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Research article

Risk of female-specific cancers according to obesity and menopausal status in 2•7 million Korean women: Similar trends between Korean and Western women

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ABSTRACT

Background: Studies examining the relationship between obesity and female-specific cancers have been mainly conducted in Western populations. We aimed to investigate the risk of female-specific cancers according to obesity and menopausal status using a nationwide cohort in Korea.

Methods: We identified 2,708,938 women from the National Health Insurance Service cohort, and obtained baseline body mass index (BMI), waist circumference (WC), and other healthcare data, measured and collected during a health examinations and cancer-screening survey. By setting a normal weight/WC group (BMI, 18•5–22•9 kg/m^2 or WC, 80•0–84•9 cm) as the reference, we conducted multivariate analyses using the Cox proportional hazard model to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (95% CIs) for each cancer.

Findings: The total follow-up duration was 22389854•63 person-years. In post-menopausal women, the risk of breast, endometrial, and ovarian cancers significantly increased as the BMI classification level increased from normal to class II obesity (aHRs [95% CIs], 1•49 [1•38–1.61], 2•11 [1•81–2•46], and 1•38 [1•20–1•58], respectively). The risk of breast and endometrial cancers also increased as the WC classification increased from $<$ 75•0 to $\geq$ 95•0 cm. With a WC of 80•0–84•9 cm as the reference, the lowest risk of breast and endometrial cancers was observed in WC $<$ 75•0 cm (aHRs [95% CIs], 0•85 [0•81–0•89] and 0•75 [0•67–0•84], respectively) while the highest risk was observed in WC $\geq$ 95•0 cm (aHRs [95% CIs], 1•19 [1•10–1•29] and 1•56 [1•33–1•82], respectively). In pre-menopausal women, the risk of breast cancer significantly decreased in those with class I and II obesity compared to those with normal BMI (aHRs [95% CIs], 0•96 [0•92–0•999] and 0•89 [0•81–0•97], respectively), whereas the trends of endometrial and ovarian cancer incidence in pre-menopausal women were similar to those observed in post-menopausal women. For cervical cancer, only class II obesity was significantly associated with increased risks in both post-menopausal and pre-menopausal women (aHRs [95% CIs], 1•18 [1•01–1•39] and 1•27 [1•02–1•57], respectively).

Interpretation: In this large population-based cohort study in Korean women, we observed that the impact of obesity on the development of female-specific cancers differs according to the malignancy type and menopausal status. Similar trends were observed between Korean and Western women.

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Research in context

Evidence before this study

We searched PubMed using the search terms 'breast cancer', 'endometrial cancer', 'ovarian cancer', 'cervical cancer', 'body mass index (BMI)', 'waist circumference (WC)', and 'menopause' for research articles published in English from database inception to November 13, 2020. In post-menopausal women from Western countries, the breast cancer risk was reported to be higher in the obese BMI group than in the normal BMI group. In pre-menopausal women, the association between breast cancer risk and BMI showed inconsistent results between Western and Asian women. Western cohort studies reported that women with BMI-defined obesity exhibited increased risks for endometrial, ovarian, and cervical cancers. We found no cohort studies showing a risk for the four types of female-specific cancers considered in this study, in relation to obesity and menopausal status. Studies that assessed the risk of the development of female-specific cancers showed that the association between cancer and obesity was stronger when BMI rather than WC was used as the obesity indicator. Therefore, a significant concern exists about the standard for classifying general obesity and abdominal obesity using BMI and WC. Importantly, studies assessing the effect of obesity on cancer incidence with respect to menopausal status have been conducted only in patients with breast cancer, prompting us to further investigate the effect of obesity in other female-specific cancers including endometrial, ovarian, and cervical cancers. In addition, most of the existing data related to obesity and cancer have been obtained from studies in Western women. A study on Korean women is imperative owing to the great genomic and environmental disparities between Korean and Western women. The association among female-specific cancer risk, obesity, and menopausal status needs to be evaluated in additional large-scale cohorts.

Added value of this study

To our knowledge, this is the largest cohort study to analyse the association of four types of female-specific cancers with obesity (based on BMI and WC) and menopausal status, which simultaneously increase the risk of breast, endometrial, ovarian, and cervical cancers, in Korean women (n = 2,708,938).

Implications of all the available evidence

The impact of obesity on the development of female-specific cancers differs according to the type of malignancy and the menopausal status in Korean women. Similar trends have been observed between Korean and Western women. These findings may improve the awareness of obesity- and menopause-related diseases for greater precision in preventing breast, endometrial, ovarian, and cervical cancers, and suggest that maintaining BMI and WC within specific ranges could reduce the chances of the development of certain types of female-specific cancers.

1. Introduction

Cancer is a global health burden with reported estimates of 18•1 million new cases and 9•6 million deaths in 2018 [1]. Breast cancer and the three major gynaecological malignancies – endometrial cancer, ovarian cancer, and cervical cancer – are representative female-specific cancers accounting for more than one-third (38•6%) of new cancer cases in women globally [1]. In Korea, the incidence of breast, endometrial, and ovarian cancers, except for cervical cancer, has been gradually increasing every year [2].

Obesity is an established risk factor for several malignancies. Although the precise mechanism is not fully understood, obesity-related abnormalities, such as impaired glucose tolerance, insulin resistance, and systemic inflammation, are expected to contribute to cancer development [3]. For obese post-menopausal women, increased peripheral aromatisation of androgens to oestrogens is considered to elevate the risk of breast and endometrial cancers [4]. Body mass index (BMI) has been widely used as an indicator of obesity. However, BMI is a crude parameter of body size that does not discriminate body fat composition. Meanwhile, waist circumference (WC) measures abdominal obesity and is known to have a stronger association with impaired glucose tolerance than BMI [5]. Therefore, to investigate the impact of obesity on the risk of cancer development, both BMI and WC should be considered in assessing obesity.

The relationship between obesity and female-specific cancer risk has been mainly studied in Western populations [6–9]. To investigate obesity-related health outcomes, ethnic differences in body composition should be considered. According to the Organisation for Economic Co-operation and Development (OECD) Health Statistics, the proportion of the Korean population with BMI > 25•0 kg/m^2 was only 33•7%, which was remarkably lower than the average (58•2%) for all OECD member countries [10]. Meanwhile, Asian populations generally have higher body fat percentage and prevalence of type 2 diabetes, and more increased cardiovascular risk factors than Western populations at the same BMI. Thus, the World Health Organisation expert consultations suggested different BMI cut-off points for Asian populations [11]. However, only a few extensive population-based cohort studies have examined the association between obesity and the incidence of female-specific cancers in Asian populations.

In addition, there is a growing interest in unravelling epidemiological evidence associated with menopausal status in women. Menopause is characterised by the permanent cessation of menstruation that results from the loss of ovarian function, and physiological changes occur after menopause. For example, hormonal changes during the perimenopausal period substantially contribute to increased abdominal obesity. Accordingly, the prevalence of impaired glucose tolerance and diabetes dramatically increases in post-menopausal women [12]. As female-specific cancers are oestrogen-related malignancies that mostly occur in female reproductive organs, the detailed effect size of obesity in the development of these cancers might differ according to the menopausal status.

Therefore, this study aimed to investigate the risk of female-specific cancers according to obesity and menopausal status using a large population-based cohort in Korea. We analysed BMI and WC separately and together, and performed multivariate analyses to adjust for confounding factors.

2. Methods

2.1. Data sources

This nationwide population-based cohort study was conducted after obtaining approval from the institutional review board of Seoul National University Hospital (no. 1811-048-983). The requirement for informed consent was waived because we used anonymous and de-identified data according to the confidential guidelines of the National Health Insurance Service (NHIS) of Korea.

The NHIS is the single universal health coverage system in Korea, providing universal and comprehensive medical care to most of the entire population. In this study, we constructed a customised database by merging the NHIS Medical check-up DB, consisting of 2009 NHIS health examinations and cancer-screening questionnaire results, and the NHIS claim DB.

2.2. Study population and data collection

The cohort included women aged >19 years who underwent the NHIS health examinations and completed the cancer-screening questionnaire in 2009 (n = 3,280,834). Among them, women with the following conditions were excluded: (i) had undergone hysterectomy (n = 206,481), (ii) with insufficient data (n = 289,290), and (iii) had been diagnosed with any malignancies before the date of health examinations (i.e., all cancer washout; n = 64,036). Additionally, to ensure a causal relationship and to reduce detection bias, we excluded 12,089 women diagnosed with breast, endometrial, ovarian, and cervical cancers for a year after the NHIS health examinations (i.e., 1-year lag period). As a result, 2,708,938 women were set as the study population.

Women's age at the time of 2009 NHIS health examinations were calculated as the time interval between the birth date, inferred from the National Identification Number, and the date of health examinations. From the 2009 NHIS health examinations data, we retrieved women's laboratory test results and height, body weight, and WC, measured at that time. From the 2009 NHIS cancer-screening questionnaire results, we obtained the following data: parity, smoking, alcohol consumption, physical activity, age at menarche, breastfeeding, oral contraceptive use, menopausal status, and history of hormone replacement therapy (HRT). All missing data, except oral contraceptive use and history of HRT, were excluded in this analysis.

In terms of comorbidities, we used women's laboratory test results of the 2009 NHIS health examinations and the NHIS claim DB with the International Classification of Diseases, 10th revision code (ICD-10). Hypertension was defined as a systolic blood pressure (SBP) ≥140 mmHg or a diastolic blood pressure ≥90 mmHg, or presence of I10–13 and I15 with antihypertensive medications at the time of screening. Diabetes was defined as a fasting plasma glucose level ≥126 mg/dL or presence of E11–14 with antidiabetic medications. Dyslipidemia was defined as a total cholesterol ≥240 mg/dL or presence of E78 with antihyperlipidemic medications.

For the study purpose, the study population was divided into two groups based on the women's menopausal status in 2009: pre-menopausal (n = 1,146,486) and post-menopausal (n = 1,562,452). Thereafter, they were followed up until the development of female-specific cancers or December 31, 2018 (Fig. 1).

2.3. Classification and outcomes

We classified the women into five categories of BMI according to the WHO cut-offs for Asian populations [11]: < 18•5 kg/m^2 (underweight), 18•5–22•9 kg/m^2 (normal), 23•0–24•9 kg/m^2 (overweight), 25•0–29•9 kg/m^2 (obese class I), and ≥ 30 kg/m^2 (obese class II). We also classified the women into six categories based on WC with 5-cm intervals: < 75•0, 75•0–79•9, 80•0–84•9, 85•0–89•9, 90•0–94•9, and ≥ 95•0 cm.

We also defined general obesity and abdominal obesity as BMI ≥ 25•0 kg/m^2 and WC ≥ 85•0 cm, respectively. We classified the women into four categories based on the combination of general and abdominal obesity: BMI < 25•0 kg/m^2 and WC < 85•0 cm (reference), BMI < 25•0 kg/m^2 and WC ≥ 85•0 cm (abdominal obesity only), BMI ≥ 250 kg/m^2 and WC < 85•0 cm (general obesity only), and BMI ≥ 25•0 kg/m^2 and WC ≥ 85•0 cm (both general and abdominal obesity).

By inquiring the NHIS claim DB, women with newly diagnosed female-specific cancers were identified when they made a documented visit to the hospital with the registration code V193 and the ICD-10 for the specific cancer (C50, C54–55, C56, and C53 for breast, endometrial, ovarian, and cervical cancers, respectively).

2.4. Statistical analysis

Differences in baseline characteristics were evaluated between the pre-menopausal and post-menopausal groups using Student's t-test for continuous variables and Pearson's chi-square test for categorical variables. To investigate the impact of BMI and WC levels on the development of female-specific cancers, we performed multivariate analyses using Cox proportional hazard regression models and calculated adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs). The person-years at risk were calculated for each woman from the date of 2009 NHIS health examinations to the development of the four female-specific cancers or to the date of follow-up loss (e.g., death or emigration) or December 31, 2018, whichever came first. Model 1 did not adjust for any clinical variable. Model 2 adjusted for age at the time of 2009 NHIS health examinations. Model 3 further adjusted for smoking status, alcohol consumption, physical activity, and diabetes. Model 4 in the total women further adjusted for parity, menopausal status, and age at menarche. In model 4 confined to pre-menopausal women, parity and age of menarche were further adjusted for in addition to the adjusted variables in model 3. In model 4 confined to post-menopausal women, parity, age of menarche, and hormonal replacement therapy duration were further adjusted for in addition to the adjusted variables in model 3. We also tested for linear trends by testing the significance of the term in a likelihood ratio test. All statistical analyses were performed using SAS software (version 9•4; SAS Institute, Cary, NC, USA). A two-sided p-value of < 0•05 was considered statistically significant.

Role of funding Source

The funders of this study had no role in the study design, data collection, data analysis, interpretation or the writing of this report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

3. Results

3.1. Characteristics of the study population

The baseline characteristics of the study population are presented in Table 1. The post-menopausal group had significantly higher proportions of parous women and non-smokers, and less alcohol consumption than the pre-menopausal group. In terms of comorbidities, hypertension, diabetes, and dyslipidaemia were more frequent in the post-menopausal group. Post-menopausal women were likely to have histories of breastfeeding and oral contraceptive use. Both BMI and WC were higher in the post-menopausal group.

The mean follow-up duration was 8•37 years and the total follow-up duration was 22389854•63 person-years, during which, 31,046, 5296, 7383, and 5817 women were newly diagnosed with breast, endometrial, ovarian, and cervical cancers, respectively (Supplementary Table 1).

3.2. BMI and risks of female-specific cancers

3.2.1. Breast cancer

Overall, the incidence of breast cancer increased with increasing BMI (p for trend <0.0001) (Supplementary Table 1). Multivariate analyses revealed that the risk of breast cancer gradually increased as the BMI classification increased from underweight to class II obesity (Fig. 2A). With normal BMI as the reference, the aHR of class II obesity for the development of breast cancer was 1•16 (95% CI, 1•09–1•23).

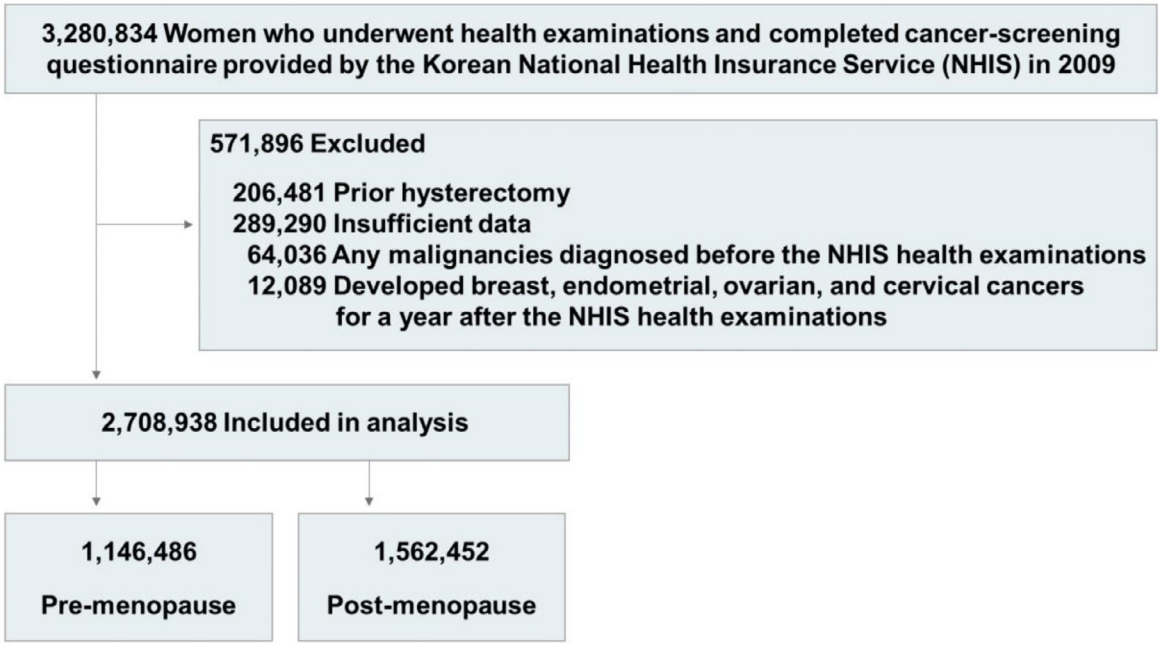

Fig. 1. Flow diagram of the study population selection.

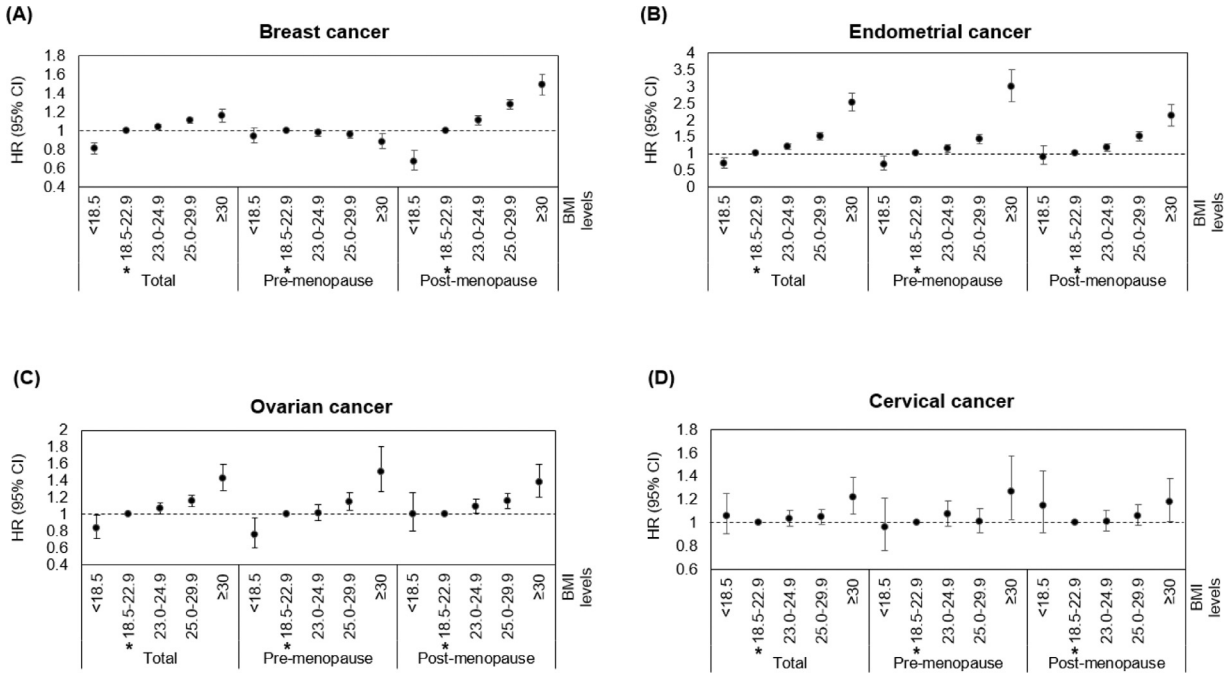

Fig. 2. Association of body mass index and incidence of female-specific cancers among all women, pre-menopausal women, and post-menopausal women: (A) breast cancer, (B) endometrial cancer, (C) ovarian cancer, and (D) cervical cancer. In the total women, age, smoking status, alcohol consumption, physical activity, diabetes, parity, menopausal status, and age at menarche were adjusted. In the pre-menopausal women, age, smoking status, alcohol consumption, physical activity, diabetes, parity, and age of menarche. In the post-menopausal women, age, smoking status, alcohol consumption, physical activity, diabetes, parity, age of menarche, and hormonal replacement therapy duration were adjusted. *Reference.

In the pre-menopausal group, the risk of breast cancer did not differ between underweight and normal BMI, and between overweight and normal BMI, whereas a decreased risk was observed in women with class I obesity (aHR, 0•96; 95% CI, 0•92–0•999; p=0•04) and class II obesity (aHR, 0•89; 95% CI, 0•81–0•97) (Supplementary Table 2).

In the post-menopausal group, the risk of breast cancer gradually increased as the BMI classification increased from underweight to class II obesity (p for trend <0.0001) (Supplementary Table 3). With normal BMI as the reference, the risk was the highest in class II obesity (aHR, 1•49; 95% CI, 1•38–1•61).

3.2.2. Endometrial cancer

Overall, the incidence of endometrial cancer increased with increasing BMI (p for trend <0.0001) (Supplementary Table 1). Multivariate analyses revealed that the risk of endometrial cancer gradually increased as the BMI classification increased from underweight to class II obesity (Fig. 2B). With normal BMI as the reference, the

Table 1
Characteristics of the study population.

Characteristics	All (n = 2,708,938, %)	Pre-menopausal group (n = 1,146,486, %)	Post-menopausal group (n = 1,562,452, %)	p-Value
Age at screening (years)				
Mean ± SD	54•0 ± 11•5	43•8 ± 5•4	61•5 ± 8•7	< 0•0001
Parity				< 0•0001
Null	113,269 (4•2)	74,748 (6•5)	38,521 (2•5)	
1	270,098 (10•0)	175,013 (15•3)	95,085 (6•1)	
≥ 2	2,325,571 (85•8)	896,725 (78•2)	1,428,846 (91•4)	
Smoking				< 0•0001
None	2,585,831 (95•5)	1,082,883 (94•5)	1,502,948 (96•2)	
Past smoker	38,628 (1•4)	21,828 (1•9)	16,800 (1•1)	
Current smoker	84,479 (3•1)	41,775 (3•6)	42,704 (2•7)	
Alcohol consumption				< 0•0001
None	2,168,394 (80•0)	805,154 (70•2)	1,363,240 (87•3)	
Mild	518,647 (19•1)	327,692 (28•6)	190,955 (12•2)	
Heavy	21,897 (0•8)	13,640 (1•2)	8,257 (0•5)	
Regular physical activity	471,425 (17•4)	187,961 (16•4)	283,464 (18•1)	< 0•0001
Comorbidity				
Hypertension	875,327 (32•3)	151,687 (13•2)	723,640 (46•3)	< 0•0001
Diabetes	245,021 (9•0)	38,729 (3•4)	206,292 (13•2)	< 0•0001
Dyslipidaemia	657,260 (24•3)	122,199 (10•7)	535,061 (34•2)	< 0•0001
Age at menarche (years)				
Mean ± SD	15•9 ± 2•1	15•0 ± 1•9	16•5 ± 2•0	< 0•0001
Breastfeeding				
Among all women				< 0•0001
None	391,756 (14•5)	289,809 (25•3)	101,947 (6•5)	
< 6 months	564,698 (20•8)	292,874 (25•5)	271,824 (17•4)	
≥ 6 and < 12 months	1421,852 (52•5)	336,056 (29•3)	1,085,796 (69•5)	
≥ 12 months	330,632 (12•2)	227,747 (19•9)	102,885 (6•6)	
Among parous women				< 0•0001
None	217,363 (8•4)	152,999 (14•3)	64,364 (4•2)	
< 6 months	391,756 (15•1)	289,809 (27•0)	101,947 (6•7)	
≥ 6 and < 12 months	564,698 (21•8)	292,874 (27•3)	271,824 (17•8)	
≥ 12 months	1,421,852 (54•8)	336,056 (31•4)	1,085,796 (71•3)	
Among nulliparous women				
None	113,269 (100•0)	74,748 (100•0)	38,521 (100•0)	N/A
Oral contraceptive use				< 0•0001
None	2,199,167 (81•2)	949,132 (82•8)	1,250,035 (80•0)	
< 12 months	250,302 (9•2)	110,938 (9•7)	139,364 (8•9)	
≥ 12 months	131,184 (4•8)	37,956 (3•3)	93,228 (6•0)	
Unknown	128,285 (4•7)	48,460 (4•2)	79,825 (5•1)	
HRT				< 0•0001
None	2,414,378 (89•1)	1,146,486 (100•0)	1,267,892 (81•1)	
< 2 years	139,235 (5•1)	0	139,235 (8•9)	
≥ 2 and < 5 years	55,556 (2•1)	0	55,556 (3•6)	
≥ 5 years	42,461 (1•6)	0	42,461 (2•7)	
Unknown	57,308 (2•1)	0	57,308 (3•7)	
Height (cm)				
Mean ± SD	155•3 ± 5•9	157•8 ± 5•2	153•5 ± 5•8	< 0•0001
Body weight (kg)				
Mean ± SD	57•2 ± 8•3	57•5 ± 8•2	57•0 ± 8•3	< 0•0001
BMI (kg/m^2)				
Mean ± SD	23•7 ± 3•2	23•1 ± 3•1	24•2 ± 3•2	< 0•0001
< 18.5	74,417 (2•7)	40,864 (3•6)	33,553 (2•1)	< 0•0001
18.5–22.9	1,112,044 (41•1)	578,753 (50•5)	533,291 (34•1)	
23.0–24.9	667,929 (24•7)	256,625 (22•4)	411,304 (26•3)	
25.0–29.9	751,500 (27•7)	235,579 (20•5)	515,921 (33•0)	
≥ 30.0	103,048 (3•8)	34,665 (3•0)	68,383 (4•4)	
WC (cm)				
Mean ± SD	77•9 ± 8•8	74•9 ± 8•2	80•1 ± 8•6	< 0•0001
< 75.0	1,003,890 (37•1)	601,082 (52•4)	402,808 (25•8)	< 0•0001
75.0–79.9	604,304 (22•3)	252,301 (22•0)	352,003 (22•5)	
80.0–84.9	530,207 (19•6)	162,965 (14•2)	367,242 (23•5)	
85.0–89.9	315,382 (11•6)	77,515 (6•8)	237,867 (15•2)	
90.0–94.9	159,673 (5•9)	32,788 (2•9)	126,885 (8•1)	
≥ 95.0	95,482 (3•5)	19,835 (1•7)	75,647 (4•84)	

Abbreviations: BMI, body mass index; HRT, hormone replacement therapy; N/A, not applicable; SD, standard deviation; WC, waist circumference.

aHR of class II obesity for the development of endometrial cancer was 2•49 (95% CI, 2•23–2•78).

In the pre-menopausal group, the risk of endometrial cancer gradually increased as the BMI classification increased (p for trend <0.0001) (Supplementary Table 2). Women with class II obesity had a significantly increased risk of endometrial cancer (aHR, 2•95; 95% CI, 2•53–3•45), whereas women with underweight had a significantly decreased risk (aHR, 0•69; 95% CI, 0•51–0•92).

In the post-menopausal group, underweight had no protective effect against the development of endometrial cancer. However, women with overweight, class I obesity, and class II obesity were at a high risk of developing endometrial cancer (aHRs [95% CIs],

1•19 [1•07–1•31], 1•51 [1•37–1•65], and 2•11 [1•81–2•46], respectively) (Supplementary Table 3).

3.2.3. Ovarian cancer

Overall, the incidence of ovarian cancer increased with increasing BMI (p for trend <0.0001) (Supplementary Table 1). Multivariate analyses revealed that the risk of ovarian cancer gradually increased as the BMI classification increased from underweight to class II obesity (Fig. 2C). With normal BMI as the reference, the aHR of class II obesity for the development of ovarian cancer was 1•42 (95% CI, 1•27–1•58).

In the pre-menopausal group, women with underweight showed a decreased risk of ovarian cancer, whereas those with class I and class II obesity were at a high risk of developing ovarian cancer (aHRs [95% CIs], 1•15 [1•05–1•26] and 1•49 [1•25–1•78], respectively) (Supplementary Table 2). In the post-menopausal group, underweight did not affect the development of ovarian cancer; however, overweight, class I obesity, and class II obesity were associated with a high risk of ovarian cancer development (aHRs [95% CIs], 1•09 [1•01–1•18], 1•16 [1•08–1•25], and 1•38 [1•20–1•58], respectively) (Supplementary Table 3).

3.2.4. Cervical cancer

Overall, relationship between BMI and the incidence of cervical cancer showed different trend, compared with those of breast, endometrial, and ovarian cancers. (Supplementary Table 1). In multivariate analyses, compared to women with normal BMI, only women with class II obesity showed a higher risk of developing cervical cancer (aHR, 1•22; 95% CI, 1•08–1•39) (Fig. 2D).

In the pre-menopausal group, only class II obesity, rather than normal BMI, significantly increased the risk of cervical cancer (aHR, 1•27; 95% CI, 1•02–1•57) (Supplementary Table 2). In the post-menopausal group, only class II obesity, rather than normal BMI, significantly increased the risk of cervical cancer (aHR, 1•18; 95% CI, 1•01–1•39) (Supplementary Table 3).

3.3. WC and risks of female-specific cancers

3.3.1. Breast cancer

Overall, multivariate analyses with a WC of 80•0–84•9 cm as the reference revealed that WC < 75•0 cm was associated with a reduced risk of breast cancer (aHR, 0•94; 95% CI, 0•91–0•98) (Fig. 3A and Supplementary Table 4).

In the pre-menopausal group, the WC classification did not affect the development of breast cancer (Supplementary Table 5). In the post-menopausal group, the risk of breast cancer also increased as the WC classification increased from < 75•0 to ≥ 95•0 cm (p for trend <0.0001) (Supplementary Table 6). With a WC of 80•0–84•9 cm as the reference, the lowest risk was observed in WC < 75•0 cm (aHR, 0•85; 95% CI, 0•81–0•89) while the highest risk was observed in WC ≥ 95•0 cm (aHR, 1•19; 95% CI, 1•10–1•29).

3.3.2. Endometrial cancer

Overall, the risk of endometrial cancer increased as the WC classification increased from < 75•0 to ≥ 95•0 cm (p for trend <0.001). In multivariate analyses with a WC of 80•0–84•9 cm as the reference, WC < 75•0 cm was associated with a reduced risk of endometrial cancer (aHR, 0•73; 95% CI, 0•67–0•79) (Supplementary Table 4). The risk of endometrial cancer increased with increasing WC, up to an aHR of 1•72 (95% CI, 1•52–1•96) (Fig. 3B).

In the pre-menopausal group, a WC of < 75•0 cm had a protective effect against the development of endometrial cancer (aHR, 0•76; 95% CI, 0•68–0•85), whereas a WC of ≥ 95•0 cm was significantly associated with an increased risk of endometrial cancer (aHR, 2•38; 95% CI, 1•94–2•93) (Supplementary Table 5). In the post-menopausal group, with a WC of 80•0–84•9 cm as the reference, the lowest risk was observed in WC < 75•0 cm (aHR, 0•75; 95% CI, 0•67–0•84) while the highest risk was observed in WC ≥ 95•0 cm (aHR, 1•56; 95% CI, 1•33–1•82) (Supplementary Table 6).

3.3.3. Ovarian cancer

In multivariate analyses with a WC of 80•0–84•9 cm as the reference, WC < 75•0 cm was associated with a reduced risk of ovarian cancer (aHR, 0•88; 95% CI, 0•83–0•94, respectively) (Supplementary Table 4). In contrast, only women with WC ≥ 95•0 cm showed a higher risk for the development of ovarian cancer (aHR, 1•23; 95% CI, 1•10–1•39) (Fig. 3C).

In the pre-menopausal group, compared to the reference, WC < 75•0 cm was associated with a reduced risk of ovarian cancer (aHR, 0•84; 95% CI, 0•76–0•94), whereas WC ≥ 95•0 cm was associated with a high risk of ovarian cancer (aHR, 1•50; 95% CI, 1•20–1•88) (Supplementary Table 5). In the post-menopausal group, only WC ≥ 95•0 cm significantly increased the risk of ovarian cancer, compared to the reference (aHR, 1•19; 95% CI, 1•03–1•36) (Supplementary Table 6).

3.3.4. Cervical cancer

In multivariate analyses with a WC of 80•0–84•9 cm as the reference, only those with a WC of 90•0–94•9 cm showed a higher risk for the development of cervical cancer (aHR, 1•19; 95% CI, 1•06–1•33) (Fig. 3D and Supplementary Table 4). In the pre-menopausal group, WC ≥ 95•0 significantly increased the risk of cervical cancer, compared to the reference (aHR, 1•55; 95% CI, 1•19–2•01) (Supplementary Table 5). In the post-menopausal group, WC of 90•0–94•9 cm significantly increased the risk of cervical cancer, compared to the reference (aHR, 1•20; 95% CI, 1•06–1•37) (Supplementary Table 6).

3.4. Combination of general and abdominal obesity and risks of female-specific cancers

We further investigated relationships between combination of general and abdominal obesity and risks of female-specific cancers. Fig. 4 presents a summary of the results.

3.4.1. Breast cancer

In the general obesity only group, the risk of breast cancer was significantly increased, compared to the reference group (aHR, 1•10; 95% CI, 1•06–1•13). Women with both general obesity and abdominal obesity were at a high risk of developing breast cancer (aHR, 1•11, 95% CI, 1•08–1•15) (Fig. 5A and Supplementary Table 7).

In the pre-menopausal group, the coexistence of general obesity and abdominal obesity was associated with a decreased risk of breast cancer, compared to the reference group (aHR, 0•94; 95% CI, 0•89–0•99) (Supplementary Table 8). In the post-menopausal group, women with general obesity only were at a high risk of developing breast cancer (aHR, 1•22; 95% CI, 1•17–1•28). The coexistence of general and abdominal obesity was also associated with an increased risk of breast cancer (aHR, 1•29; 95% CI, 1•24–1•35) (Supplementary Table 9).

3.4.2. Endometrial cancer

Compared to the reference group, the abdominal obesity only, general obesity only, and general and abdominal obesity groups showed significantly increased risks of endometrial cancer (aHRs [95% CIs], 1•25 [1•09–1•45], 1•42 [1•32–1•53], and 1•69 [1•58–1•81], respectively) (Fig. 5B and Supplementary Table 7).

In the pre-menopausal group, women with general obesity only showed significantly increased risk of endometrial cancer (aHR, 1•36; 95% CI, 1•22–1•51). The coexistence of general and abdominal obesity was associated with an increased risk of endometrial cancer (aHR, 1•88; 95% CI, 1•68–2•1.0) (Supplementary Table 8).

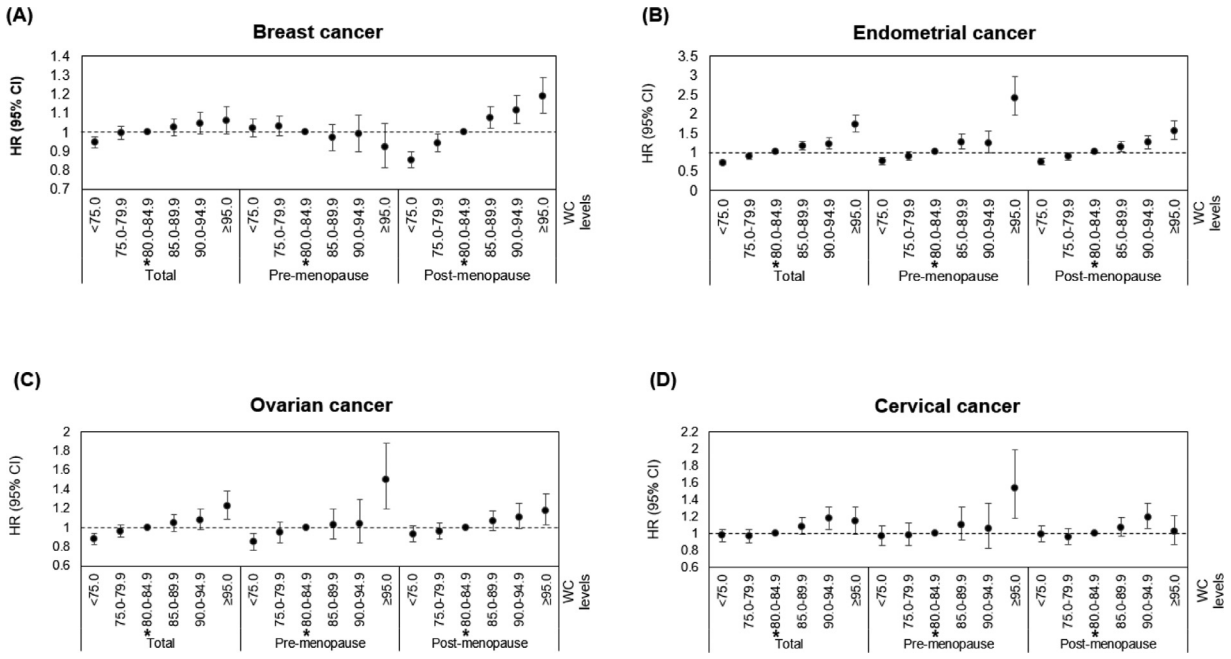

Fig. 3. Association of waist circumference and incidence of female-specific cancers among all women, pre-menopausal women, and post-menopausal women: (A) breast cancer, (B) endometrial cancer, (C) ovarian cancer, and (D) cervical cancer. In the total women, age, smoking status, alcohol consumption, physical activity, diabetes, parity, menopausal status, and age at menarche were adjusted. In the pre-menopausal women, age, smoking status, alcohol consumption, physical activity, diabetes, parity, and age of menarche. In the post-menopausal women, age, smoking status, alcohol consumption, physical activity, diabetes, parity, age of menarche, and hormonal replacement therapy duration were adjusted. *Reference.

	Obesity classification		Hazard ratio (95% CI)			
			Breast cancer	Endometrial cancer	Ovarian cancer	Cervical cancer
Total women	Normal	BMI <25 kg/m^2 and WC <85 cm	1	1	1	1
	Abdominal obesity	BMI <25 kg/m^2 and WC ≥85 cm	0.95	1.25	1.10	1.21
	General obesity	BMI ≥25 kg/m^2 and WC <85 cm	1.10	1.42	1.14	1.01
	General + Abdominal obesity	BMI ≥25 kg/m^2 and WC ≥85 cm	1.11	1.69	1.21	1.13
Pre-menopause	Normal	BMI <25 kg/m^2 and WC <85 cm	1	1	1	1
	Abdominal obesity	BMI <25 kg/m^2 and WC ≥85 cm	0.95	1.31	1.10	1.34
	General obesity	BMI ≥25 kg/m^2 and WC <85 cm	0.97	1.36	1.16	0.96
	General + Abdominal obesity	BMI ≥25 kg/m^2 and WC ≥85 cm	0.94	1.88	1.28	1.14
Post-menopause	Normal	BMI <25 kg/m^2 and WC <85 cm	1	1	1	1
	Abdominal obesity	BMI <25 kg/m^2 and WC ≥85 cm	1.06	1.29	1.12	1.18
	General obesity	BMI ≥25 kg/m^2 and WC <85 cm	1.22	1.39	1.11	1.04
	General + Abdominal obesity	BMI ≥25 kg/m^2 and WC ≥85 cm	1.29	1.59	1.18	1.12

Increase p <0.0001 | Increase p <0.001 | Increase p <0.01 | Increase p <0.05

Decrease p <0.05

Fig. 4. Summary of relationships between combinations of general and abdominal obesity and risks of female-specific cancers. In the total women, age, smoking status, alcohol consumption, physical activity, diabetes, parity, menopausal status, and age at menarche were adjusted. In the pre-menopausal women, age, smoking status, alcohol consumption, physical activity, diabetes, parity, and age of menarche. In the post-menopausal women, age, smoking status, alcohol consumption, physical activity, diabetes, parity, age of menarche, and hormonal replacement therapy duration were adjusted.

In the post-menopausal group, the abdominal obesity only, general obesity only, and general and abdominal obesity groups showed significantly increased risks of endometrial cancer (aHRs [95% CIs], 1•29 [1•09–1•52], 1•39 [1•22–1•53], and 1•59 [1•46–1•74], respectively) (Supplementary Table 9).

3.4.3. Ovarian cancer

Compared to the reference group, the general obesity group showed significantly increased risk of ovarian cancer (aHR, 1•14; 95% CI, 1•07–1•22). The coexistence of general obesity and abdominal obesity was associated with an increased risk of ovarian cancer (aHR, 1•21; 95% CI, 1•14–1•29) (Fig. 5C and Supplementary Table 7).

In the pre-menopausal group, women with general obesity only and those with both general and abdominal obesity showed significantly increased risks of ovarian cancer (aHRs [95% CIs], 1•16 [1•05–1•28] and 1•28 [1•14–1•43], respectively) (Supplementary Table 8). In the post-menopausal group, women with general obe-

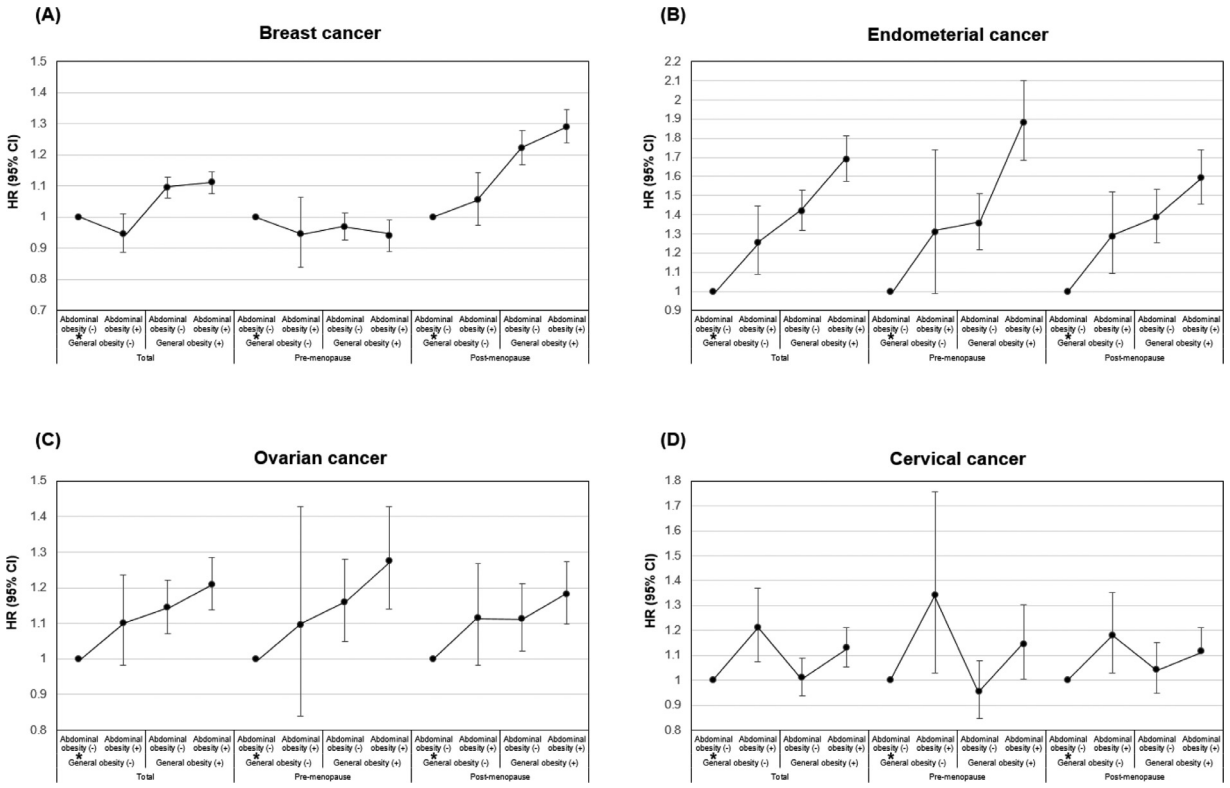

Fig. 5. Risk of female-specific cancers according to the combination of general and abdominal obesity among all women, pre-menopausal women, and post-menopausal women: (A) breast cancer, (B) endometrial cancer, (C) ovarian cancer, and (D) cervical cancer. In the total women, age, smoking status, alcohol consumption, physical activity, diabetes, parity, menopausal status, and age at menarche were adjusted. In the pre-menopausal women, age, smoking status, alcohol consumption, physical activity, diabetes, parity, and age of menarche. In the post-menopausal women, age, smoking status, alcohol consumption, physical activity, diabetes, parity, age of menarche, and hormonal replacement therapy duration were adjusted. *Reference.

sity only and those with both general and abdominal obesity were at high risks of developing ovarian cancer (aHRs [95% CIs], 1•11 [1•02–1•21] and 1•18 [1•10–1•27], respectively) (Supplementary Table 9).

3.4.4. Cervical cancer

Compared to the reference group, the abdominal obesity only group showed an increased risk of cervical cancer was observed (aHR, 1•21; 95% CI, 1•08–1•37). The coexistence of general obesity and abdominal obesity was associated with an increased risk of cervical cancer (aHR, 1•13; 95% CI, 1•05–1•21) (Fig. 5D and Supplementary Table 7).

In the pre-menopausal group, women with abdominal obesity only and those with both general and abdominal obesity were at high risks of developing cervical cancer (aHRs [95% CIs], 1•34 [1•03–1•76] and 1•14 [1•004–1.30], respectively) (Supplementary Table 8). In the post-menopausal group, women with abdominal obesity only and those with both general and abdominal obesity were at high risks of developing cervical cancer (aHRs [95% CIs], 1•18 [1•03–1•35] and 1•12 [1•03–1.21], respectively) (Supplementary Table 9).

4. Discussion

In this nationwide population-based cohort study including > 2•7 million Korean women, we comprehensively investigated the impact of obesity and menopausal status on the development of female-specific cancers (breast, endometrial, ovarian, and cervical cancers). In particular, obesity was evaluated using two parameters: BMI and WC, representing general obesity and abdominal obesity, respectively. Obesity had a different effect on cancer incidence depending on the specific malignancy type and menopausal status. To our knowledge, this is the largest cohort study to date encompassing all four of the investigated female-specific cancers.

The most common female-specific cancer developed during the observation was breast cancer, followed by ovarian cancer, endometrial cancer, and cervical cancer, in order of incidence rates. This order is quite different from that of national cancer statistics in Korea [13]. Such differences might originate from the definition of unique study population in this study and the fact that age-standardised incidence rates were not calculated.

In the current study, the risk of endometrial cancer significantly increased as the BMI classification increased from normal to class II obesity, regardless of the menopausal status (aHRs [95% CIs], 2•95 [2•53–3•45] and 2•11 [1•81–2•46] in pre-menopausal and post-menopausal women, respectively). In pre-menopausal women, underweight even had a protective effect against endometrial cancer development. An increase in the WC classification was also associated with a gradual increase in endometrial cancer risk, especially in post-menopausal women. This positive association between obesity and endometrial cancer risk was consistent with the findings of previous studies in both Western [6, 14–16] and Asian populations [17, 18].

The use of unopposed oestrogen is a well-known risk factor for endometrial cancer. Physiologically, rich adipocytes in the fat tissue of obese women produce excess oestrogen, mediated by increased aromatase levels and activity. Adipocytes are the predominant source of oestrogen in post-menopausal women. Furthermore, adiposity is negatively associated with sex hormone-binding globulin levels, leading to an increase in the bioactive oestrogen pool. In addition, the obesity-related inflammatory/abnormal environment seems to further stimulate the development of endometrial cancer [19].

Similar to endometrial cancer, an increased risk of ovarian cancer was observed as the BMI classification increased from normal to class II obesity, although the HRs for ovarian cancer were relatively lower than those for endometrial cancer. Our results were inconsistent with those of Japanese cohort studies that showed no association between BMI and the risk of ovarian cancer [20, 21]. In contrast, British [6] and American [7] cohort studies, and a meta-analysis of prospective studies [22] reported a positive association between obesity and ovarian cancer risk. In terms of WC, both in pre-menopausal and post-menopausal women, only ≥ 95•0 cm, compared with the reference, was associated with an increased risk of ovarian cancer, suggesting that the dose-response relationship between obesity and ovarian cancer risk is smaller than those between obesity and endometrial cancer risk. This might indicate that obesity accounts for a much smaller portion in the development of ovarian cancer than endometrial cancer. The coexistence of general and abdominal obesity also increased the ovarian cancer risk significantly, regardless of the menopausal status. In the literature, excessive oestrogen and chronic inflammation have been suggested as factors linking obesity and ovarian cancer development [7].

Incidence rates for breast cancer are lower in Asian populations than they are in Western populations. Moreover, Asian patients with breast cancer are much younger and leaner than their Western counterparts [23] The prevalence of triple-negative breast cancer, defined as absence of oestrogen receptor and progesterone receptor and no overexpression of human epidermal growth factor receptor 2, also varies among different ethnicities. Compared to African-American, Hispanic, and white women, Asians had the lowest risk of developing triple-negative breast cancer [24]. In Korean women, there is a rapid increase in the incidence rate and clinical characteristics of breast cancer are changing to the patterns of Western countries [25].

In post-menopausal women, an increased risk of breast cancer was observed as the BMI classification increased from underweight to class II obesity. A positive association between obesity and breast cancer risk in post-menopausal women was also reported in previous studies in both Western and Asian populations, including British [6], American [8], European [9], and Japanese cohorts [26, 27]. It is well known that oestrogen promotes the development and growth of breast cancer in post-menopausal women [28].

In contrast, in pre-menopausal women, class I and II obesity showed inverse associations with breast cancer risk in the current study. The coexistence of general and abdominal obesity also decreased the risk of breast cancer. However, inconsistent results were observed in previous studies. Similar to our study results, Western studies reported a negative relationship between BMI and breast cancer risk in pre-menopausal women [6, 29–31], whereas Japanese cohort studies failed to show statistical significance [26, 27]. Such inconsistency may be attributed to specific study designs across the studies and ethnic differences, mentioned above. Although we could not investigate further by histologic types or hormone receptor status, a recent multicentre study reported that the inverse association of BMI and pre-menopausal breast cancer risk was predominant in hormone receptor-positive breast cancer rather than hormone receptor-negative breast cancer [32]. According to an ancillary study of the Nurses' Health Study II, the higher BMI pre-menopausal women had, the lower oestradiol, progesterone, and sex hormone-binding globulin levels were observed [33]. Therefore, BMI-related differences in sex-hormone profile seem to be a possible explanation for the protective effect of obesity on breast cancer development in Korean and Western pre-menopausal women. The frequent anovulatory menstrual cycles in severe obese women, which result in low progesterone levels during the luteal phase, might also explain this relationship, partly [34].

Meanwhile, cervical cancer seems to be less affected by obesity or excessive oestrogen than other female-specific cancers in Korean women. In both pre-menopausal and post-menopausal women, compared with normal BMI, only class II obesity was associated with an increased cervical cancer risk. Similar to our study results, both British and American cohort studies also reported that obese women had a higher risk of cervical cancer than women with a normal BMI [6, 35].

Our study results demonstrated that the effect size of obesity female-specific cancers differed according to the specific malignancy type and menopausal status. Nevertheless, the relationship between obesity and the risk of female-specific cancers in Korean women showed similar trends to those in Western women. The rapid changes in environmental and lifestyle factors, such as a Westernised diet, low exercise levels, and an obese status, among Korean women might play a greater role than the difference in tumour biology resulting from different ethnicities. Moreover, considering that the prevalence of general obesity and abdominal obesity is rapidly increasing in Korean women [36], the trends are expected to become more similar to those observed in Western populations.

This study had several limitations. First, although we observed an increased risk of female-specific cancers in obese women, it was difficult to elucidate the mechanisms underlying this relationship. Therefore, additional cell-line or animal studies are warranted to understand the effect of excessive fat, especially abdominal adiposity, on tumourigenesis. Second, not all factors associated with cancer development were adjusted for in this study. For example, human papillomavirus vaccination, which known to substantially reduce the risk of cervical cancer, and predisposing genetic factors, such as germline *BRCA1/2* gene mutations for breast cancer and ovarian cancer and Lynch syndrome for endometrial cancer, were not considered in the current study. Such information and family history of cancers are not available in the NHIS database. Third, we did not investigate the relationship between obesity and specific histological types or prognosis of each female-specific cancer. Especially, it was unavailable to figure out histological types of each cancer from the NHIS database. Fourth, we only considered obesity at the time of the baseline examination. We are planning to conduct future studies investigating serial changes in BMI and WC in a large cohort. Such studies might more precisely clarify the relationship between obesity and female-specific cancers. Lastly, the study cohort was limited to Koreans, and further validations are necessary in different ethnic populations. Nevertheless, the advantage of this study is that it included more than 2•7 million women, the largest number to date, to our knowledge, with a very long follow-up period. Moreover, the current study employed methods that could minimise the risk of various biases such as selection bias and recall bias.

In conclusion, this large, population-based cohort study demonstrated that the impact of obesity on the development of female-specific cancers differs according to the specific malignancy type and menopausal status in Korean women. Considering the degree of risk, it seems necessary to establish an individualised, appropriate cancer screening and prevention strategy. Further studies are warranted.

Author Contributions

ISP and SIK contributed to the study design, data interpretation, and writing of the first draft of the manuscript. YH contributed to data interpretation and review of the manuscript. JY was involved in data analysis. HAJ, AS, JL, and WW were involved in data interpretation. KH contributed to the study design, analysis of the

data, and advice on the study conception. YSS supervised the entire project. All authors reviewed or revised the manuscript and approved the final manuscript for submission.

Declaration of Interests

All authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanwpc.2021.100146.

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