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Breast Cancer

Distinct Effects of Body Mass Index and Waist/Hip Ratio on Risk of Breast Cancer by Joint Estrogen and Progestogen Receptor Status: Results from a Case-Control Study in Northern and Eastern China and Implications for Chemoprevention

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Breast neoplasms • Body mass index • Waist/hip ratio • Estrogen receptors • Progesterone receptors

Abstract

Background. Obesity is a consideration in the pharmacologic intervention for estrogen receptor (ER) positive (ER+) breast cancer risk. Body mass index (BMI) and waist/hip ratio (WHR) have demonstrated different effects on breast cancer risk in relation to estrogen receptor (ER) status, but the results have been inconsistent. Furthermore, the situation in Chinese women remains unclear.

Materials and Methods. We conducted a case-control study including 1,439 breast cancer cases in Northern and Eastern China. Both ER and progesterone receptor (PR) statuses were available for 1,316 cases. Associations between body size-related factors and breast cancer risk defined by receptor status were assessed by multiple polytomous unconditional logistic regression analysis.

Results. Body mass index and WHR were positively associated with overall breast cancer risk. Body mass index was positively associated with both ER+/PR positive (PR+) and ER negative (ER−)/PR negative(PR−) subtype risks, although only significantly for ER+/PR+ subtype. Waist–hip ratio was only positively correlated with ER−/PR− subtype risk, although independent of BMI. Body mass index was positively associated with risk of ER+/PR+ and ER−/PR− subtypes in premenopausal women, whereas WHR was inversely correlated with ER+/PR− and

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positively with ER−/PR− subtype risks. Among postmenopausal women, WHR >0.85 was associated with increased risk of ER−/PR− subtype.

Conclusion. Both general and central obesity contribute to breast cancer risk, with different effects on specific subtypes. General obesity, indicated by BMI, is more strongly associated with ER+/PR+ subtype, especially among premenopausal women, whereas central obesity, indicated by WHR, is more specific for ER−/PR− subtype, independent of menopausal status. These results suggest that different chemoprevention strategies may be appropriate in selected individuals. ***The Oncologist*** 2017;22:1431–1443

Implications for Practice: The results of this study suggest that general and central obesity may play different roles in different breast cancer subtypes, supporting the hypothesis that obesity affects breast carcinogenesis via complex molecular interconnections, beyond the impact of estrogens. The results also imply that different chemoprevention strategies may be appropriate for selected individuals, highlighting the need to be particularly aware of women with a high waist/hip ratio but normal body mass index. Given the lack of any proven pharmacologic intervention for estrogen receptor negative breast cancer, stricter weight-control measures may be advised in these individuals.

Introduction

Breast cancer is the most common cancer among women in China and the fifth leading cause of cancer-related deaths [1, 2]. The incidence of breast cancer in both urban and rural areas of China has increased over the previous 2 decades, resulting in great social and economic burdens [3]. This ever-increasing trend highlights the need for and potential impact of effective breast cancer risk reduction strategies, such as dietary modifications and weight control. Moreover, pharmacologic interventions for reducing the risk of breast cancer have been adopted worldwide [4]. Tamoxifen is the first drug approved by the U.S. Food and Drug Administration and recommended by the American Society of Clinical Oncology (ASCO) for reducing breast cancer risk in high-risk women, based on four phase III clinical trials (NSABP P-1, IBIS-1, Italian, and Royal Marsden) [5–9] that demonstrated risk reductions in breast cancer of 31%–67%. However, this risk reduction was limited to estrogen receptor (ER) positive (ER+) breast cancers [10]. Despite numerous clinical trials of selective estrogen receptor modulators (SERMs) and aromatase inhibitors, no preventive interventions have yet been shown to decrease the risk of ER negative (ER−) breast cancer [10]. Considering the potential side effects of long-term use of drugs [4], it is necessary to identify those individuals at the highest risk of developing ER+ breast cancer, who might thus benefit most from such treatments.

Pharmacologic chemoprevention of breast cancer is mainly based on breast cancer risk determined by risk assessment tools such as the Gail model [11], the National Cancer Institute Breast Cancer Risk Assessment Tool (http://www.cancer.gov/bcrisktool), and other validated models (e.g., Tyrer-Cuzick) [12, 13]. However, none of these tools can distinguish between ER+ and ER− breast cancer risk, and other risk-assessment factors are therefore needed. Obesity is a well-known and well-accepted risk factor for female breast cancer [14], especially among postmenopausal women [15–18]. Obesity is also an additional clinical consideration for the use of SERMs for breast cancer prevention according to the ASCO guidelines [4]. Actually, obesity is a worldwide public health burden [19], and was reported to occur in up to 50% of all breast cancer cases in older women [20]. It has been estimated that the incidence of breast cancer in the European Union could be halved by weight control [21]. Importantly, several studies have suggested that obesity, indicated by high body mass index (BMI), is more strongly associated with ER+ than with ER− breast cancer, particularly among postmenopausal women [22–25]. These associations were confirmed in two pharmacologic intervention trials (NSABP P-1 and STAR) [26]. Conversely, another study found a direct association between abdominal adiposity (indicated by waist circumference [WC] and waist/hip ratio [WHR]) and ER− breast cancer only [27], although this association has not been well characterized or confirmed by other studies.

The association between obesity and breast cancer defined by ER and progesterone receptor (PR) status among women remains poorly characterized. We therefore conducted a case-control study among women in Northern and Eastern China to clarify the possible associations between both general and central obesity and breast cancer risk according to joint ER and PR status. We also conducted analyses stratified by menopausal status, based on previous evidence of differing effects in pre- and postmenopausal women.

Materials and Methods

Study Population

Inpatients with breast cancer were recruited from 21 hospitals in 11 provinces or municipalities (Shandong Province, Hebei Province, Jiangsu Province, Henan Province, Shanxi Province, Liaoning Province, Jilin Province, Heilongjiang Province, Anhui Province, Tianjin municipality, and Beijing municipality) in Northern and Eastern China from June 2012 to June 2013. Han Chinese females aged 25–70 years who were newly diagnosed with histopathologically confirmed primary breast cancer were included in the study. Exclusion criteria were as follows: diagnosed with recurrent or metastatic breast cancer; diagnosed with other concurrent malignancies; or a prior history of cancer. Controls were randomly selected healthy outpatients who visited the center for regular physical examinations. Controls were matched 1:1 with cases from the same hospital based on the following criteria: same age (±3 years); and similar visiting period (±2 months). All controls were confirmed as having no diagnosis of breast cancer, with negative findings on physical breast examination, breast ultrasound scans, and mammographic screening.

All study participants provided written informed consent, and the study protocol and procedures were approved by the institutional review boards at the Second Hospital of Shandong University and the other participating hospitals.

Data Collection

All participants completed face-to-face interviews based on a self-designed structured questionnaire, as described previously [28], to gather information on the following factors: demographic characteristics, female physiological and reproductive factors, medical and family history, dietary habits, lifestyle habits, and breast cancer-related knowledge. With the exception of the basic demographic information, all questions had multiple-choice responses and attempts were made to quantify or categorize the answer choices (e.g., yes/no or 1/2/3/4). Current weight, standing height, WC, and hip circumference (HC) were measured, and BMI (weight [kg]/height [m]^2) and WHR (WC/HC) were computed from the obtained measurements. The results of clinical examinations including visual examination, palpation, and related diagnostic tests such as breast ultrasound, mammography, and blood tests, were also collected.

Medical and pathology records from the hospital where the patient was originally diagnosed were reviewed to obtain information on ER and PR statuses and other pathological results. Both ER and PR status were primarily determined immunohistochemically, and all the participating hospitals had national quality certifications for pathological diagnosis. Following ASCO/College of American Pathologists (2010) recommendations, ER positivity was defined as >1% of tumor cells with positive staining. Of the total 1,489 breast cancer cases, data on ER status were available for 1,325 (89.0%) cases, data on PR status for 1,358 (91.2%) cases, and joint ER/PR status for 1,316 (88.4%) cases.

Statistical Analysis

Breast cancer cases were grouped into four categories according to the joint ER and PR statuses: ER+/PR+, ER+/PR−, ER−/PR−, and ER−/PR+. The frequencies and percentages of variables at baseline were calculated. Analysis of variance and Pearson's chi-square tests were used to compare differences in frequency distributions between case and control groups and across case subgroups.

Multiple polytomous unconditional logistic regression analysis was used to calculate odds ratios (OR) and corresponding 95% confidence intervals (CI) for body size indicators in relation to breast cancer case subtype (ER+/PR+, ER+/PR−, and ER−/PR−); ER−/PR+ cases were excluded from the final OR analysis because of the limited number of cases ($n = 21$). The following variables were included in the logistic regression analysis: height, weight, WC, HC, WHR, physical activity (yes/no), and menopausal status (pre-/postmenopause). We also extended our analysis by stratifying the results according to menopausal status, because the associations of these variables with breast cancer may differ between pre- and postmenopausal women. We also conducted stratified analysis according to BMI category ($\leq$24.0 kg/m^2/>24.0 kg/m^2) to determine if central obesity indicators were independent of BMI.

Tests for trends were carried out by fitting ordinal values corresponding to different categories, and multivariable polytomous unconditional logistic regression was used to conduct Wald tests to evaluate the heterogeneity of the associations across breast cancer subtypes.

The database was established using EpiData 3.1 (The EpiData Association, Odense, Denmark, http://www.epidata.dk), as recommended by World Health Organization, and was subsequently converted into SPSS 21.0 format. All statistical tests were based on two-sided probabilities with $p < .05$ considered significant.

Results

Frequency distributions of demographic variables and body size factors for all participants are shown in Tables 1 and 2, respectively. Among the 1,316 cases with clear joint ER/PR statuses, 885 (67.2%) were ER+/PR+, 112 (8.5%) were ER+/PR−, 298 (22.6%) were ER−/PR−, and 21 (1.6%) were ER−/PR+. Compared with the controls, more breast cancer cases were from urban areas (75.8% vs. 62.1%), were postmenopausal (34.1% vs. 29.0%), and had an earlier age at menarche (14.00 vs. 14.59 years). Regarding body size-related variables, cases tended to be lighter (61.50 kg vs. 61.64 kg), but have a higher BMI (24.03 kg/m^2 vs. 23.99 kg/m^2), a larger WC (80.00 cm vs 78.43 cm), and a higher WHR (0.85 vs. 0.84). Age at breast cancer diagnosis ($p = .003$), residence ($p < .001$), menopausal status ($p < .001$), WC ($p < .001$), and WHR ($p < .001$) differed across the four subgroups with known receptor statuses.

Associations between body size-related factors and breast cancer according to joint ER/PR status are shown in Table 3. Body weight, BMI, WC, and WHR were positively associated with breast cancer risk for all cases. No differences in risk were found across the three analyzed ER/PR breast cancer subtypes in relation to body height, HC, age at menarche, or physical activity. However, women weighing >62.0 kg had a 21% increased risk (OR = 1.21, 95% CI: 1.02–1.45) of ER+/PR+ breast cancer and a 34% increased risk (OR = 1.34, 95% CI: 1.03–1.73) of ER−/PR− breast cancer, compared with women with a body weight <62.0 kg. Waist circumference was positively associated with risks of ER+/PR+ (p trend $< .001$) and ER−/PR− (p trend $= .004$) breast cancer. Women in the highest quartile of WC (>83.33 cm) had 64% (OR = 1.64, 95% CI: 1.27–2.13) and 77% (OR = 1.77, 95% CI: 1.23–2.56) increased risks of ER+/PR+ and ER−/PR− breast cancer, respectively. Body mass index was positively associated with both ER+/PR+ and ER−/PR− breast cancer, although trend tests were only significant for ER+/PR+ subtype (p trend for ER−/PR− subtype = .093). Hip circumference was only positively associated with ER+/PR+ subtype (p trend = .027), with a 35% increase (OR = 1.35, 95% CI: 1.04–1.76) in risk for women in the highest quartile of HC (>100.33 cm). Waist/hip ratio was only positively correlated with ER−/PR− subtype, with a 64% increase (OR = 1.64, 95% CI: 1.23–2.18) in risk for women with WHR >0.85. The association with menopausal status differed between subtypes defined by receptor status ($p < .001$), with postmenopausal status being correlated with increased risks of ER+/PR− and ER−/PR− breast cancers.

We also investigated associations between body size-related factors and breast cancer according to joint ER/PR status in relation to menopausal status (Tables 4 and 5). Similar to all breast cancer cases, body weight, BMI, WC, and HC were positively associated with premenopausal breast cancer, whereas no significant associations were observed for WHR (OR = 1.01, 95% CI: 0.82–1.24). In contrast, only WHR was associated with postmenopausal breast cancer risk, with a 54% increase (OR = 1.54, 95% CI: 1.14–2.10) in risk for women with WHR >0.85. Among premenopausal women, the risks differed across the three analyzed ER/PR subtypes for body weight

Table 1. Demographic characteristics of cases and controls by joint estrogen and progesterone receptor status

						ER/PR status								
	Controls ($n = 1{,}316$)		Cases ($n = 1{,}316$)			ER+/PR+ ($n = 885$)		ER+/PR− ($n = 112$)		ER−/PR− ($n = 298$)		ER−/PR+ ($n = 21$)		p value[b] for four subgroups
Variables	n (%)	Mean (SD)	n (%)	Mean (SD)	p value[a]	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	
Age (y)		47.06 (8.83)		48.00 (8.67)	.210		47.22 (8.61)		50.63 (9.03)		48.52 (8.48)		48.71 (9.1)	.003
25-	98 (7.4)		80 (6.1)			57 (6.4)		7 (6.3)		16 (5.4)		0 (0.0)		
35-	48 (32.5)		394 (29.9)			286 (32.3)		23 (20.5)		77 (25.8)		8 (38.1)		
45-	505 (38.4)		523 (39.7)			351 (39.7)		36 (32.1)		129 (43.3)		7 (33.3)		
55-	248 (18.8)		283 (21.5)			166 (18.8)		42 (37.5)		70 (23.5)		5 (23.8)		
65-	37 (2.8)		36 (2.7)			25 (2.8)		4 (3.6)		6 (2.0)		1 (4.8)		
Residence					<.001									<.001
Urban	817 (62.1)		997 (75.8)			420 (47.5)		47 (42.0)		135 (45.3)		13 (61.9)		
Rural	445 (33.8)		530 (40.3)			436 (49.3)		63 (56.3)		149 (50.0)		6 (28.6)		
Unknown	54 (4.1)		31 (2.4)			29 (3.3)		2 (1.8)		14 (4.7)		2 (9.5)		
Menopausal status					.007									<.001
Premenopause	882 (67.0)		828 (62.9)			582 (65.8)		53 (47.3)		179 (60.1)		14 (66.7)		
Postmenopause	381 (29.0)		449 (34.1)			278 (31.4)		57 (50.9)		107 (35.9)		7 (33.3)		
Unknown	53 (4.0)		39 (3.0)			25 (2.8)		2 (1.8)		12 (4.0)		0 (0.0)		
Age at menarche (y)		14.59 (1.74)		14.00 (1.94)	.028		14.68 (2.00)		14.81 (1.73)		14.80 (1.85)		14.67 (1.56)	.155
≤13	175 (17.2)		227 (17.2)			154 (17.4)		14 (12.5)		56 (18.8)		3 (14.3)		
14	415 (28.4)		374 (28.4)			241 (27.2)		42 (37.5)		81 (27.2)		10 (47.6)		
15–16	358 (26.1)		344 (26.1)			231 (26.1)		29 (25.9)		80 (26.8)		4 (19.0)		
≥17	344 (25.9)		341 (25.9)			240 (27.1)		24 (21.4)		73 (24.5)		4 (19.0)		
Unknown	24 (2.3)		30 (2.3)			19 (2.1)		3 (2.7)		8 (2.7)		0 (0.0)		
Physical activity					.127									.753
Yes	349 (26.5)		384 (29.2)			258 (29.2)		31 (27.7)		89 (29.9)		6 (28.6)		
No	957 (72.7)		922 (70.1)			621 (70.2)		81 (72.3)		205 (68.8)		15 (71.4)		
Unknown	10 (0.8)		10 (0.8)			6 (0.7)		0 (0.0)		4 (1.3)		0 (0.0)		

[a] p value for cases versus controls from a chi-square test (categorical variables) or analysis of variance (continuous variables).
[b] p value for comparison across the three known joint estrogen and progesterone receptor status subtypes.
Abbreviations: ER, estrogen receptor; ER−, estrogen receptor negative; ER+, estrogen receptor positive; PR, progesterone receptor; PR−, progesterone receptor negative; PR+, progesterone receptor positive; SD, standard deviation.

Table 2. Body size-related indicators distribution of cases and controls by joint estrogen and progesterone receptor status

Variables	Controls ($n = 1,316$)		Cases ($n = 1,316$)		p value[a]	ER/PR status								p value[b] for four subgroups
						ER+/PR+ ($n = 885$)		ER+/PR− ($n = 112$)		ER−/PR− ($n = 298$)		ER−/PR+ ($n = 21$)		
	n (%)	Mean (SD)	n (%)	Mean (SD)		n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	
Weight (kg)		61.64 (8.34)		61.50 (9.29)	.033		62.61 (9.39)		61.30 (9.54)		62.71 (8.88)		62.44 (9.99)	.149
≤62	730 (55.5)		675 (51.3)			450 (50.8)		68 (60.7)		145 (48.7)		12 (57.1)		
>62	519 (39.4)		570 (43.3)			388 (43.8)		36 (32.1)		138 (46.3)		8 (38.1)		
Unknown	67 (5.1)		71 (5.4)			47 (5.3)		8 (7.1)		15 (5.0)		1 (4.8)		
Height (cm)		160.32 (4.25)		160.00 (4.77)	.715		160.09 (4.71)		160.10 (3.93)		160.04 (5.22)		161.45 (4.81)	.817
≤160.2	696 (52.9)		700 (53.2)			461 (52.1)		62 (55.4)		168 (56.4)		9 (42.9)		
>160.2	554 (42.1)		541 (41.1)			374 (42.3)		42 (37.5)		114 (38.3)		11 (52.4)		
Unknown	66 (5.0)		75 (5.7)			50 (5.6)		8 (7.1)		16 (5.4)		1 (4.8)		
Body mass index (kg/m^2)		23.99 (3.12)		24.03 (3.48)	.003		24.42 (3.45)		23.90 (347)		24.51 (3.60)		23.86 (2.92)	.072
≤24.0	647 (49.2)		597 (45.4)			389 (44.0)		62 (55.4)		136 (45.6)		10 (47.6)		
24.1–27.9	475 (36.1)		462 (35.1)			317 (35.8)		29 (25.9)		108 (36.2)		8 (38.1)		
≥28.0	122 (9.3)		176 (13.4)			123 (13.9)		13 (11.6)		38 (12.8)		2 (9.5)		
Unknown	72 (5.5)		81 (6.2)			56 (6.3)		8 (7.1)		16 (5.4)		1 (4.8)		
Waist circumference (cm)		78.43 (8.49)		80.00 (9.61)	.001		80.25 (9.64)		78.56 (8.01)		80.81 (9.86)		85.11 (11.81)	<.001
≤73.33	403 (30.6)		317 (24.1)			212 (24.0)		30 (26.8)		74 (24.8)		1 (4.8)		
73.33–76.67	249 (18.9)		227 (17.2)			150 (17.0)		26 (23.2)		46 (15.4)		5 (23.8)		
76.67–83.33	302 (22.9)		293 (22.3)			200 (22.6)		27 (24.1)		62 (20.8)		4 (19.0)		
>83.33	212 (16.1)		271 (20.6)			183 (20.7)		14 (12.5)		69 (23.2)		5 (23.8)		
Unknown	150 (11.4)		207 (15.7)			139 (15.7)		15 (13.4)		47 (15.8)		6 (28.6)		
Hip circumference (cm)		93.73 (12.52)		93.33 (11.62)	.157		95.45 (11.70)		94.05 (11.97)		93.59 (11.26)		95.33 (10.14)	.112
≤86.67	344 (26.1)		315 (23.9)			200 (22.6)		30 (26.8)		81 (27.2)		4 (19.0)		
86.67–93.33	278 (21.1)		247 (18.8)			166 (18.8)		20 (17.9)		57 (19.1)		4 (19.0)		
93.33–100.00	282 (21.4)		252 (19.1)			181 (20.5)		21 (18.8)		48 (16.1)		2 (9.5)		
>100.00	224 (17.0)		255 (19.4)			176 (19.9)		22 (19.6)		52 (17.4)		5 (23.8)		
Unknown	188 (14.3)		246 (18.7)			161 (18.2)		19 (17.0)		60 (20.1)		6 (28.6)		
Waist/hip ratio		0.84 (0.08)		0.85 (0.08)	.044		0.85 (0.08)		0.84 (0.09)		0.87 (0.08)		0.89 (0.06)	<.001
≤0.85	547 (41.6)		473 (35.9)			335 (37.9)		49 (43.8)		87 (29.2)		2 (9.5)		
>0.85	580 (44.1)		596 (45.3)			388 (43.8)		44 (39.8)		151 (50.7)		13 (61.9)		
Unknown	189 (14.4)		247 (18.8)			162 (18.3)		19 (17.0)		60 (20.1)		6 (28.6)		

[a] p value for cases versus controls from a chi-square test (categorical variables) or analysis of variance (continuous variables).
[b] p value for comparison across the three known joint estrogen and progesterone receptor status subtypes.
Abbreviations: ER, estrogen receptor; ER−, estrogen receptor negative; ER+, estrogen receptor positive; PR, progesterone receptor; PR−, progesterone receptor negative; PR+, progesterone receptor positive; SD, standard deviation.

Table 3. Odds ratio for breast cancer according to body size-related indicators by joint estrogen and progesterone receptor status

Variables	Controls ($n = 1,316$)	Cases ($n = 1,316$)			ER/PR status									
					ER+/PR+ ($n = 885$)			ER+/PR− ($n = 112$)			ER−/PR− ($n = 298$)			
	n	*n*	OR	95% CI	*n*	OR	95% CI	*n*	OR	95% CI	*n*	OR	95% CI	*p* value[a]
Weight (kg)														
≤62	730	675	1	ref	450	1	ref	68	1	ref	145	1	ref	
>62	519	570	1.19	1.01–1.39	388	1.21	1.02–1.45	36	0.75	0.49–1.13	138	1.34	1.03–1.73	
p_{trend}[b]		—			—			—			—			.011
Height (cm)														
≤160.2	696	700	1	ref	461	1	ref	62	1	ref	168	1	ref	
>160.2	554	541	1.03	0.88–1.21	374	1.02	0.86–1.22	42	0.85	0.57–1.28	114	0.85	0.66–1.11	
p_{trend}		—			—			—			—			.518
Body mass index (kg/m^2)														
≤24.0	647	597	1	ref	389	1	ref	62	1	ref	136	1	ref	
24.1–27.9	475	462	1.05	0.89–1.25	317	1.11	0.92–1.34	29	0.64	0.40–1.00	108	1.08	0.82–1.43	
≥28.0	122	176	1.56	1.21–2.02	123	1.68	1.27–2.22	13	1.11	0.59–2.09	38	1.48	0.99–2.23	
p_{trend}		.003			.001			.471			.093			.005
Waist circumference (cm)														
≤73.33	403	317	1	ref	212	1	ref	30	1	ref	74	1	ref	
73.33–76.67	249	227	1.16	0.92–1.46	150	1.15	0.88–1.19	26	1.40	0.81–2.43	46	1.01	0.67–1.50	
76.67–83.33	302	293	1.23	0.99–1.53	200	1.26	0.99–1.61	27	1.20	0.70–2.06	62	1.12	0.77–1.62	
>83.33	212	271	1.63	1.29–2.05	183	1.64	1.27–2.13	14	0.89	0.46–1.71	69	1.77	1.23–2.56	
p_{trend}		<.001			<.001			.870			.004			.002
Hip circumference (cm)														
≤86.67	344	315	1	ref	200	1	ref	30	1	ref	81	1	ref	
86.67–93.33	278	247	0.97	0.77–1.22	166	1.03	0.79–1.33	20	0.83	0.46–1.48	57	0.87	0.60–1.27	
93.33–100.00	282	252	0.98	0.78–1.23	181	1.10	0.86–1.43	21	0.85	0.48–1.52	48	0.72	0.50–1.07	
>100.33	224	255	1.24	0.98–1.57	176	1.35	1.04–1.76	22	1.13	0.63–2.00	52	0.99	0.67–1.45	
p_{trend}		.115			.027			.776			.582			.456
Waist/hip ratio														
≤0.85	547	473	1	ref	335	1	ref	49	1	ref	87	1	ref	
>0.85	580	596	1.26	1.00–1.60	388	1.09	0.91–1.32	44	0.85	0.55–1.29	151	1.64	1.23–2.18	
p_{trend}		—			—			—			—			.005
Menopausal status														
Premenopause	882	828	1	ref	582	1	ref	53	1	ref	179	1	ref	
Postmenopause	381	449	1.26	1.06–1.48	278	1.11	0.92–1.33	57	2.5	1.68–3.69	107	1.38	1.06–1.81	
p_{trend}		—			—			—						<.001

(continued)

Table 3. (continued)

Variables	Controls ($n = 1,316$)	Cases ($n = 1,316$)			ER/PR status								
					ER+/PR+ ($n = 885$)			ER+/PR− ($n = 112$)			ER−/PR− ($n = 298$)			
	n	*n*	OR	95% CI	*n*	OR	95% CI	*n*	OR	95% CI	*n*	OR	95% CI	*p* value[a]
Age at menarche (y)														
≤13	344	341	1	ref	240	1	ref	24	1	ref	73	1	ref	
14	358	344	0.97	0.79–1.20	231	0.93	0.73–1.17	29	1.16	0.66–2.03	80	1.05	0.74–1.50	
15–16	415	374	0.91	0.74–1.12	241	0.83	0.66–1.05	42	1.45	0.86–2.44	81	0.92	0.65–1.30	
≥17	175	227	1.31	1.02–1.68	154	1.26	0.96–1.66	14	1.15	0.58–2.27	56	1.51	1.02–2.23	
p_{trend}		.195			.496			.339			.186			.051
Physical activity														
Less	957	922	1	ref	621	1	ref	81	1	ref	205	1	ref	
Frequently	349	384	0.88	0.74–1.04	258	1.14	0.94–1.38	31	1.05	0.68–1.61	89	1.19	0.90–1.57	
p_{trend}		—			—			—			—			.458

[a]Test for heterogeneity of p_{trend} values between the three subtypes, calculated using multivariable polytomous logistic regression.
[b]p_{trend} values were carried out by fitting ordinal values corresponding to different categories.
Abbreviations: —, no data; CI, confidence interval; ER, estrogen receptor; ER−, estrogen receptor negative; ER+, estrogen receptor positive; OR, odds ratio; PR, progesterone receptor; PR−, progesterone receptor negative; PR+, progesterone receptor positive; ref, reference category.

($p = .001$), BMI ($p = .001$), WC ($p < .001$), HC ($p = .045$), and WHR ($p = .026$): body weight, BMI, and WC were positively associated with ER+/PR+ and ER−/PR− subtypes. There was a 121% increase (OR = 2.21, 95% CI: 1.52–3.21) in risk of ER+/PR+ breast cancer and a 105% increase (OR = 2.05, 95% CI: 1.18–3.56) in risk of ER−/PR− breast cancer among women with a BMI ≥28.0 kg/m^2 compared with women with a BMI <24.0 kg/m^2. Among women in the highest quartile of WC (>83.33 cm), risks were increased by 87% (OR = 1.87, 95% CI: 1.34–2.60) for ER+/PR+ and 152% (OR = 2.52, 95% CI: 1.56–4.07) for ER−/PR− subtypes. Waist/hip ratio was inversely correlated with risk of ER+/PR− (OR = 0.51, 95% CI: 0.28–0.93) and positively associated with risk of ER−/PR− subtypes (OR = 1.38, 95% CI: 0.96–1.98), although the result was only significant for ER+/PR− breast cancer. Unlike premenopausal women, there was no difference in risk for any of the three analyzed breast cancer subtypes in relation to body weight, body height, BMI, WC, or HC among postmenopausal women. However, the association between WHR and postmenopausal breast cancer differed across the three groups (heterogeneity test: $p = .013$), and WHR >0.85 was associated with a 125% increased risk of ER−/PR− breast cancer (OR = 2.25, 95% CI: 1.34–3.80).

To clarify the value of central obesity indicators, we further analyzed the associations with breast cancer after adjusting for BMI (Table 6). There were no differences in risks associated with WC, HC, or WHR across the three analyzed subgroups regardless of BMI. However, higher WHR was associated with an increased risk of ER−/PR− breast cancer, independent of BMI.

Discussion

We carried out a case-control study including 1,316 breast cancer cases with known ER and PR statuses, and analyzed the associations between body size-related factors and risks of different breast cancer subtypes. Both BMI and WHR were positively associated with overall breast cancer risk, supporting the view that obesity, including general and central obesity, increased breast cancer risk. However, the associations varied for different breast cancer subtypes. Body mass index was positively associated with both ER+/PR+ and ER−/PR− breast cancers, although trend tests were only significant for ER+/PR+ subtype, whereas WHR was only positively correlated with ER−/PR− subtype. Further stratified analyses showed that the association between WHR and ER−/PR− breast cancer was independent of menopausal status and BMI category. These results indicated that general and central obesity had different effects on the risk of different breast cancer subtypes, indicating the need to consider different chemoprevention strategies for selected individuals, especially for those with normal BMI but high WHR.

The ASCO clinical practice guidelines for pharmacologic interventions for breast cancer risk reduction [4] list obesity as an additional clinical consideration for the use of SERMs. Based on the post hoc analysis of the STAR and NSABP-P1 trials [26], which showed no significant interaction among BMI, treatment group, and the incidence of invasive breast cancer, ASCO guidelines reported that "there is no direct evidence to suggest that women who are overweight or obese should not be offered tamoxifen or raloxifene for breast cancer prevention." However, the STAR and NSABP-P1 trials [26] only analyzed BMI and

Table 4. Relationship between body size-related indicators and risk of premenopausal breast cancer by joint estrogen and progesterone receptor status

Variables	Controls ($n = 882$)	Cases ($n = 828$)			ER/PR status									
					ER+/PR+ ($n = 582$)			ER+/PR− ($n = 53$)			ER−/PR− ($n = 179$)			
	n	*n*	OR	95% CI	*n*	OR	95% CI	*n*	OR	95% CI	*n*	OR	95% CI	*p* value[a]
Weight (kg)														
≤62	520	422	1	ref	300	1	ref	32	1	ref	83	1	ref	
>62	320	366	1.41	1.16–1.72	257	1.39	1.12–1.73	17	0.86	0.47–1.58	86	1.68	1.21–2.35	
p_{trend}[b]		—			—			—			—			.001
Height (cm)														
≤160.2	443	408	1	ref	285	1	ref	28	1	ref	91	1	ref	
>160.2	398	379	1.03	0.85–1.26	271	1.06	0.85–1.31	21	0.84	0.47–1.50	78	0.95	0.69–1.33	
P_{trend}		—			—			—			—			.825
Body mass index (kg/m^2)														
≤24.0	461	380	1	ref	265	1	ref	29	1	ref	80	1	ref	
24.1–27.9	615	299	1.15	0.94–1.42	211	1.17	0.93–1.47	14	0.71	0.37–1.36	68	1.24	0.87–1.77	
≥28.0	59	103	2.12	1.50–3.00	75	2.21	1.52–3.21	6	1.62	0.64–4.06	21	2.05	1.18–3.56	
p_{trend}		<.001			<.001			.876			.003			.001
Waist circumference (cm)														
≤73.33	301	208	1	ref	147	1	ref	18	1	ref	43	1	ref	
73.33–76.67	188	152	1.17	0.89–1.54	104	1.13	0.83–1.55	14	1.25	0.61–2.56	30	1.12	0.68–1.84	
76.67–83.33	189	198	1.52	1.16–1.98	147	1.59	1.19–2.13	11	0.97	0.45–2.11	37	1.37	0.85–2.21	
>83.33	114	153	1.94	1.44–2.62	104	1.87	1.34–2.60	5	0.73	0.27–2.02	41	2.52	1.56–4.07	
p_{trend}		<.001			.022			.192			.020			<.001
Hip circumference (cm)														
≤86.67	257	195	1	ref	129	1	ref	17	1	ref	47	1	ref	
86.67–93.33	210	175	1.10	0.84–1.44	125	1.19	0.87–1.61	8	0.58	0.24–1.36	39	1.02	0.64–1.61	
93.33–100.00	191	175	1.21	0.92–1.59	131	1.37	1.01–1.86	11	0.87	0.40–1.90	32	0.92	0.56–1.49	
>100.33	109	143	1.73	1.27–2.36	98	1.79	1.27–2.53	12	1.66	0.77–3.60	29	1.46	0.87–2.43	
p_{trend}		.001			.259			.842			.61			.045
Waist/hip ratio														
≤0.85	368	330	1	ref	238	1	ref	31	1	ref	59	1	ref	
>0.85	398	359	1.01	0.82–1.24	246	0.96	0.76–1.20	17	0.51	0.28–0.93	88	1.38	0.96–1.98	
p_{trend}		—			—			—			—			.026

[a]Heterogeneity of p_{trend} values between the three subtypes, calculated using multivariable polytomous logistic regression.
[b]p_{trend} values were carried out by fitting ordinal values corresponding to different categories.
Abbreviations: —, no data; CI, confidence interval; ER, estrogen receptor; ER−, estrogen receptor negative; ER+, estrogen receptor positive; OR, odds ratio; PR, progesterone receptor; PR−, progesterone receptor negative; PR+, progesterone receptor positive; ref, reference category.

Table 5. Relationship between body size-related indicators and risk of postmenopausal breast cancer by joint estrogen and progesterone receptor status

Variables	Controls ($n = 381$)	Cases ($n = 449$)			ER/PR status									
					ER+/PR+ ($n = 278$)			ER+/PR− ($n = 57$)			ER−/PR− ($n = 107$)			
	n	*n*	OR	95% CI	*n*	OR	95% CI	*n*	OR	95% CI	*n*	OR	95% CI	*p* value[a]
Weight (kg)														
≤62	189	228	1	ref	135	1	ref	34	1	ref	54	1	ref	
>62	174	193	0.92	0.69–1.22	124	1.00	0.73–1.37	19	0.61	0.33–1.10	48	0.97	0.62–1.50	
p_{trend}[b]		—			—			—			—			.407
Height (cm)														
≤160.2	228	272	1	ref	166	1	ref	32	1	ref	69	1	ref	
>160.2	135	147	0.91	0.68–1.22	91	0.93	0.66–1.29	21	1.11	0.61–2.00	33	0.81	0.51–1.29	
p_{trend}		—			—			—			—			.765
Body mass index (kg/m^2)														
≤24.0	164	195	1	ref	111	1	ref	31	1	ref	49	1	ref	
24.1–27.9	140	151	0.91	0.67–1.24	97	1.02	0.72–1.46	15	0.57	0.29–1.10	37	0.89	0.55–1.43	
≥28.0	59	72	1.03	0.69–1.53	48	1.2	0.77–1.89	7	0.63	0.26–1.50	16	0.91	0.48–1.72	
p_{trend}		.930			.486			.025			.307			.570
Waist circumference (cm)														
≤73.33	92	100	1	ref	60	1	ref	12	1	ref	27	1	ref	
73.33–76.67	51	67	1.21	0.76–1.92	40	1.20	0.71–2.04	11	1.65	0.68–4.01	15	1.00	0.50–2.06	
76.67–83.33	98	89	0.84	0.56–1.25	50	0.78	0.49–1.25	15	1.17	0.52–2.64	23	0.80	0.43–1.49	
>83.33	93	115	1.14	0.77–1.69	78	1.29	0.83–2.00	9	0.74	0.30–1.85	26	0.95	0.52–1.76	
p_{trend}		.862			<.001			.308			.041			.641
Hip circumference (cm)														
≤86.67	79	112	1	ref	65	1	ref	13	1	ref	32	1	ref	
86.67–93.33	58	66	0.80	0.51–1.27	38	0.80	0.47–1.34	12	1.26	0.54–2.96	15	0.64	0.32–1.29	
93.33–100.00	80	72	0.64	0.41–0.98	47	0.71	0.44–1.16	10	0.76	0.32–1.83	14	0.43	0.24–0.87	
>100.33	105	108	0.73	0.50–1.08	76	0.88	0.57–1.37	9	0.52	0.21–1.28	22	0.52	0.28–0.96	
p_{trend}		.075			.002			.994			.820			.418
Waist/hip ratio														
≤0.85	154	133	1	ref	92	1	ref	17	1	ref	24	1	ref	
>0.85	168	224	1.54	1.14–2.10	133	1.33	0.94–1.87	27	1.46	0.76–2.78	59	2.25	1.34–3.80	
p_{trend}		—			—			—			—			.013

[a]Heterogeneity of p_{trend} values between the three subtypes, calculated using multivariable polytomous logistic regression.
[b]p_{trend} values were carried out by fitting ordinal values corresponding to different categories.
Abbreviations: —, no data; CI, confidence interval; ER, estrogen receptor; ER−, estrogen receptor negative; ER+, estrogen receptor positive; OR, odds ratio; PR, progesterone receptor; PR−, progesterone receptor negative; PR+, progesterone receptor positive; ref, reference category.

Table 6. Relationships between waist/hip ratio and risk of breast cancer by joint estrogen and progesterone receptor status and BMI

Variables	Controls	Cases			ER/PR status									
					ER+/PR+			ER+/PR−			ER−/PR−			
	n	*n*	OR	95% CI	*n*	OR	95% CI	*n*	OR	95% CI	*n*	OR	95% CI	*p* value[a]
BMI ≤24.0 kg/m^2	647	597			389			62			136			
Waist circumference (cm)														
≤73.33	329	254	1	ref	169	1	ref	23	1	ref	61	1	ref	
73.33–76.67	135	125	1.199	0.90–1.61	78	1.125	0.81–1.57	21	2.225	1.19–4.16	23	0.919	0.55–1.55	
76.67–83.33	102	106	1.346	0.98–1.85	72	1.374	0.96–1.96	11	1.543	0.73–3.27	23	1.216	0.72–2.06	
>83.33	34	39	1.486	0.91–2.42	24	1.374	0.79–2.39	3	1.262	0.36–4.42	10	1.589	0.75–3.38	
p_{trend}[b]		.022			<.001			.011			<.001			.064
Hip circumference (cm)														
≤86.67	247	214	1	ref	136	1	ref	22	1	ref	52	1	ref	
86.67–93.33	157	122	0.897	0.67–1.21	79	0.914	0.65–1.29	15	1.073	0.54–2.13	28	0.547	0.51–1.40	
93.33–100.00	131	112	0.987	0.72–1.35	81	1.123	0.80–1.59	11	0.943	0.44–2.00	20	0.725	0.42–1.27	
>100.33	46	60	1.505	0.98–2.30	37	1.461	0.90–2.36	8	1.953	0.82–4.65	13	1.342	0.68–2.66	
p_{trend}		.215			<.001			.096			<.001			.180
Waist/hip ratio														
≤0.85	298	236	1	ref	160	1	ref	31	1	ref	45	1	ref	
>0.85	282	271	1.213	0.96–1.54	172	1.14	0.87–1.49	25	0.85	0.49–1.48	68	1.6	1.06–2.40	
p_{trend}		—			—			—			—			.108
BMI >24.0 kg/m^2	597	638			389			62			136			
Waist circumference (cm)														
≤73.33	64	61	1	ref	41	1	ref	7	1	ref	13	1	ref	
73.33–76.67	111	100	0.945	0.61–1.47	71	0.998	0.61–1.63	5	0.412	0.13–1.35	22	0.976	0.46–2.07	
76.67–83.33	197	186	0.991	0.66–1.48	128	1.014	0.65–1.59	16	0.743	0.29–1.89	38	0.950	0.48–1.89	
>83.33	176	228	1.359	0.91–2.03	155	1.375	0.88–2.15	11	0.571	0.21–1.54	59	1.650	0.85–3.21	
p_{trend}		.035			<.001			.005			<.001			.215
Hip circumference (cm)														
≤86.67	92	99	1	ref	62	1	ref	8	1	ref	29	1	ref	
86.67–93.33	119	123	0.961	0.66–1.40	87	1.085	0.71–1.66	5	0.483	0.15–1.53	27	0.72	0.40–1.30	
93.33–100.00	147	138	0.872	0.61–1.26	98	0.989	0.66–1.49	10	0.782	0.30–2.05	28	0.604	0.34–1.08	
>100.33	173	193	1.037	0.73–1.47	137	1.175	0.79–1.74	14	0.931	0.38–2.30	39	0.715	0.42–1.23	
p_{trend}		.842			<.001			.012			.008			.495
Waist/hip ratio														
≤0.85	241	235	1	ref	173	1	ref	18	1	ref	42	1	ref	
>0.85	290	319	1.128	0.89–1.43	212	1.02	0.78–1.33	19	0.88	0.45–1.71	81	1.6	1.06–2.42	
p_{trend}		—			—			—			—			.120

[a]Test for heterogeneity of p_{trend} values between the three subtypes, calculated using multivariable polytomous logistic regression.
[b]p_{trend} values were carried out by fitting ordinal values corresponding to different categories.
Abbreviations: —, no data; BMI, body mass index; CI, confidence interval; ER, estrogen receptor; ER−, estrogen receptor negative; ER+, estrogen receptor positive; OR, odds ratio; PR, progesterone receptor; PR−, progesterone receptor negative; PR+, progesterone receptor positive; ref, reference category.

showed a stronger relationship with ER+ than ER− breast cancer, whereas data on WHR and WC were not collected. Importantly, a meta-analysis [29] including nine randomized SERM-based trials showed an overall reduction of 38% in the incidence of only ER+ breast cancer, although 42 women needed to be treated to prevent one case of breast cancer over a 10-year follow-up period. These results suggest that it would be preferable to be able to identify individuals at increased risk of ER+ breast cancer, to optimize the benefit-harm balance.

Extensive epidemiological evidence supports a close association between breast cancer and obesity. And with the increasing trends in central obesity among adults with normal BMI [30, 31], especially among Asian women, there have been suggestions that central obesity may play a more important role in breast cancer risk than general obesity [32]. Central obesity, also known as abdominal obesity, is defined as excessive abdominal fat around the stomach and abdomen [32] and is indicated by WHR and WC, compared with general obesity, which is measured by BMI [33].

Body mass index has been the most widely used indicator for studying the association between obesity and breast cancer. Extensive studies in Western countries have revealed positive and inverse associations between BMI and breast cancer among postmenopausal and premenopausal women, respectively. The association between BMI and breast cancer also appeared to be strong among Asian-Pacific women [20], although few Asian studies have been carried out and the results have been inconsistent [34]. In the current study, higher BMI was correlated with an increased risk of breast cancer risk among the overall population and among premenopausal women, but not in postmenopausal women. This was in accord with our previous case-control study based on a cross-sectional epidemiological survey, which also showed a significant relationship between BMI and overall breast cancer risk [28, 35]. Similarly, a dose-response meta-analysis also supported a significant positive association between BMI and premenopausal breast cancer risk [36] among Asian populations. However, another systematic review [20] based on prospective observational studies showed positive associations among both premenopausal (risk ratio [RR] = 1.16, 95% CI: 1.01–1.32) and postmenopausal (RR = 1.31, 95% CI: 1.15–1.48) Asian-Pacific populations, whereas two Japanese cohort studies [37, 38] showed a positive association in postmenopausal women, but no association in premenopausal women.

Kaaks et al. [39] and Mannisto et al. [40] reported that WHR was a more specific indicator of breast cancer risk than BMI, and other studies have shown a similar association in other malignancies, such as prostate cancer [41]. However, although several studies have indicated a relationship between high WHR and increased breast cancer risk [42], the conclusions remain controversial. In the current study, increased WHR was related to elevated breast cancer risk overall and among postmenopausal but not premenopausal women. In contrast, a systematic review and dose-response meta-analysis including 30 studies [36] showed that increased WHR was positively associated with premenopausal breast cancer (RR = 1.08, 95% CI: 1.01–1.16), especially among Asian women (RR = 1.19, 95% CI: 1.15–1.24). Nonetheless, Lahmann et al. [43] and Shin et al. [44] found no significant association between WHR (body size) and breast cancer. Inconsistencies also exist regarding WC. According to our study, WC was positively associated with breast cancer risk overall and among premenopausal women. This was in accordance with Harvie et al. [45], who showed that WC (as well as WHR) was specifically associated with an increased risk of breast cancer among premenopausal women, although this association among postmenopausal women was abolished by adjustment for BMI. However, an updated meta-analysis by Chen et al. [46] suggested that central obesity measured by WC, but not by WHR, was associated with modestly increased risks of both pre- (RR = 1.05, 95% CI: 0.99–1.10) and postmenopausal (RR = 1.06, 95% CI: 1.04–1.09) breast cancer, independent of general obesity.

These apparent discrepancies regarding the effect of body size indicators on breast cancer risk may be partly due to differences in ethnic groups, regions, and study designs, but may also reflect the nature of breast cancer as a sophisticated and heterogeneous disease with a variety of histopathological and molecular classifications. The most widely employed classification, also determined by gene expression profiling [47], was based on ER and PR expression of tumor cells. Epidemiological studies have also indicated that associations between body fat and breast cancer risk may vary according to ER/PR status [48].

Numerous studies have shown that excess endogenous estrogen due to obesity are more closely associated with risk of HR+ than HR− breast cancer [48, 49]. In the present study, higher BMI was related to increased risks of both ER+/PR+ and ER−/PR− breast cancers among the overall and premenopausal populations. However, there was an indication of heterogeneity between the risk estimates for subtypes, indicating a weaker tendency toward an increased risk of ER−/PR− subtypes (48% vs. 68% among overall population, and 105% vs. 121% among premenopausal women), whereas no associations were observed for either subtype among postmenopausal women. This result was consistent with previous studies in demonstrating a stronger association between obesity and ER+/PR+ breast cancer [48, 50]. However, in contrast, most studies also showed a positive association between BMI and ER+/PR+ breast cancer among postmenopausal women, and a negative association among premenopausal women [48]. A pooled analysis of 12 population-based studies [48] showed that a higher BMI in younger women (<50 years old) was correlated with an increased risk of ER+ or PR+ tumors, but not triple-negative tumors. It has been suggested that a higher BMI may increase the levels of serum steroids and reduce the levels of sex hormone-binding globulin [51], resulting in elevated overall levels of bioactivated estrogens, which may in turn promote the development of ER+ breast cancer through binding to ER.

The relationship between WHR and different breast cancer subtypes defined by ER/PR status is also controversial. Waist/hip ratio was positively associated with ER−/PR− breast cancer risk with and without stratification by menopausal status, but not with ER+/PR+ breast cancer risk among the overall or subpopulations, whereas heterogeneity across tumor subtypes was observed in both the overall and stratified analyses. Most previous studies showed that higher WHR contributed to increased risks of different breast cancer subtypes equally [50], although others found no association with any subtype defined by ER/PR status [52]. To exclude any effect of BMI on WHR, we performed a further analysis after adjustment for BMI, and found an equally positive association between WHR and ER−/PR− breast cancer among women with normal BMI compared with overweight and obese women (BMI ≥24.0 kg/m^2;

OR = 1.60, 95% CI: 1.06–2.40 vs. OR = 1.60, 95% CI: 1.06–2.42). However, importantly, the positive associations were still limited to ER−/PR− subtypes. Comprehensive consideration of all these results suggests that the correlation between WHR and ER−/PR− breast cancer should be paid due attention. Waist/hip ratio is also known to be related to increased insulin levels and insulin-like growth factors [53] as well as reduced sex hormone-binding globulin, which may stimulate tumor growth independently of ER/PR mediation. Chronic inflammation and visceral fat-related metabolic abnormalities such as elevated levels of insulin-like growth factor-1 and hyperinsulinemia may also contribute to this association [54–56].

Similar to the risk pattern for BMI, increased WC and body weight both showed close positive associations with ER+/PR+ and ER−/PR− subtypes among overall and premenopausal women. However, unlike BMI, they showed a stronger association with ER−/PR− subtypes. This was in agreement with the findings of Ritte et al. [49] and further supported the importance of central obesity in ER−/PR− breast cancer risk. Further studies are needed to reveal the potential mechanisms responsible for the effects of general and central obesity on breast cancer risk. These mechanisms are currently unclear, and interlinked molecular mechanisms have been supposed to be involved in the pathogenesis [57]. Increased levels of free estrogens due to aromatization of adipose tissue, inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and prostaglandin E2, insulin resistance and hyperactivation of insulin-like growth factors pathways, and adipokines such as adiponectin have all been reported to contribute to carcinogenesis. Furthermore, the differential effect of WHR on ER−/PR− and ER+/PR+ subtypes suggests that the elevated risk of breast cancer associated with central obesity may not be explicable simply by the sex hormone hypothesis.

Increasing evidence suggests that ER+/PR− breast cancer may be etiologically distinct [58]. The current study found few significant results for this specific subtype, except a negative association between WHR and the ER+/PR− subtype amongst premenopausal women. However, the current and previous studies [50] have all had relatively small sample sizes for this subtype, and further studies with larger sample sizes are needed.

To the best of our knowledge, the present study was one of few to focus on the association between body size indicators and breast cancer risk according to joint ER/PR status among Chinese women. Nevertheless, this study had several potential limitations. Firstly, it was a case-control study, and only included body size-related parameters measured at diagnosis, and some measurements such as BMI at young age, weight gain, and hormone replacement therapy were not included for analysis. However, all the indicators reported in this study were recorded by objective measurements rather than by self-reporting, thus avoiding recall errors. Secondly, the sample size of ER+/PR− and ER−/PR+ breast cancer cases was relatively small, thus limiting the statistical power in these two subtypes. However, based on the usual distribution characteristics of ER/PR expression patterns, 112 ER+/PR− cases represents a relatively large sample.

Conclusion

The results of this study revealed that both general and central obesity contributed to breast cancer risk, but with different effects on specific subtypes. General obesity, indicated by BMI, is more strongly associated with ER+/PR+ breast cancer risk, especially among premenopausal women, whereas central obesity, indicated by WHR, is more specific for ER−/PR− breast cancer in both pre- and postmenopausal women. This result reflects the potentially complicated molecular interconnections between obesity, especially central obesity, and breast cancer beyond the effect of estrogens. Importantly, the results suggest that different chemoprevention strategies should be considered in selected individuals.

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Disclosures

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