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ORIGINAL ARTICLE

Associations of body mass index and waist circumference with incidence of overall and of 27 site-specific cancers: a population-based retrospective cohort study

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Abstract

Background: Overweight and obesity are known risk factors for cancer. The aim of this study was to investigate associations of body mass index (BMI) and waist circumference (WC) with incidence of 27 site-specific cancers stratified by sex and menopausal status accounting for non-linearity.

Methods: We performed a population-based retrospective cohort study using the Korean National Health Insurance Service (KNHIS 2009-2020) database. We included 3,986,155 participants (aged ≥ 20 years), and the mean follow-up duration was 9.0 ± 1.6 years. The primary outcome was the incidence of cancer.

Results: There were positive associations between BMI or WC and incidences of cancers including overall cancer, digestive tract cancer (except for esophageal

Abbreviations: BMI, body mass index; CI, confidence interval; CNS, central nervous system; df, degrees of freedom; HL, Hodgkin's lymphoma; H. pylori, Helicobacter pylori; HR, hazard ratio; ICD-10, International Classification of Diseases, 10th revision; KCCR, Korea Central Cancer Registry; KNHIS, Korean National Health Insurance System; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; UK, United Kingdom; WC, waist circumference.

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cancer), hepato-bilio-pancreatic cancer, hematological cancer, sex-specific cancers, brain/central nervous system (postmenopausal women), thyroid, renal, and bladder cancers. We observed inverse associations for several cancers, including lung and laryngeal cancers.
Conclusions: Our findings of differential associations of BMI and WC with incidence of various cancers contribute to the understanding of the relationship between obesity and cancer risk in Asian populations. These results may provide evidence to support the implementation of active surveillance and targeted management strategies for obesity.

KEYWORDS
Obesity, Abdominal obesity, Adiposity marker, Body mass index, Waist circumference, Cancer

1 | BACKGROUND

Overweight and obesity are known risk factors for several cancers [1–9]. The burden of obesity-related cancers has been increasing as the global prevalence of obesity has more than doubled since 1990 [10]. In 2022, approximately 2.5 billion (43%) and 890 million (16%) adults were overweight and obesity globally [10]. Investigating associations between obesity and site-specific cancer risk is important to prevent and mitigate the obesity-related cancer burden on public health.

Increased cancer incidences associated with higher adiposity markers including body mass index (BMI) and waist circumference (WC) were reported for overall cancers [1–9] and specific cancers, including esophageal (adenocarcinoma) [11, 12], stomach (cardia) [11, 12], colorectal [12–14], head and neck (head/neck) [1, 15, 16], liver [12, 17, 18], biliary tract [17, 18], gallbladder [19], pancreatic [12, 20], leukemia [5, 21], lymphoma [5, 21], multiple myeloma (MM) [5, 21], prostate (advanced) [22, 23], breast (postmenopausal women) [24–26], cervical [25, 27], uterine [25, 27], ovarian [25, 27], brain/central nervous system (CNS) [28, 29], malignant melanoma (men) [3, 5, 8], thyroid [2, 8, 30], renal [31] and bladder cancer [5, 6, 32]. However, there are several limitations in previous studies. First, many prior studies focused on specific cancers and did not provide comprehensive overviews of the obesity-cancer relationship. As different cancers have different associations with obesity, showing the various relationships by cancer type in a specific population is important. Second, prior studies mostly estimated obesity-related cancer incidence with adiposity markers in categorical variables (e.g., World Health Organization BMI classification) [33] or reported associations between obesity and cancer risk per 5 kg/m^2 of BMI, per 5-10 cm increments of WC, and per 1-standard deviation of adiposity markers [2, 4, 6-9]. Only some studies provided spline curve and tested for potential non-linear associations between adiposity markers and cancer incidence [2, 6, 7, 9].

Third, comprehensive considerations of associations between sex difference and menopausal status and various site-specific cancers were not conducted in many studies [2, 6-9] despite differences in body fat accumulation and distribution between men and women [34], and pre-and post-menopausal women [35]. Stratification by menopausal status was not conducted in previous studies, except for women-specific cancers including breast, cervical, uterine, and ovarian cancer [2, 5-9].

Finally, relatively few studies on obesity-cancer relationships were published in Asian countries. Asians tend to have a higher percentage of body fat and higher accumulation of visceral adipose tissue compared to Caucasians [36, 37], which can influence cancer incidence. Indeed, studies from Korea [5] or China [9] showed some different patterns of association between adiposity markers and several cancer types (e.g. esophageal cancer or stomach cancer) from those identified from Western countries. While several Western studies showed spline curves for site-specific cancers and tested for non-linear associations [2, 6, 7], to our knowledge, only one study from an Asian country (China) showed such results [9], and no such study has been conducted in Korea.

In this regard, this present study aimed to investigate associations of BMI and WC with incidences from overall cancer and 27 site-specific cancers among the Korean population accounting for potential non-linearity after stratification by sex and menopausal status.

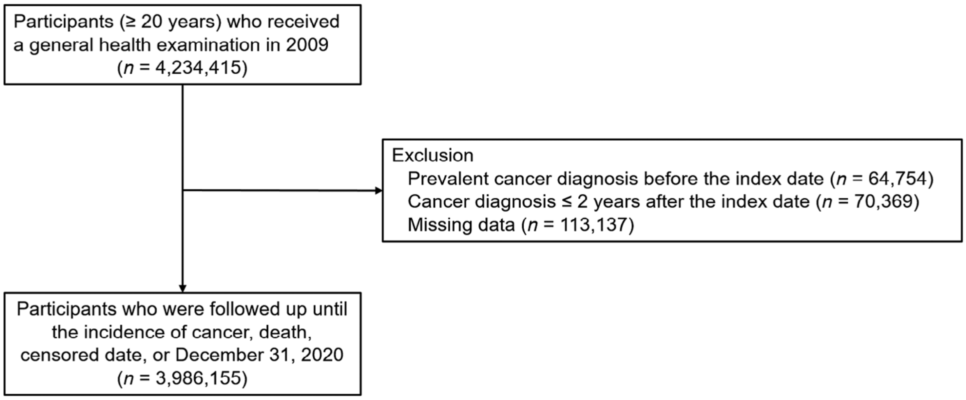

FIGURE 1 Flow chart of study enrollment

2 | MATERIALS AND METHODS

2.1 | Data source

This study was conducted using the Korean National Health Insurance System (KNHIS) database. The KNHIS is a single insurer that provides comprehensive medical coverage to nearly the whole Korean population because approximately 97% of the population are mandatory subscribers to the KNHIS and the remaining 3% of the population are covered by the Medical Aid program. Furthermore, the KNHIS manages all administrative processes and reimbursements for medical providers and pharmacies based on claims data.

Employees and self-employees who pay insurance premiums (regardless of age) and all individuals aged ≥ 40 years can participate in biennial general health examinations [38]. Therefore, the KNHIS database contains information regarding qualification for insurance, diagnosis codes by International Classification of Disease 10th revision (ICD-10), medical utilization, and results of general health examinations.

2.2 | Study population

We obtained data of 40% participants randomly sampled from individuals (aged ≥ 20 years) who received a general health examination in 2009, and 4,234,415 participants were initially included. We excluded participants 1) with a prevalent cancer diagnosis in the index year (n = 64,754) and 2) who were diagnosed with cancer within the first two years of follow-up (n = 70,369) to minimize the bias from reverse causality [2, 5-7, 9]. We further excluded participants with missing data (n = 113,137). Finally, 3,986,155 eligible individuals were included (Figure 1). This study received approval by the Institutional Review Board of Soongsil University (IRB File No. SSU-202007-HR-236-02). The requirement for informed consent was waived because we used de-identified data under confidentiality guidelines.

2.3 | Assessment of adiposity

We used BMI and WC as indicators of general and abdominal obesity, respectively. Anthropometric data including body weight and height were measured directly using a stadiometer and a scale, respectively. BMI was calculated by dividing body weight in kilograms into the square of height in meters (kg/m^2). WC in cm was measured with a measuring tape at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. We defined general obesity (BMI ≥ 25 kg/m^2) [39] and abdominal obesity (WC ≥ 90 cm for male, WC ≥ 85 cm for female) [40, 41] based on the criteria for the Asia-Pacific and the Korean populations.

2.4 | Study outcomes and follow-up

The primary outcome of this study was the incidence of cancer, as represented by ICD-10 cancer diagnosis codes in the KNHIS database: oral cavity (C00-06), esophagus (C15), stomach (C16), colon (C18-19), rectal (C20), liver (C22.0), biliary tract (C22.1, C24), gallbladder (C23), pancreatic (C25), laryngeal (C32), lung (C33-34), malignant melanoma (C43), breast (C50), cervical (C53), uterine (C54), ovarian (C56), prostate (C61), testicular (C62), renal (C64), bladder (C67), brain/CNS (C71-72), thyroid (C73), Hodgkin's lymphoma (HL) (C81), non-Hodgkin's lymphoma (NHL) (C82-85), MM (C90), lymphoid leukemia (C91), and myeloid leukemia (C92).

In Korea, patients who are diagnosed with cancer are registered with the Korea Central Cancer Registry (KCCR) and rare and intractable disease registration program to receive reduced medical expenses for at least five years. The sensitivity for cancer patient verification based on the KNHIS database is greater than 90% (lowest in colorectal cancer, 91.5%; highest in breast cancer, 98.1%) validated with the KCCR database, which is a nationwide, hospital-based cancer registry [42]. Therefore, the KNHIS database has been used extensively as a reliable pool for epidemiological studies conducted in Korea [5, 26, 43]. The study participants were followed from two years after the index date to the incidence of cancer, death, censored date, or December 31, 2020, whichever came first.

2.5 | Covariates

Income levels were divided into four groups, and we assigned the lowest 25% income group as the first quartile (Q1) according to the monthly insurance premiums. Comorbidities of hypertension, diabetes mellitus, and dyslipidemia were identified based on ICD-10 codes from claims data before the health examination date. Hypertension was defined as at least one claim for I10–I11 or a prescription for antihypertensive medications. Diabetes mellitus was defined as at least one claim for E10–E14 or a prescription for antidiabetic medications. Dyslipidemia was defined as at least one claim for E78 or a prescription for lipid-lowering medications. Smoking status was divided into three groups: never smokers, ex-smokers, and current smokers. Alcohol intake was divided into three groups: non-drinkers, mild drinkers (< 30 g/day), and heavy drinkers (≥ 30 g/day). Regular exercise was defined as moderate intensity activity for more than 30 minutes per session and ≥ five days per week or vigorous activity for more than 20 minutes per session and ≥ three days per week.

2.6 | Statistical analyses

Descriptive statistics were conducted using Student's t-test for continuous variables and the chi-square test for categorical variables according to status of general obesity (BMI ≥ 25 kg/m^2) and abdominal obesity (WC ≥ 90 cm for male, WC ≥ 85 cm for female) [40, 41]. We stratified participants by sex and menopausal status to investigate cancer risks according to BMI and WC. As we lacked exact data on menopausal status, we defined women aged ≥ 50 years at the index date as a proxy indicator of the postmenopausal status [5, 9, 44]. Penalized spline curves were plotted to investigate possible non-linear associations [45–47] between adiposity markers (BMI as a continuous variable in kg/m^2 and WC as a continuous variable in cm) and cancer incidence after adjusting for confounders of age, diabetes mellitus [48], smoking statue [49], alcohol intake [49, 50], and regular exercise [51]. Non-linearity was tested by likelihood ratio tests [52] and all *P*-values were corrected for multiple testing using Holm's method [53, 54]. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Penalized spline curves were plotted using the 'pspline' function in R software (degrees of freedom [df] = 4; number of splines in the basis = 2.5 * df; degree of splines = 3) [55, 56].

3 | RESULTS

3.1 | Baseline characteristics

In this study, a total of 3,986,155 participants were included, and the number of incident cancer cases was 242,243 (6.1%) over a mean follow-up of 9.0 ± 1.6 years (median, 9.3 years; range, 9.1−9.6 years). The mean age of overall participants was 46.7 ± 14.0 years (median, 46.0 years; range, 36.0−56.0 years), and 55.4% were male. The proportions of chronic diseases (hypertension, diabetes mellitus, and dyslipidemia), current smoking, and heavy alcohol intake were higher among participants with general obesity or abdominal obesity than those without such conditions. Participants with general obesity performed regular exercise more frequently (19.5%) than those without obesity (Table 1). Baseline characteristics of the subgroups of men, premenopausal women, and postmenopausal women are presented in Supplementary Tables S1-S3. The numbers of newly diagnosed overall cancer cases were 242,243 in the overall population, 135,299 in men, 40,662 in premenopausal women, and 66,282 in postmenopausal women, respectively (Table 2).

3.2 | Associations of BMI and WC with incidence of cancers

We depicted BMI- and WC-cancer associations by plotting penalized spline curves. Detailed information on incidences of cancers according to presence of general and abdominal obesity is presented in the Supplementary Tables S4-S7. *P*-values corrected for multiple testing are presented in Supplementary Table S8.

3.2.1 | Overall cancers

For men, the association of overall cancer incidence with BMI was non-linear, but the association with WC was linear. All such associations were linear for both pre-and post-menopausal women (Figure 2).

TABLE 1 Baseline characteristics of the study population

Characteristic	Overall population (n = 3,986,155)	General obesity: Present[a] (n = 1,305,213)	General obesity: Absent[b] (n = 2,680,942)	P value[c]	Abdominal obesity: Present[d] (n = 777,835)	Abdominal obesity: Absent[e] (n = 3,208,320)	P value[f]
Age (years)	46.7 ± 14.0	48.5 ± 13.3	45.8 ± 14.2	<0.001	51.7 ± 14.0	45.5 ± 13.7	<0.001
Sex (%)				<0.001			<0.001
Men	2,207,727 (55.4)	823,332 (63.1)	1,384,395 (51.6)		466,237 (59.9)	1,741,490 (54.3)	
Women	1,178,428 (44.6)	481,881 (36.9)	764,577 (28.5)		311,598 (40.1)	1,466,830 (45.7)	
Premenopausal (age <50)	929,240 (23.3)	164,663 (12.6)	764,577 (28.5)		78,463 (10.1)	850,777 (26.5)	
Postmenopausal (age ≥50)	849,188 (21.3)	317,218 (24.3)	531,970 (19.9)		233,135 (30.0)	616,053 (19.2)	
Income				<0.001			<0.001
Q1, lowest 25%	851,999 (21.4)	266,103 (20.4)	585,896 (21.9)		159,239 (20.5)	692,760 (21.6)	
Q2	895,925 (22.5)	268,119 (20.5)	627,806 (23.4)		155,140 (19.9)	740,785 (23.1)	
Q3	1,068,826 (26.8)	358,178 (27.5)	710,648 (26.5)		209,746 (27.0)	859,080 (26.8)	
Q4, highest 25%	1,169,405 (29.3)	412,813 (31.6)	756,592 (28.2)		253,710 (32.6)	915,695 (28.5)	
Body mass index (kg/m^2)	23.7 ± 3.2	27.3 ± 2.2	22.0 ± 2.0	<0.001	27.5 ± 2.8	22.8 ± 2.6	<0.001
Waist circumference (cm)	80.2 ± 9.1	88.2 ± 7.0	76.4 ± 7.3	<0.001	92.7 ± 5.2	77.2 ± 7.0	<0.001
Comorbidities							
Hypertension	1,057,421 (26.5)	512,006 (39.2)	545,415 (20.3)	<0.001	366,827 (47.2)	690,594 (21.5)	<0.001
Diabetes mellitus	337,711 (8.5)	164,472 (12.6)	173,239 (6.5)	<0.001	128,457 (16.5)	209,254 (6.5)	<0.001
Dyslipidemia	716,570 (18.0)	337,592 (25.9)	378,978 (14.1)	<0.001	230,427 (29.6)	486,143 (15.2)	<0.001
Smoking status				<0.001			<0.001
Never smoker	2,352,091 (59.0)	705,678 (54.1)	1,646,413 (61.4)		434,090 (55.8)	1,918,001 (59.8)	
Ex-smoker	568,861 (14.3)	225,940 (17.3)	342,921 (12.8)		132,879 (17.1)	435,982 (13.6)	
Current smoker	1,065,203 (26.7)	373,595 (28.6)	691,608 (25.8)		210,866 (27.1)	854,337 (26.6)	
Alcohol intake				<0.001			<0.001
Non-drinker	2,036,066 (51.1)	638,272 (48.9)	1,397,794 (52.1)		405,934 (52.2)	1,630,132 (50.8)	
Mild-drinker (< 30 g/d)	1,630,423 (40.9)	534,422 (41.0)	1,096,001 (40.9)		290,767 (37.4)	1,339,656 (41.8)	
Heavy-drinker (≥ 30 g/d)	319,666 (8.0)	132,519 (10.1)	187,147 (7.0)		81,134 (10.4)	238,532 (7.4)	
Regular exercise (yes)	714,490 (17.9)	253,806 (19.5)	460,684 (17.2)	<0.001	139,262 (17.9)	575,228 (17.9)	0.599
Cancer incidence	242,243 (6.1)	86,338 (6.6)	155,905 (5.8)	<0.001	61,833 (8.0)	180,410 (5.6)	<0.001
Follow-up duration, years	9.0 ± 1.6	9.0 ± 1.6	9.0 ± 1.6	0.348	8.8 ± 1.8	9.0 ± 1.5	<0.001

Note: Data are presented as number (%) or the mean ± standard deviation.
Abbreviations: n, number; Q, quartile.
[a]Presence of general obesity was defined as body mass index ≥ 25 kg/m^2.
[b]Absence of general obesity was defined as body mass index < 25 kg/m^2.
[c]Comparison between those with general obesity and those without general obesity using Student's t-test or the chi-square test.
[d]Presence of abdominal obesity was defined as waist circumference ≥ 90 cm for males and waist circumference ≥ 85 cm for females.
[e]Absence of abdominal obesity was defined as waist circumference < 90 cm for males and waist circumference < 85 cm for females.
[f]Comparison between those with abdominal obesity and those without abdominal obesity using Student's t-test or the chi-square test.

3.2.2 | Digestive tract cancers

Both BMI and WC were inversely associated with esophageal cancer in men, but there was no association in women. For gastric and colon cancers, there were positive associations with BMI and WC among men and postmenopausal women but not among premenopausal women. Both adiposity markers were positively associated with rectal cancer incidence among postmenopausal women, whereas only WC had similar associations among men and premenopausal women (Figure 2).

TABLE 2 Cancer incidences of the study population

	Overall population		Men		Premenopausal women[a]		Postmenopausal women[b]	
Cancer site	Event	Incidence (per 1,000 person-years)	Event	Incidence (per 1,000 person-years)	Event	Incidence (per 1,000 person-years)	Event	Incidence (per 1,000 person-years)
Overall	242,243	6.78	135,299	6.85	40,662	4.80	66,282	8.81
Esophagus	3,059	0.08	2,776	0.14	46	0.01	237	0.03
Stomach	37,012	1.01	26,242	1.31	2,444	0.28	8,326	1.07
Colon	38,919	1.07	22,688	1.13	4,331	0.50	11,900	1.54
Rectal	12,773	0.35	8,564	0.42	999	0.12	3,210	0.41
Oral cavity	1,593	0.04	1,050	0.05	142	0.02	401	0.05
Lung	33,214	0.91	23,379	1.16	1,852	0.21	7,983	1.03
Larynx	1,594	0.04	1,516	0.08	14	0.00	64	0.01
Liver	16,658	0.46	12,718	0.63	699	0.08	3,241	0.42
Bile duct	9,408	0.26	5,899	0.29	357	0.04	3,152	0.41
Gallbladder	3,544	0.10	1,773	0.09	191	0.02	1,580	0.20
Pancreas	20,323	0.56	12,385	0.61	1,475	0.17	6,463	0.83
Myeloid leukemia	2,646	0.07	1,617	0.08	320	0.04	709	0.09
Lymphoid leukemia	849	0.02	513	0.03	94	0.01	242	0.03
Hodgkin's lymphoma	356	0.01	232	0.01	48	0.01	76	0.01
Non-Hodgkin's lymphoma	5,700	0.16	3,441	0.17	579	0.07	1,680	0.22
Multiple myeloma	2,625	0.07	1,576	0.08	163	0.02	886	0.11
Prostate	23,350	1.16	23,350	1.16	N/A	N/A	N/A	N/A
Testis	477	0.02	477	0.02	N/A	N/A	N/A	N/A
Breast	22,110	0.61	215	0.01	12,156	1.41	9,739	1.26
Cervix	3,943	0.24	N/A	N/A	1,909	0.22	2,034	0.26
Uterus	3,122	0.19	N/A	N/A	1,608	0.19	1,514	0.19
Ovary	5,319	0.32	N/A	N/A	2,463	0.29	2,856	0.37
Brain/CNS	3,956	0.11	2,213	0.11	447	0.05	1,296	0.17
Malignant melanoma	1,013	0.03	506	0.03	116	0.01	391	0.05
Thyroid	36,112	0.99	9,861	0.49	15,243	1.78	11,008	1.43
Kidney	6,450	0.18	4,678	0.23	462	0.05	1,310	0.17
Bladder	8,099	0.22	6,766	0.34	178	0.02	1,155	0.15

Note: The study population covers 3,986,155 subjects, comprising of 2,207,727 men and 1,778,428 women (929,240 premenopausal and 849,188 postmenopausal).
Abbreviation: N/A, not applicable.
[a]Age <50 years.
[b]Age ≥ 50 years.

3.2.3 | Head/neck and thoracic cancers

Both BMI and WC had no significant association with oral cavity cancer. For lung cancer, the only non-linear, inverse association with BMI was observed among men. For laryngeal cancer, the only linear, inverse association with BMI was also observed among men (Figure 3).

3.2.4 | Hepato-bilio-pancreatic cancers

For liver and biliary tract cancers, positive associations with adiposity markers were observed in all sex groups, and non-linearity was found only in men. For gallbladder cancer, there were positive associations with BMI in premenopausal women and with WC in postmenopausal

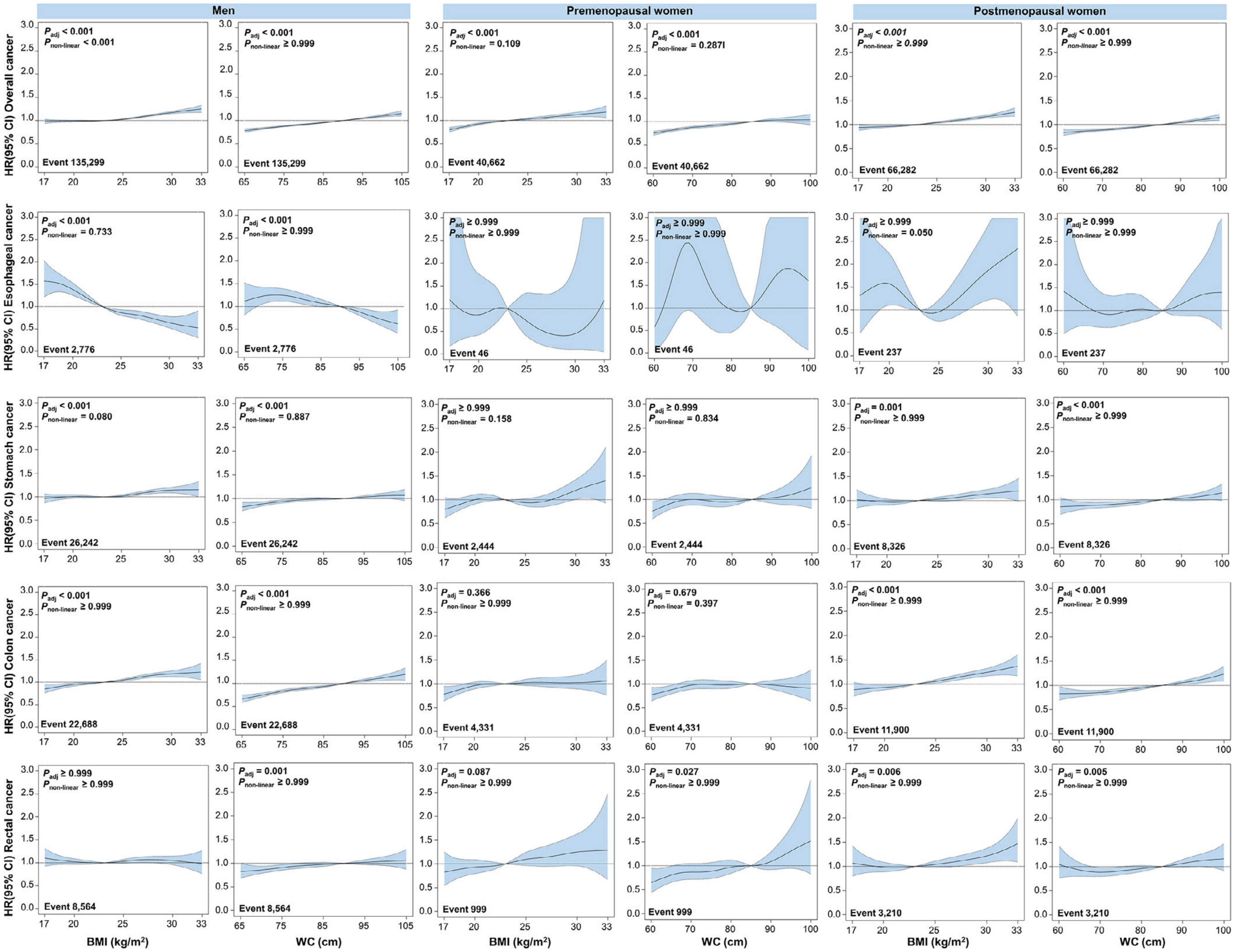

FIGURE 2 Associations of adiposity with incidence of overall and digestive tract cancers. Penalized spline curves are presented to illustrate associations between adiposity markers and cancer incidences adjusted for age, diagnosis of diabetes mellitus, smoking status, alcohol intake, and regular exercise. The 95% confidence intervals are presented as shaded areas. All *P*-values were corrected for multiple testing using Holm's method.

Abbreviations: BMI, body mass index; WC, waist circumference; HR, hazard ratio; CI, confidence interval.

women. There were positive associations of BMI and WC with pancreatic cancer incidence among men and postmenopausal women; among premenopausal women, only BMI was positively associated with pancreatic cancer incidence (Figure 4).

3.2.5 | Hematological cancers

For hematological cancers, associations with adiposity markers varied by subtypes of leukemia and lymphoma. For myeloid leukemia, positive associations with adiposity markers were observed among men (for both BMI and WC) and postmenopausal women (for WC). For NHL, there were positive associations with BMI and WC among men (Figure 5).

3.2.6 | Sex-specific cancers

For prostate cancer, there were non-linear associations with BMI and WC. For breast cancer, we observed linear associations with BMI and WC among only postmenopausal women. WC was positively associated with cervical cancer among postmenopausal women. For uterine and ovarian cancers, there were linear associations with BMI and WC among both premenopausal and postmenopausal women (Figure 6).

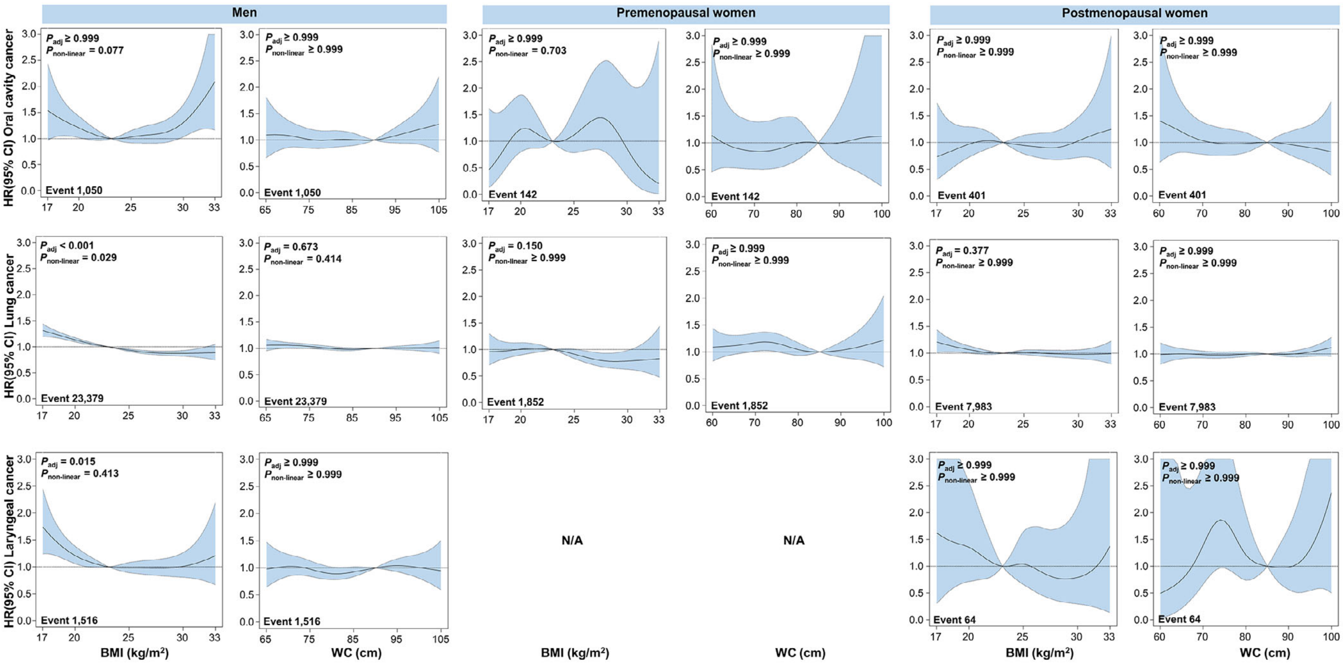

FIGURE 3 Associations of adiposity with incidence of head/neck and thoracic cancers. Penalized spline curves are presented to illustrate associations between adiposity markers and cancer incidences adjusted for age, diagnosis of diabetes mellitus, smoking status, alcohol intake, and regular exercise. The 95% confidence intervals are presented as shaded areas. All *P*-values were corrected for multiple testing using Holm's method. *P*-values could not be calculated for laryngeal cancer among premenopausal women due to the low incidence. Abbreviations: BMI, body mass index; WC, waist circumference; HR, hazard ratio; CI, confidence interval; N.A., not applicable.

3.2.7 | Other cancers

We observed positive linear associations between adiposity markers and brain/CNS cancer incidence among postmenopausal women only. No significant association was found between adiposity markers and malignant melanoma. For thyroid cancer, non-linear associations with adiposity markers were observed among men, premenopausal women (for both BMI and WC), and postmenopausal women (for BMI). There was a positive linear association between WC and thyroid cancer among postmenopausal women. Positive linear associations with adiposity markers were found for the incidence of renal cancer across all participants. Positive linear associations between adiposity markers and bladder cancer were observed among men and postmenopausal women (Figure 7).

4 | DISCUSSION

This population-based retrospective cohort study investigated associations of BMI and WC with various site-specific cancer incidences accounting for potential non-linearity stratified by sex and menopausal status. Our findings generally corroborate the results of previous studies that demonstrated positive associations between adiposity markers and incidences of cancers including overall cancer [1–9], digestive tract cancer (except for esophageal cancer) [6–8], hepato-bilio-pancreatic cancer [6–8], hematological cancer [5, 7, 8], sex-specific cancers [2, 6-9], brain/CNS (postmenopausal women) [7], thyroid [2, 7, 8], renal [6–8], and bladder cancers [5–6], and inverse association for several cancers, including lung and laryngeal cancers [2, 9].

In this study, we observed some significant non-linear associations for several cancers, such as liver, biliary tract, and prostate cancer in men and thyroid cancer in both sexes. Many other associations were not significant for the non-linearity. Previous study findings vary regarding linearity of associations: for example, studies from the UK Clinical Practice Research Datalink [2], Spanish Information System for Research in Primary Care [7], and China Kadoori Biobank [9] reported non-linear associations for many cancers, including esophageal [2, 7], stomach [2, 7, 9], colon [2], head/neck [2, 7], lung [2, 9],

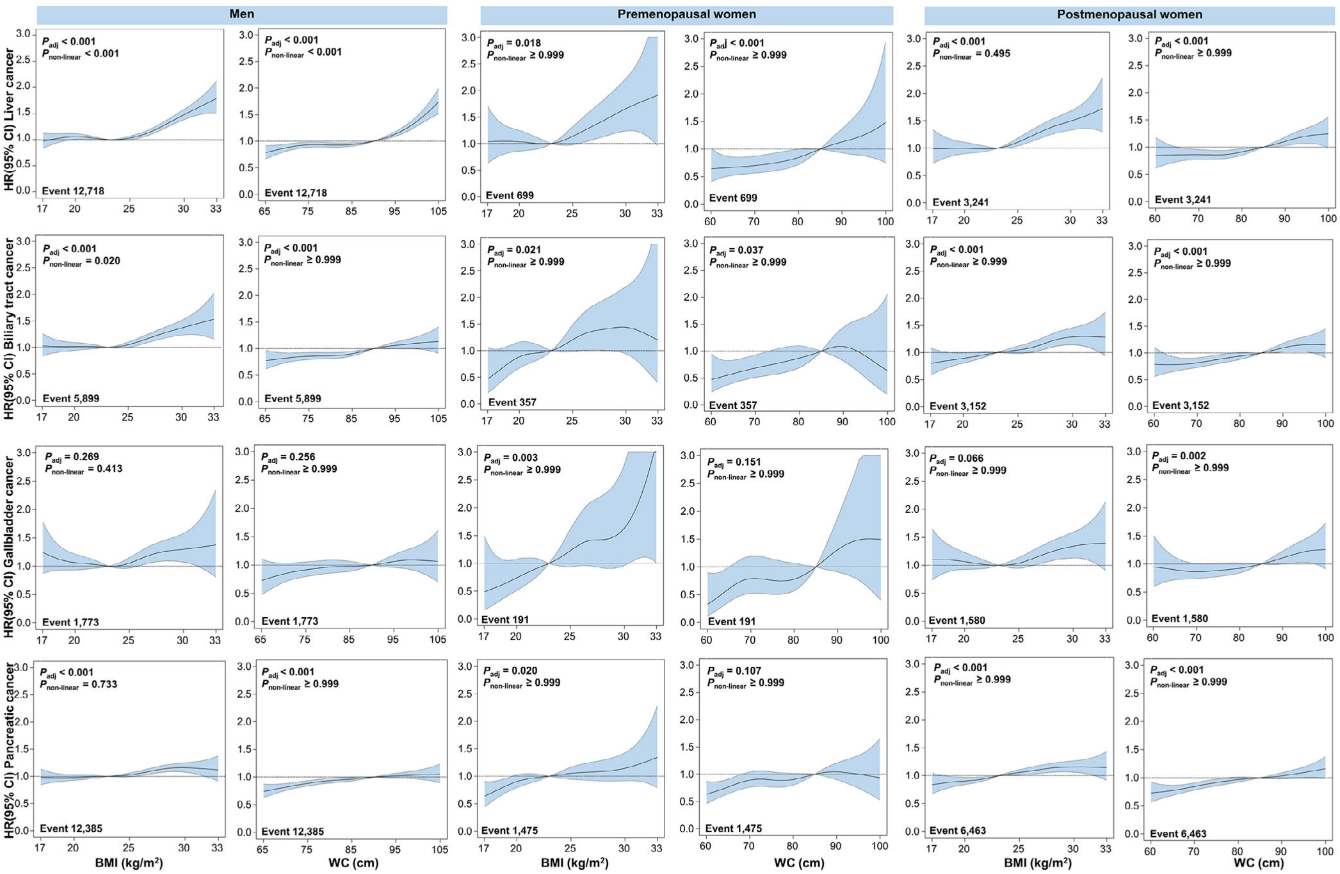

FIGURE 4 Associations of adiposity with incidence of hepato-bilio-pancreatic cancers. Penalized spline curves are presented to illustrate associations between adiposity markers and cancer incidences adjusted for age, diagnosis of diabetes mellitus, smoking status, alcohol intake, and regular exercise. The 95% confidence intervals are presented as shaded areas. All *P*-values were corrected for multiple testing using Holm's method.
Abbreviations: BMI, body mass index; WC, waist circumference; HR, hazard ratio; CI, confidence interval.

laryngeal [7], liver [2, 7], HL [7], prostate [2, 7, 9], breast [2, 7, 9], cervix [9], uterine [2, 7], malignant melanoma [2], thyroid [2], and bladder cancer [2]. However, according to the UK Biobank study, in which *P*-values were corrected for multiple testing, only prostate, breast, and uterine cancer showed significant non-linear associations [6]. Therefore, methodological difference should be considered to determine non-linearity and to compare the results from different studies.

Previous studies examining potential non-linear associations usually presented spline curves without stratification by sex and/or menopausal status (except for some specific cancers, such as pre- and post-menopausal breast cancer) [2, 6, 7, 9]. Given that men/women and pre-and postmenopausal women have different levels and distributions of BMI and WC, and that the associations often differ by sex or menopausal status, we evaluated the associations by subgroup. Indeed, different patterns by subgroups were noted for several cancers, such as esophageal, stomach, colon, lung, laryngeal, gallbladder, myeloid leukemia, NHL, breast cancer, brain/CNS, and bladder cancer.

Findings for specific cancers are noteworthy compared to previous studies. We observed an inverse association between adiposity markers and esophageal cancer incidence among men. While relationships between obesity and esophageal adenocarcinoma are well known [6, 11], most cases of esophageal cancer in South Korea are squamous cell carcinoma (91.3%) [57, 58], of which major risk factors are smoking and alcohol intake [3]. Similarly, a cohort study from China reported an inverse association between adiposity markers and esophageal cancer incidence [9]. Absence of a significant association with obesity in the female population could reflect low smoking and alcohol consumption rate in Korean women [59].

There was a positive association of stomach cancer with BMI and WC among men and postmenopausal women,

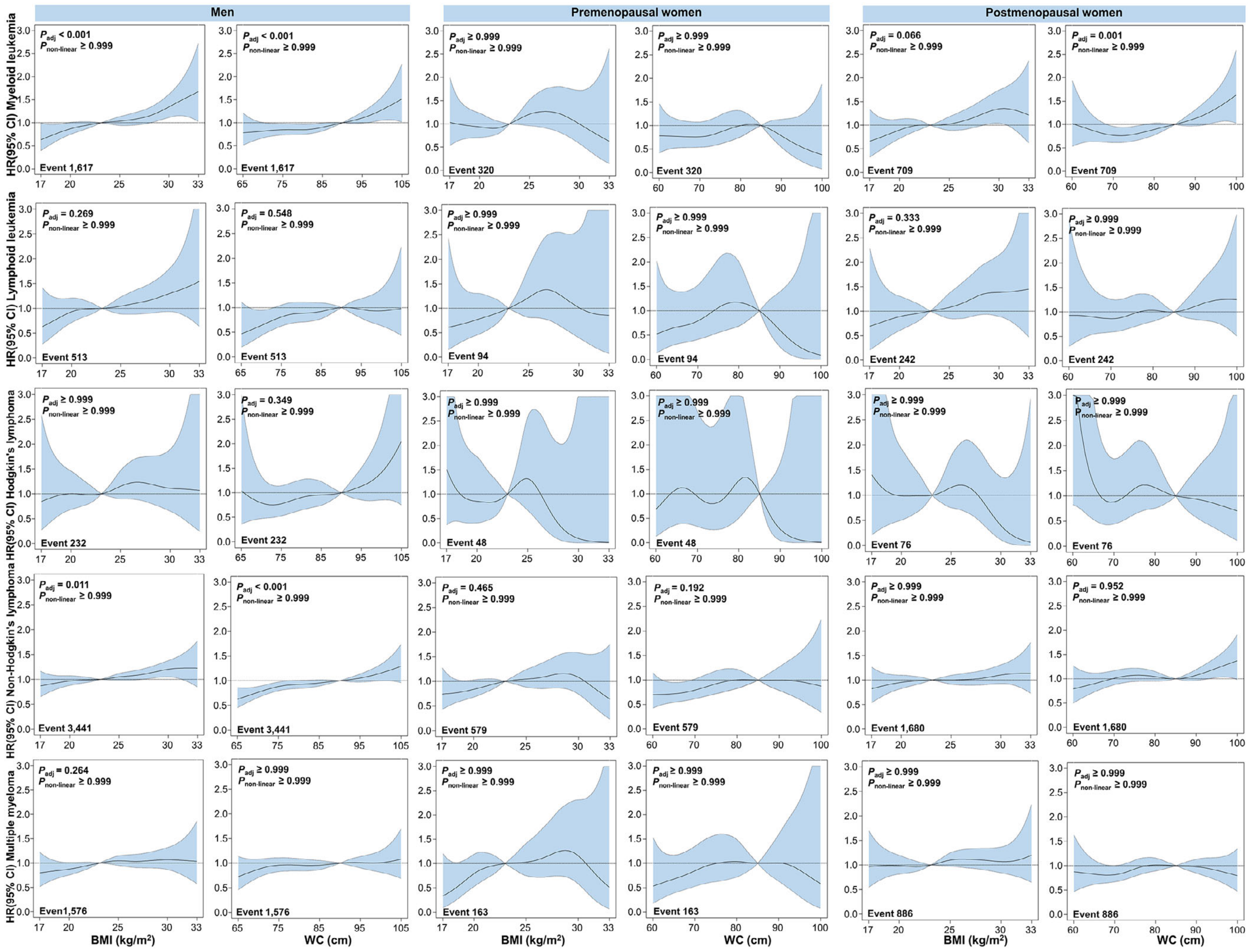

FIGURE 5 Associations of adiposity with incidence of hematological cancers. Penalized spline curves are presented to illustrate associations between adiposity markers and cancer incidences adjusted for age, diagnosis of diabetes mellitus, smoking status, alcohol intake, and regular exercise. The 95% confidence intervals are presented as shaded areas. All *P*-values were corrected for multiple testing using Holm's method.
Abbreviations: BMI, body mass index; WC, waist circumference; HR, hazard ratio; CI, confidence interval.

concordant with previous studies in Korea [5] and Western countries [2, 6, 7]. Approximately ≥ 90% of Korean stomach cancer survivors were diagnosed with a non-cardia stomach cancer [60], of which major causes are infection with *Helicobacter pylori* (*H. pylori*) [61] as well as smoking and alcohol consumption [3]. However, our finding is contrary to that of a Chinese study, where most stomach cancer is non-cardia and an inverse association between obesity and stomach cancer was shown [9]. Similarly, a positive association was evident for liver cancer in our study, consistent with previous studies in Korea [5] and Western countries [2, 6, 7]. The major cause of liver cancer in Korea is hepatitis B infection [62], which is similar to China [63] but contrary to western countries [64]. However, a Chinese study showed an inverse association between obesity and liver cancer [9]. The discrepant results between Korea and China, which share some risk factors, warrant further investigation. One possible explanation is the availability of national stomach and liver cancer screening programs [65, 66], which would increase the likelihood of early detection of stomach and liver cancer, before weight loss occurs.

This study was conducted using a large-scale nationwide cohort database representing almost the entire Korean population to investigate associations between obesity and incidences of various cancers. Our findings sug-

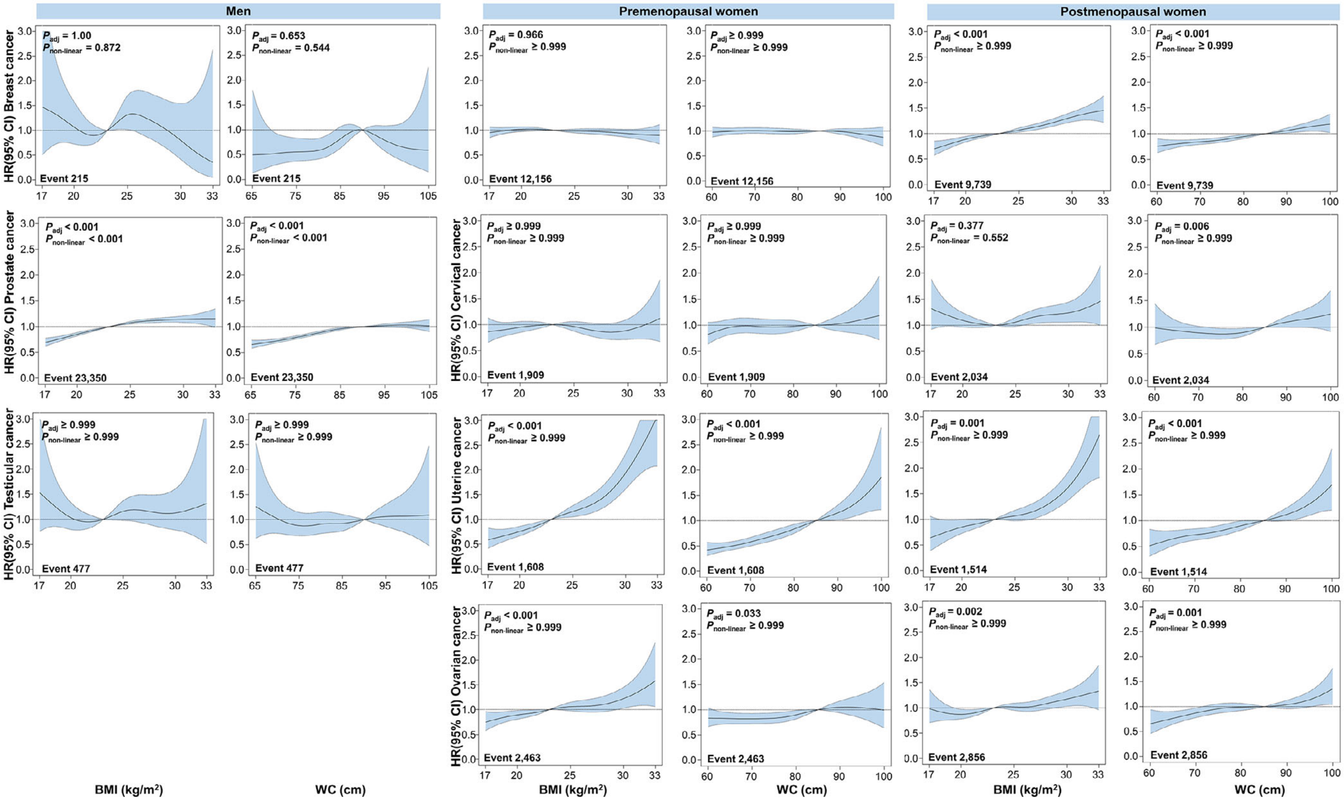

FIGURE 6 Associations of adiposity with incidence of sex-specific cancers. Penalized spline curves are presented to illustrate associations between adiposity markers and cancer incidences adjusted for age, diagnosis of diabetes mellitus, smoking status, alcohol intake, and regular exercise. The 95% confidence intervals are presented as shaded areas. All *P*-values were corrected for multiple testing using Holm's method.
Abbreviations: BMI, body mass index; WC, waist circumference; HR, hazard ratio; CI, confidence interval.

gest methodological consideration of non-linearity and stratification by sex and menopausal status in reporting obesity-associated cancer risks. Despite these strengths, there are several limitations to address. First, we did not consider longitudinal changes of BMI and WC during the follow-up period. Previous studies on weight change and cancer risk showed inconsistent results depending on cancer sites and cohorts [67–69]. Further studies are warranted to investigate the association between longitudinal changes in various adiposity markers and the risk of cancer. Second, although BMI and WC are widely used adiposity markers, they have limitations in assessing body fat distribution. In this regard, new adiposity markers are being developed, including the waist-to-height ratio [70], weight-adjusted waist index [71], body roundness index [72], a body shape index [73], and the Conicity Index [74]. Further investigation is warranted on the performance of such composite indices in predicting cancer incidence. Third, we could not collect detailed information, including locations and histological classifications of cancers, from the KNHIS database. Fourth, given lack of exact information on menopausal status, we applied an operational definition based on the age of women at the index date. Therefore, we could not ignore possible misclassifications of menopausal status. Fifth, there might be residual confounding effects that we could not consider, such as use of hormone replacement therapy and infectious causes of cancer (*H. pylori*, hepatitis virus, and human papillomavirus). Last, we included individuals who participated in a general health examination in 2009, which may imply a selection bias toward a healthier population.

5 | CONCLUSION

We investigated differential associations of BMI and WC with incidences of overall cancer and of 27 site-specific cancers stratified by sex and menopausal status. Our findings contribute to the understanding of the relationship between obesity and cancer risk in Asian populations. These results may provide evidence to support the implementation of active surveillance and targeted management strategies for obesity.

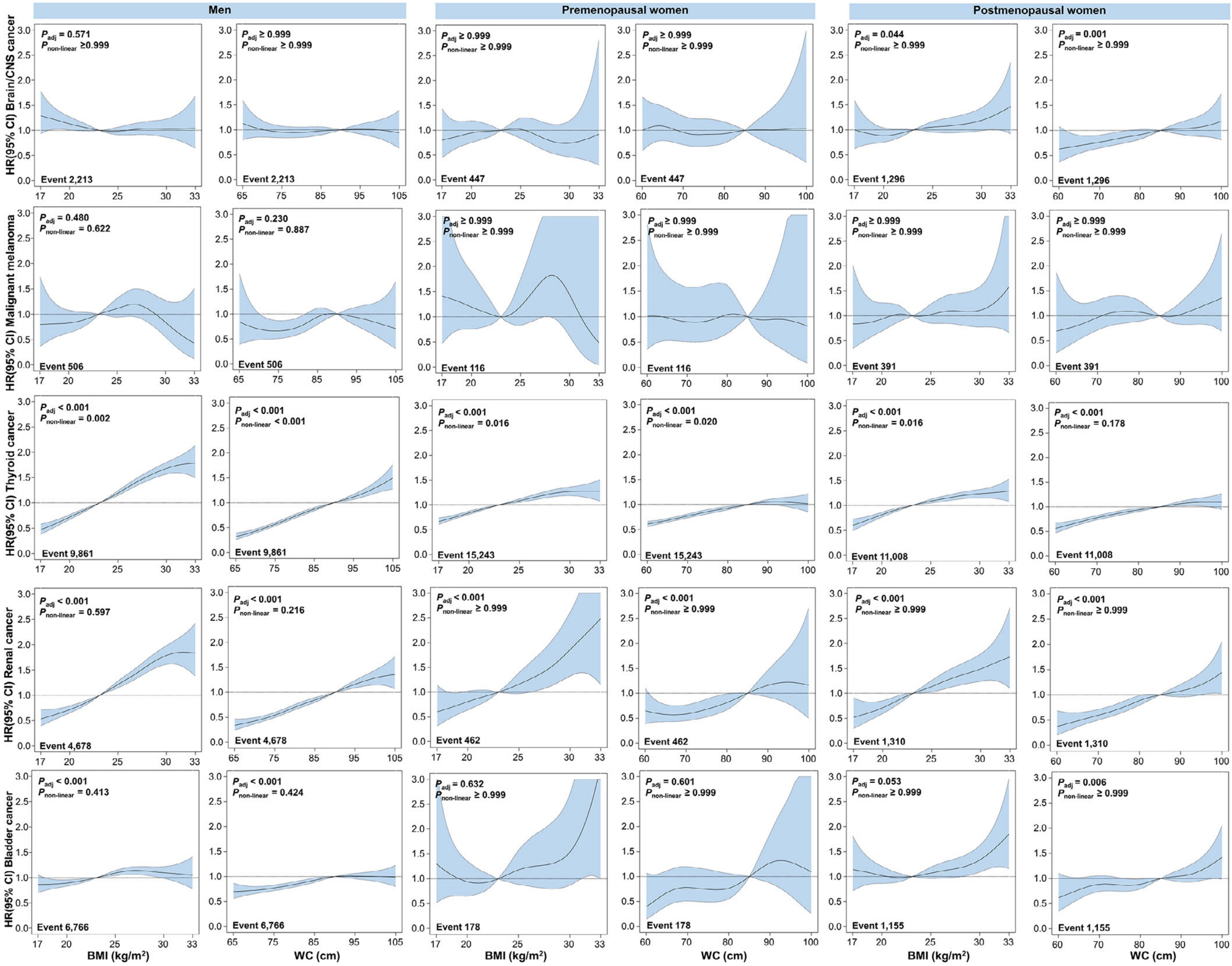

FIGURE 7 Associations of adiposity with incidence of other cancers. Penalized spline curves are presented to illustrate associations between adiposity markers and cancer incidences adjusted for age, diagnosis of diabetes mellitus, smoking status, alcohol intake, and regular exercise. The 95% confidence intervals are presented as shaded areas. All *P*-values were corrected for multiple testing using Holm's method. Abbreviations: BMI, body mass index; WC, waist circumference; HR, hazard ratio; CI, confidence interval.

AUTHOR CONTRIBUTIONS

Seonghye Kim contributed to study concept, study design, data interpretation/visualization, literature review, writing of the original draft, and critical revision of the manuscript. **Bongseong Kim** contributed to data curation, statistical analysis, data interpretation/visualization, and critical revision of the manuscript. **Kyu-won Jung, Ga Eun Nam, Wonyoung Jung,** and **Junhee Park** contributed to study design and critical revision of the manuscript. **Kyung-do Han** contributed to study concept, study design, data curation, statistical analysis, data interpretation/visualization, critical revision of the manuscript, supervision, and project administration. **Dong Wook Shin** contributed to study concept, study design, critical revision of the manuscript, supervision, project administration, and funding acquisition. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Seonghye Kim, Bongseong Kim, Kyu-won Jung, Ga Eun Nam, Wonyoung Jung, Junhee Park, Kyung-Do Han, and Dong Wook Shin declare that they have no conflict of interest concerning the materials or methods used in this study or the findings specified in this article.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Institutional Review Board of Soongsil University (IRB File No. SSU-202007-HR-236-02). The requirement for informed written consent from all participants was waived because the data were anonymized under confidentiality guidelines.

DATA AVAILABILITY STATEMENT

The data reported in this study are not available publicly; they are available only to licensed researchers authorized by the Korean National Health Insurance System (KNHIS).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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