrogen in addition to a family history of endometrial cancer, type 2 diabetes, hypertension, physical activity, and dietary factors [3]. A recent umbrella review suggested that among the various risk factors of endometrial cancer, obesity-related factors such as body mass index (BMI), waist-to-hip ratio, and parity have strong associations without bias [4]. Obesity is associated with 34.0% of the global endometrial cancer incidence, although the rate is higher in Western countries, with a population attributable fraction (PAF) of >40%, than in Asian countries, with a PAF of <20% [5].

Despite the lower obesity rate in Asian countries, the prevalence of obesity has been estimated to increase in Korea [6], followed by an increase in type 2 diabetes and metabolic syndrome (MetS) [7,8]. There is a close relationship between MetS and obesity, with shared mechanisms including insulin resistance, sex hormones, and energy metabolism [9,10]. Thus, MetS has also been suggested to be associated with endometrial cancer, especially the obesity-related component [11,12].

Despite the close relationship, some individuals are obese but do not have any features of MetS. On the other hand, some individuals who are not obese have components of MetS. These individuals are considered metabolically healthy obese (MHO) or metabolically unhealthy normal weight (MUNW). Several review studies have suggested that MHO individuals are at a lower risk of cardiovascular disease and mortality, although MUNW individuals are at an increased risk [13,14]. Moreover, MHO has been associated with increased cancer risks in 5 types of cancer, namely, endometrial, esophageal, renal, pancreatic, and post-menopausal breast cancer [15]. Most of the studies regarding the risk factors for endometrial cancer, including obesity or MetS, have been conducted in European populations, and studies in Asian women have been limited. In this study, we aimed to investigate the associations between obesity, MetS, the combination of these two components as a metabolic obesity phenotype, and endometrial cancer in East Asian women.

MATERIALS AND METHODS

1. Study population
The National Health Information Database (NHID) of the National Health Insurance Service (NHIS) includes information on healthcare utilization, national health screening records, sociodemographic factors, and mortality of the entire Korean population. National health screening records are composed of a self-report questionnaire (lifestyle factors, family history of chronic diseases and cancer, and reproductive factors), results of anthropometric measurements, and laboratory measurements. Each participant provided consent for the

transfer of results to the NHID. The NHID data were accessed after the approval of the study proposal by the National Health Insurance Sharing Service. The study protocol was approved by the Institutional Review Board of Hanyang University (approval No. HYI-18-175-1).

In this study, women aged ≥40 years who underwent health examinations between 2009 and 2010 were included. The biennial cycle of health examination and eligible age of health examination were taken into consideration. Of the 6,270,822 women who underwent health examinations during 2009–2010, women aged ≥80 years (n=56,057), those with missing information on any of the 5 MetS components or BMI (n=12,880), and those who reported that they had a past history of cancer (n=44,035) were excluded. To avoid the possibility of including prevalent cases, women who took healthcare services for any type of cancer and catastrophic illness code before or within 6 months from the date of the health examination (n=60,164) were excluded. In total, 6,097,686 cancer-free women were included in the study (**Fig. 1**).

2. Definition of baseline obesity and MetS

Obesity status was determined by BMI using anthropometric measurements; BMI <23.0 kg/m^2 was defined as having a normal weight, BMI 23.0–24.9 kg/m^2 was defined as overweight, and BMI ≥25.0 kg/m^2 was defined as being obese according to the criteria for Asians [16,17]. The modified National Cholesterol Rationale Education Program Adult Treatment Program III (NECP-ATP III) was used to define MetS. Based on laboratory investigations and anthropometric measurements, waist circumference (WC) of ≥80 cm was defined as high WC, fasting plasma glucose levels ≥100 mg/dL were defined as elevated fasting glucose, triglyceride (TG) levels ≥150 mg/dL were defined as high TG, high-density lipoprotein (HDL) levels <50 mg/dL were defined as low HDL, and systolic blood pressure (BP) ≥130 mmHg or diastolic BP ≥85 mmHg was defined as elevated BP [18]. The presence of three or more of the above 5 components was defined as the presence of MetS. Participants were classified into six groups: metabolically healthy normal weight (MHNW, BMI <23.0 kg/m^2 and no MetS), metabolically healthy overweight (MHOW, BMI 23.0–24.9 kg/m^2 and no MetS), MHO
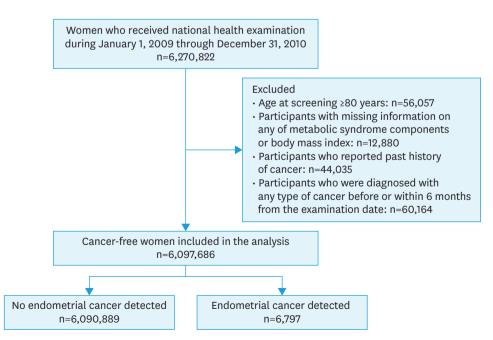

Fig. 1. Flow diagram for selection of the eligible population.

(BMI ≥25.0 kg/m² and no MetS), MUNW (BMI <23.0 kg/m² and MetS present), metabolically unhealthy overweight (MUOW, BMI 23.0–24.9 kg/m² and MetS present), and metabolically unhealthy obese (MUO, BMI ≥25.0 kg/m² and MetS present).

3. Follow-up and identification of breast cancer incidence

Endometrial cancer incidence was identified through a linkage to the NHID healthcare utilization database. A combination of codes for endometrial cancer (C54.1) of the International Classification of Disease (ICD) 10th version and catastrophic illness codes that provide reduction in the coinsurance rate for patients with diseases based on relevant clinical information was applied to define the endometrial cancer incidence. Studies have suggested that the estimation of cancer incidence based on the ICD and catastrophic illness codes is reliable [19]. Participants were considered censored if they had not developed endometrial cancer by December 31, 2018, or until death. If a woman had cancer other than endometrial cancer or 2 or more types of cancer, she was censored at the first cancer. The follow-up period was defined as the period from the date of the health examination to the first date of any of these 3: December 31, 2018, date of death, or date of first cancer.

Although we excluded cancer cases identified through catastrophic illness code within 6 months from the date of screening, additional sensitivity analysis was performed after excluding endometrial cancer cases identified within the first 2 years of follow-up to minimize possible reverse causation.

4. Covariate assessment

Other variables measured through self-administered questionnaires were included as adjusted variables. Age based on the birth year; the year of health examination; and lifestyle factors such as smoking, drinking, and physical activity were measured through questionnaires of the general health examination. Reproductive histories such as age at menarche, menopausal status and age, number of children, breastfeeding history, and oral contraceptive use were evaluated through cancer screening questionnaires.

5. Statistical analysis

The association between obesity, MetS, and endometrial cancer risk was estimated using a Cox proportional hazards regression model adjusted for the variables described above, after testing the proportional hazard assumption based on Kaplan–Meier curves, and parallels of the survival distribution function. In addition, the associations of the total number of MetS components and each of the five components of MetS on endometrial cancer risk were assessed, with or without adjusting for the other components of MetS. To identify the associations between MetS, obesity, and endometrial cancer, excluding other effects, we additionally adjusted for each of them mutually. Subsequently, the associations of MetS, each component of MetS, and endometrial cancer were assessed, stratified by the obesity status (normal weight, overweight, and obesity) with or without additionally adjusted for BMI in each stratum. The hazard ratios (HRs) and 95% confidence intervals (CIs) of the MHOW, MHO, MUNW, MUOW, and MUO groups were estimated using MHNW as a reference group to investigate the combined effect of metabolic health and obesity. In addition, the combined associations of each component of MetS and obesity were analyzed using normal-weight women without each component of MetS as a reference group. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

RESULTS

Table 1 shows the baseline characteristics of the study participants. Of the 6,097,686 women included in the analysis, 1,497,812 (24.6%) had MetS, 2,649,564 (43.5%) had normal weight, 1,507,663 (24.7%) were overweight, and 1,940,459 (31.8%) were obese. The factors included in **Table 1** showed significantly different distributions between the normal, overweight, and obese groups (p<0.05). The number of incident endometrial cancer cases was 6,797, with an incidence rate per 100,000 person-years of 12.6.

Overweight and obesity were associated with increased endometrial cancer risk, with an HR of 1.36 (95% CI=1.28–1.45) and 1.92 (95% CI=1.82–2.04), respectively (**Table 2**), after adjusting for age, smoking, drinking, vigorous physical activity, moderate physical activity, walking, age at menarche, age at menopause, number of children, breast feeding, oral contraceptive use, and family history of cancer. MetS and all components of MetS at baseline significantly increased endometrial cancer risk by 1.21- to 1.49-fold. After adjusting for BMI or other components of MetS, the associations remained significant. In particular, MetS defined as 3 or more MetS components and high WC increased the endometrial cancer risk (HR=1.42; 95% CI=1.34–1.50 for MetS; HR=1.49; 95% CI=1.42–1.57 for high WC).

Table 3 shows the association between MetS and endometrial cancer risk stratified by obesity status. In women who were of normal weight or overweight, MetS and all MetS components were not associated with increased endometrial cancer risk. Only reduced HDL increased the likelihood of endometrial cancer in overweight women (HR=1.12; 95% CI=1.01–1.24). However, MUO women with MetS were more likely to develop endometrial cancer (HR=1.29; 95% CI=1.20–1.39) than MHO women. Furthermore, all MetS components were significantly more likely to develop endometrial cancer (HR range: 1.13–1.26). After additionally adjusting for BMI in each stratum, the results did not change (**Table S1**).

The combined association of MetS and obesity with endometrial cancer risk is presented in **Table 4**. MUNW women did not have increased endometrial cancer risk compared to MHNW women. MHOW women were had an increased risk (HR=1.37; 95% CI=1.27–1.46) compared to MHNW women, and the HR was comparable to that of MUOW women (HR=1.38; 95% CI=1.23–1.55). The HR of MHO women was 1.75 (95% CI=1.64–1.87) and it was more prominent in MUO women (HR=2.18; 95% CI=2.03–2.34). The four components of MetS showed a similar trend: no increased risk in normal-weight women with each component of MetS, increased risk in overweight women with or without each component, increased risk in obese women without each component, and highest risk in obese women with the components. Interestingly, normal-weight women with high WC showed significantly increased endometrial cancer risk than women with normal weight and normal WC (HR=1.23; 95% CI=1.07–1.41).

Sensitivity analysis excluded any identified cancers within the first 2 years of the screening date and showed comparable results, minimizing the possibility of reverse causation (data not shown).

Table 1. Baseline characteristics of study participants

Characteristics	BMI		
	Normal (<23 kg/m^2)	Overweight (23–25 kg/m^2)	Obese (≥25 kg/m^2)
Age (yr)	51.5±10.6	54.7±10.3	56.5±10.4
Age at menarche			
<15 years	649,555 (24.5)	311,311 (20.6)	376,918 (19.4)
15–16 years	1,000,585 (37.8)	568,461 (37.7)	709,674 (36.6)
≥17 years	703,627 (26.6)	491,009 (32.6)	687,917 (35.5)
Missing	295,797 (11.2)	136,882 (9.1)	165,950 (8.6)
Age at menopause			
Premenopause	1,285,464 (48.5)	584,477 (38.8)	655,987 (33.8)
<45 years	77,549 (2.9)	51,923 (3.4)	81,942 (4.2)
45–52 years	736,844 (27.8)	515,903 (34.2)	714,443 (36.8)
≥ 53 years	217,939 (8.2)	191,292 (12.7)	287,751 (14.8)
Missing	331,768 (12.5)	164,068 (10.9)	200,336 (10.3)
Delivery			
Nullipara	291,726 (11.0)	124,236 (8.2)	139,635 (7.2)
Para	2,104,768 (79.4)	1,272,189 (84.4)	1,668,946 (86.0)
Missing	253,070 (9.6)	111,238 (7.4)	131,878 (6.8)
Breast feeding			
Never	461,092 (17.4)	181,093 (12.0)	175,361 (9.0)
<1 year	536,149 (20.2)	295,555 (19.6)	336,132 (17.3)
≥ 1 year	1,388,895 (52.4)	914,445 (60.7)	1,289,924 (66.5)
Missing	263,428 (9.9)	116,570 (7.7)	139,042 (7.2)
Oral contraceptive use			
Never	1,969,875 (74.3)	1,123,003 (74.5)	1,434,555 (73.9)
Ever	423,389 (16.0)	270,968 (18.0)	370,700 (19.1)
Missing	256,300 (9.7)	113,692 (7.5)	135,204 (7.0)
Family history of cancer			
No	1,939,504 (73.2)	1,142,825 (75.8)	1,504,057 (77.5)
Yes	501,464 (18.9)	280,098 (18.6)	338,520 (17.4)
Missing	208,596 (7.9)	84,740 (5.6)	97,882 (5.0)
Drinking frequency during the last 1 year			
No	2,044,220 (77.2)	1,196,744 (79.4)	1,577,633 (81.3)
1 day/week	365,867 (13.8)	182,501 (12.1)	208,724 (10.8)
≥2 day/week	214,931 (8.1)	113,871 (7.6)	135,583 (7.0)
Missing	24,546 (0.9)	14,547 (1.0)	18,519 (1.0)
Smoking			
Never	2,501,378 (94.4)	1,441,995 (95.6)	1,853,413 (95.5)
Ever	134,321 (5.1)	57,521 (3.8)	76,654 (4.0)
Missing	13,865 (0.5)	8,147 (0.5)	10,392 (0.5)
Vigorous physical activity			
No	1,841,554 (69.5)	1,034,814 (68.6)	1,389,025 (71.6)
1–2 day/week	435,974 (16.5)	239,121 (15.9)	277,335 (14.3)
≥3 day/week	352,755 (13.3)	223,056 (14.8)	261,032 (13.5)
Missing	19,281 (0.7)	10,672 (0.7)	13,067 (0.7)
Moderate physical activity			
No	1,614,403 (60.9)	925,499 (61.4)	1,245,696 (64.2)
1–2 day/week	514,755 (19.4)	268,274 (17.8)	318,461 (16.4)
≥3 day/week	497,679 (18.8)	300,644 (19.9)	358,942 (18.5)
Missing	22,727 (0.9)	13,246 (0.9)	17,360 (0.9)
Walking			
No	869,356 (32.8)	511,071 (33.9)	707,277 (36.4)
1–3 days/week	913,497 (34.5)	488,657 (32.4)	600,652 (31.0)
4–6 days/week	543,164 (20.5)	308,035 (20.4)	369,369 (19.0)
7 days/week	305,866 (11.5)	189,568 (12.6)	249,517 (12.9)
Missing	17,681 (0.7)	10,332 (0.7)	13,644 (0.7)

Values are presented as number (%) not otherwise specified.
BMI, body mass index.

Table 2. Associations between obesity, MetS, and the risk of endometrial cancer

BMI, metabolic phenotype	No. participants	Person-years	No. cases	HR (95% CI)*	p-value	HR (95% CI)†	p-value	HR (95% CI)‡	p-value
BMI (kg/m²)									
<23	2,649,564	23,964,689.4	2,253	1					
23–25	1,507,663	13,124,206.3	1,650	1.36 (1.28–1.45)	<0.001				
≥25	1,940,459	16,863,092.8	2,894	1.92 (1.82–2.04)	<0.001				
MetS									
No	4,599,874	40,029,489.5	4,810	1		1			
Yes	1,497,812	13,022,499.0	1,987	1.44 (1.36–1.52)	<0.001	1.42 (1.34–1.50)	<0.001		
Per 1 increment component of MetS	-	-		1.17 (1.15–1.20)	<0.001	1.17 (1.15–1.19)	<0.001		
Component of MetS									
Elevated BP									
No	3,930,473	34,198,779.3	4,220	1		1		1	
Yes	2,167,213	18,853,209.2	2,577	1.22 (1.16–1.82)	<0.001	1.21 (1.15–1.27)	<0.001	1.13 (1.07–1.19)	<0.001
Elevated FBG									
No	4,324,091	37,644,549.6	4,650	1		1		1	
Yes	1,773,595	15,407,438.8	2,147	1.19 (1.13–1.26)	<0.001	1.18 (1.12–1.25)	<0.001	1.10 (1.05–1.16)	<0.001
High WC									
No	3,636,723	31,656,013.0	3,554	1		1		1	
Yes	2,460,963	21,395,975.5	3,243	1.52 (1.45–1.60)	<0.001	1.49 (1.42–1.57)	<0.001	1.43 (1.36–1.51)	<0.001
Elevated TG									
No	4,679,785	40,706,563.9	5,042	1		1		1	
Yes	1,417,901	12,345,424.6	1,755	1.23 (1.17–1.30)	<0.001	1.22 (1.16–1.29)	<0.001	1.10 (1.03–1.16)	0.002
Reduced HDL									
No	4,257,796	37,025,479.4	4,549	1		1		1	
Yes	1,839,890	16,026,509.1	2,248	1.17 (1.12–1.24)	<0.001	1.18 (1.12–1.24)	<0.001	1.09 (1.04–1.15)	0.001

BMI, body mass index; BP, blood pressure; CI, confidence interval; FBG, fasting blood glucose; HDL, high-density lipoprotein; HR, hazard ratio; MetS, metabolic syndrome; TG, triglyceride; WC, waist circumference.
*Adjusted for age, smoking, drinking, vigorous physical activity, moderate physical activity, walking, age at menarche, age at menopause, number of children, breast feeding, oral contraceptive use, and family history of cancer; †Adjusted for the variables mentioned above and BMI; ‡Adjusted for the other components of MetS.

DISCUSSION

This large, nationally representative study identified that both obesity and MetS increased the risk of endometrial cancer in women, although the association between MetS and endometrial cancer risk was especially significant in obese women. Compared to MHNW women, MHOW, MUOW, MHO, and MUO women had an increased endometrial cancer risk, whereas in MUNW women, the risk did not increase, except for high WC. The increased risk was comparable between MHNW and MUNW women and MHOW and MUOW women. However, a higher risk was found in MUO women than in MHO women. This finding suggests an increased association between MetS and endometrial cancer in obese women. For obese women, endometrial cancer risk increases not only because of obesity but also because of their metabolic health status.

Internal and external estrogen exposure plays an important role in endometrial cancer risk. The role of obesity in endometrial cancer risk has been established as per the "unopposed estrogen" theory, which describes the increase of circulating estrogen levels from sex steroid-metabolizing enzymes expressed by adipose tissue and the influence of low levels of

Table 3. Associations between MetS and the risk of endometrial cancer according to obesity status

Metabolic phenotype	BMI					
	Normal (<23 kg/m²)		Overweight (23–25 kg/m²)		Obese (≥25 kg/m²)	
	HR (95% CI)*	p-value	HR (95% CI)*	p-value	HR (95% CI)*	p-value
MetS						
No	1		1		1	
Yes	1.02 (0.87–1.19)	0.790	1.00 (0.89–1.13)	0.998	1.29 (1.20–1.39)	<0.001
Component of MetS						
Elevated BP						
No	1		1		1	
Yes	0.98 (0.88–1.08)	0.653	0.93 (0.84–1.03)	0.177	1.26 (1.17–1.36)	<0.001
Elevated FBG						
No	1		1		1	
Yes	0.97 (0.87–1.07)	0.542	1.10 (0.99–1.23)	0.069	1.17 (1.09–1.26)	<0.001
High WC						
No	1		1		1	
Yes	1.15 (0.99–1.32)	0.058	0.92 (0.83–1.02)	0.113	1.26 (1.14–1.39)	<0.001
Elevated TG						
No	1		1		1	
Yes	1.00 (0.89–1.13)	0.980	1.00 (0.90–1.13)	0.942	1.19 (1.10–1.28)	<0.001
Reduced HDL						
No	1		1		1	
Yes	1.03 (0.93–1.13)	0.599	1.12 (1.01–1.24)	0.028	1.13 (1.05–1.22)	0.001

BP, blood pressure; CI, confidence interval; FBG, fasting blood glucose; HDL, high-density lipoprotein; HR, hazard ratio; MetS, metabolic syndrome; TG, triglyceride; WC, waist circumference.
*Adjusted for age, smoking, drinking, vigorous physical activity, moderate physical activity, walking, age at menarche, age at menopause, number of children, breast feeding, oral contraceptive use, and family history of cancer.

sex hormone-binding globulin on the increased endometrial cancer risk. A positive linear association between increased BMI and serum estrogen concentration supports this theory [20,21]. Meta-analysis and intervention studies have also shown that obesity measured through both BMI, WC, waist-hip ratio, or hip circumference increases the endometrial cancer risk, whereas weight loss interventions and management may reduce the risk [22-24]. The results of this study concurred with those of previous studies [22-24], and the association of obesity measured by BMI and high WC was found to be the most prominent [5]. Based on the "unopposed estrogen" theory, it is expected that the effect of obesity would be higher in post-menopausal women, as is the case in breast cancer [20,21]. However, a case-control study showed a stronger association between MetS and endometrial cancer in premenopausal women, compared with the association in post-menopausal women [25]. In this study, we did not observe a similar association between obesity, MetS, and endometrial cancer risk according to menopausal status (data not shown). A previous meta-analysis also found a positive association between BMI and endometrial cancer risk in both pre- and post-menopausal women [22], suggesting that the influence of MetS remains constant throughout all stages of menopause.

Other suggested mechanisms include insulin resistance, abnormal fat metabolism, and chronic inflammation, which are the common mechanisms that drive the negative effects of obesity and MetS [12,23]. Comparable results before and after adjustment for BMI in this study confirmed the independent effect of MetS and its components on endometrial cancer through the mechanism of each other. Obesity, type 2 diabetes, and hypertension are referred to as the triplets of endometrial cancer based on their frequent coexistence in patients with endometrial cancer [12]. Recently updated meta-analysis results also confirmed the association of type 2 diabetes and hypertension with increased endometrial cancer risk [4,11,26,27]. Regarding dyslipidemia, despite inconsistent results among available studies

Table 4. HR and 95% CI of the combined association of MetS, obesity and the risk of endometrial cancer

Variables		BMI (kg/m²)	No. participants	Person-years	No. cases	HR* (95% CI)	p-value
MeS							
	No	<23	2,415,963	21,028,271.6	2,067	1	
		23–25	1,143,111	9,949,836.8	1,287	1.37 (1.27–1.46)	<0.001
		≥25	1,040,800	9,051,381.1	1,456	1.75 (1.64–1.87)	<0.001
	Yes	<23	233,601	2,036,417.8	186	1.13 (0.97–1.32)	0.111
		23–25	364,552	3,174,369.5	363	1.38 (1.23–1.55)	<0.001
		≥25	899,659	7,811,711.7	1,438	2.18 (2.03–2.34)	<0.001
Elevated BP							
	No	<23	1,988,840	17,306,485.3	1,725	1	
		23–25	957,264	8,332,062.0	1,108	1.40 (1.29–1.51)	<0.001
		≥25	984,369	8,560,231.9	1,387	1.76 (1.64–1.89)	<0.001
	Yes	<23	660,724	5,758,204.1	528	1.05 (0.95–1.16)	0.319
		23–25	550,399	4,792,144.3	542	1.32 (1.19–1.45)	<0.001
		≥25	956,090	8,302,860.9	1,507	2.13 (1.98–2.29)	<0.001
Elevated FBG							
	No	<23	2,073,820	18,054,351.6	1,788	1	
		23–25	1,062,974	9,257,278.9	1,150	1.32 (1.22–1.42)	<0.001
		≥25	1,877,297	10,332,919.1	1,712	1.81 (1.69–1.94)	<0.001
	Yes	<23	575,744	5,010,337.8	465	1.01 (0.91–1.12)	0.825
		23–25	444,689	3,866,927.4	500	1.45 (1.32–1.61)	<0.001
		≥25	753,162	6,530,173.6	1,182	2.08 (1.93–2.24)	<0.001
High WC							
	No	<23	2,392,369	20,824,185.1	2,024	1	
		23–25	896,336	7,803,106.0	1,051	1.42 (1.31–1.53)	<0.001
		≥25	348,018	3,028,721.9	479	1.66 (1.50–1.84)	<0.001
	Yes	<23	257,195	2,240,504.3	229	1.23 (1.07–1.41)	0.003
		23–25	611,327	5,321,100.3	599	1.32 (1.20–1.45)	<0.001
		≥25	1,592,441	13,834,370.9	2,415	2.02 (1.90–2.15)	<0.001
Elevated TG							
	No	<23	2,263,454	19,698,543.4	1,941	1	
		23–25	1,132,443	9,854,374.7	1,260	1.36 (1.27–1.46)	<0.001
		≥25	1,283,888	11,153,645.8	1,841	1.82 (1.70–1.94)	<0.001
	Yes	<23	386,110	3,366,146.0	312	1.06 (0.94–1.19)	0.361
		23–25	375,220	3,269,831.6	390	1.37 (1.26–1.53)	<0.001
		≥25	656,571	5,709,447.0	1,053	2.14 (1.98–2.31)	<0.001
Reduced HDL							
	No	<23	2,020,563	17,575,636.9	1,717	1	
		23–25	1,023,987	8,908,487.7	1,093	1.32 (1.22–1.42)	<0.001
		≥25	1,213,246	10,541,354.7	1,739	1.84 (1.72–1.97)	<0.001
	Yes	<23	629,001	5,489,052.5	536	1.05 (0.96–1.16)	0.303
		23–25	483,676	4,215,718.6	557	1.47 (1.34–1.62)	<0.001
		≥25	727,213	6,321,738.1	1,155	2.08 (1.93–2.25)	<0.001

BP, blood pressure; CI, confidence interval; FBG, fasting blood glucose; HDL, high-density lipoprotein; HR, hazard ratio; MetS, metabolic syndrome; TG, triglyceride; WC, waist circumference.
*Adjusted for age, smoking, drinking, vigorous physical activity, moderate physical activity, walking, age at menarche, age at menopause, number of children, breast feeding, oral contraceptive use, and family history of cancer.

[28-30], a meta-analysis showed significantly increased endometrial cancer risk in women with high TG levels, but no association was observed with low HDL [11]. In this study, after adjusting for BMI, all components of MetS, including even high TG and low HDL, were significantly associated with increased endometrial cancer risk. The higher influence of blood cholesterol on the bioavailability of estrogen from adipose tissue after menopause might explain these results [31].

Despite strong evidence of the association between obesity, type 2 diabetes, hypertension, and endometrial cancer, studies investigating the effect of a combination of these factors have been less studied compared with those investigating other diseases, such as

cardiovascular diseases or breast cancer. A few studies have identified that type 2 diabetes or hypertension is a significant risk factor for endometrial cancer in obese women [25,31-34]. This study identified that hypertension and type 2 diabetes, as well as other components of MetS and MetS itself, increased the endometrial cancer risk, especially in obese women. Cao et al. [15] also identified that the combination of MetS and obesity, MUO, MHO, MHOW, and MUOW were all associated with increased endometrial cancer risk, although there was no association between MUNW and endometrial cancer risk. These findings are consistent with those of this study. In this study, the association between the presence of each of the five components of MetS and obesity showed a consistent pattern, although women with normal weight and high WC were also likely to have increased endometrial cancer risk, which is consistent with previous results [15,33], suggesting a possible role of body shape. The lower levels of circulating insulin in non-obese women with diabetes than in obese women could explain the greater effect of MetS in obese women [32]. These results suggest that despite the independent association, the impact of obesity might outweigh metabolic health in general. However, obese women with impaired metabolic health had increased endometrial cancer risk compared to MHO women, suggesting that obese women are more vulnerable to metabolic health issues. Despite a high percentage of body fat, MHO women showed higher insulin sensitivity and adiponectin concentration, lower inflammation biomarkers such as C-reactive protein [35], and better fitness [36]. These characteristics may reduce their endometrial cancer risk compared to MUO women. Considering that obese women have a higher endometrial cancer risk, the additional risk due to metabolic health issues should be carefully considered. In addition, a previous study showed that endometrial cancer risk in MUO women was higher (HR=4.03) than the risk of other types of cancer (HR<2) [22], suggesting a higher vulnerability of MUO women to endometrial cancer. Considering the association of insulin resistance with the more advanced stages and higher invasion at diagnosis [37], the management of MetS is important not only for the prevention of endometrial cancer, especially in obese women, but also for a better prognosis of the endometrial cancer.

There are several limitations to be considered. First, although the NECP-ATP III guideline for MetS considers pharmacologic treatment of BP, fasting glucose, TG, and HDL, we did not include the information because we did not obtain the medication data. Thus, women who took medications to control their BP, fasting glucose, TG, or HDL were classified into the normal group. Second, only baseline MetS and obesity status were considered, and changes over the follow-up period were not analyzed in this study. However, we expected non-differential changes in the MetS status and BMI to be related to baseline estimates based on the results from another longitudinal study [38] and that the effect would yield conservative results. Considering that weight loss management through bariatric surgery or medication reduces endometrial cancer risk and hyperplastic changes in the endometrium [23], further studies considering the short- and long-term changes in weight and the components of MetS need to be conducted. Third, women who did not participate in the national health examinations were excluded. The participation rate of the national health examination increased from 43% in 2002 to 75% in 2017 [39]; thus, considering the high participation rate (>70%) in the NHIS health examination and inclusion of all women who underwent a national health examination, the selection bias of this study would not be significant. Fourth, unconsidered confounders may have caused residual confounding effects.

In conclusion, obesity, each component of MetS, and MetS itself, increased the endometrial cancer risk. The associations of MetS, components of MetS, and endometrial cancer risk

were more prominent in obese women. The observed associations of obesity, MetS, and endometrial cancer in South Korean women were comparable with the results in Western populations [15,33]. As a preventive measure for endometrial cancer, weight control should take on a scientifically rigorous approach. Moreover, for obese women, controlling MetS may also significantly reduce their endometrial cancer risk. Thus, efforts for lifestyle management and healthy behaviors need to be implemented to increase the likelihood of women transitioning from MUO to MHO, and in so doing, reduce the endometrial cancer risk.

SUPPLEMENTARY MATERIAL

Table S1
Associations between metabolic syndrome and the risk of endometrial cancer according to obesity status, adjusted for the BMI as a continuous variable within the obesity strata

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