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EPIDEMIOLOGY

Adult weight change and the risk of pre- and postmenopausal breast cancer in the Chinese Wuxi Exposure and Breast Cancer Study

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Abstract

Purpose The accumulating evidence indicates that weight gain in adulthood is more predictive of breast cancer risk than absolute body weight. However, the relative impact of timing of weight gain in adulthood on breast cancer as well as other characteristics of the association between weight and breast cancer has not been well documented.

Methods This population-based case–control study of breast cancer included 818 patients with newly diagnosed primary breast cancer and 935 residence and age-matched healthy controls. The body weight values at 18 years old, 1 year before diagnosis, and at menopause were obtained during in-person interviews. Unconditional logistic regression was used to estimate the effects of the weight change over adulthood on breast cancer risk. Linear mixed-effects regression was also applied as a secondary analysis.

Results We found that the increased risk of breast cancer was associated with the weight gain in adulthood among postmenopausal women (OR 1.23; 95% CI 1.10–1.37 per 5 kg increase) but not in the premenopausal women. The risk associated with weight gain since menopause (OR 1.65; 95% CI 1.28–2.14 a 5-kg increase) was higher than that from age 18 to menopause (OR 1.14; 95% CI 1.02, 1.28 a 5-kg increase). The association tended to be stronger in those with higher waist circumference and who had never used hormone replacement therapy (HRT). Women who had never used HRT, the increased risk of breast cancer associated with weight gain was more consistent in leaner women at age 18 (BMI < 18.5) or at menopause (BMI < 24).

Conclusions Our findings indicated that weight gain has significant impact on postmenopausal breast cancer risk. The time periods of weight gain, central body fat, and HRT may affect the observed association, which should be further studied.

Keywords Breast cancer · Weight gain · Central obesity · Hormone replacement therapy · Case–control study

Introduction

The role of obesity in the carcinogenesis of breast cancer has been confirmed by many epidemiologic studies, and consistent evidence shows an association between body size and postmenopausal breast cancer [1–5]. Although body mass index (BMI) is the most widely used metric of adiposity in adults, adult weight gain has been suggested to be a better metric because it represents the dynamic pattern of weight trajectory throughout adult life [4]. The World Cancer Research Fund has declared that the long-term adult weight gain could increase the risk of postmenopausal breast cancer, with the estimated relation to independent of dietary intake and physical activity as "probable" [6].

The relationship between adiposity and breast cancer is complex and varies during lifetime. However, most studies investigated the association between long-term weight

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gain and breast cancer risk, and few focused on the relative impact of timing of weight gain in adult life as well as other characteristics of association between the weight and breast cancer [2, 7–9]. Adiposity may reduce the risk of breast cancer, in early reproductive period [10–13], while an increase of the risk was noted after the menopause [13–15]. Understanding the timing of weight gain in relation to risk could provide a comprehensive insight into the mechanism of the observed associations with the breast cancer.

Our study was performed to examine the association of adulthood weight change with pre- and postmenopausal breast cancer in Chinese women, especially the impact of the timing of weight change on postmenopausal breast cancer risk. As some studies suggest, the relationship between weight change and breast cancer is more pronounced present in lean women [8, 12], non-HRT users [16], and central adiposity [17]. We also studied the association of breast cancer risk modified by BMI and HRT, and the interrelationships between central adiposity and weight gain.

Methods

Participants

The Chinese Wuxi Exposure and Breast Cancer Study was a case–control study. We included women who lived in Wuxi city, Jiangsu Province, China for more than 5 years, because the cancer registration system is most complete there. According to this registration system, newly diagnosed breast cancer patients within 1 year were selected as the case group. All cases were identified according to the International Classification of Diseases for Oncology (ICD-10, code C50) and were confirmed by pathology. For those with multiple incident cancers, we included the breast cancer case only if it was the first diagnosed malignancy, and those with secondary or recurrent breast cancer were excluded. Controls were matched to the cases by same residence and age range of 5 years in a ratio of 1:1, excluding individuals with any cancer history. The study protocol was approved by the Institutional Review Boards of Jiangsu CDC, and the informed consents were obtained from all subjects.

Data collection

Data pertaining to study subjects were obtained from a structured questionnaire through in-person interviews conducted by trained interviewers. Subjects were asked to recall their body weight at the age of 18, 1 year before diagnosis of the breast cancer, or 1 year before participating in the study. They were also asked to recall the body weight during menopause. Current height, weight, and central adiposity (waist circumference and hip circumference) of the subjects were measured at the interview according to a standardized protocol. For the analyses reported here, current weight as reported weight 1 year before diagnosis, weight at 1 year before diagnosis, and measured weight were highly correlated ($r = 0.87$) (Figs. 1, 2).

Statistical analysis

The adulthood weight change was calculated as the difference between weight at age 18 and weight 1 year before diagnosis of breast cancer or the interview. Weight changes were also calculated from age 18 to menopause and menopause to 1 year before diagnosis of breast cancer or the interview. All analyses were stratified by menopausal status at diagnosis. Women were considered to be postmenopausal as absence of menstruation in the past 12 months.

Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI). The cutoff for the categorical analyses was derived from the distribution of controls. Quartiles of weight gain were determined as well as another category of women who

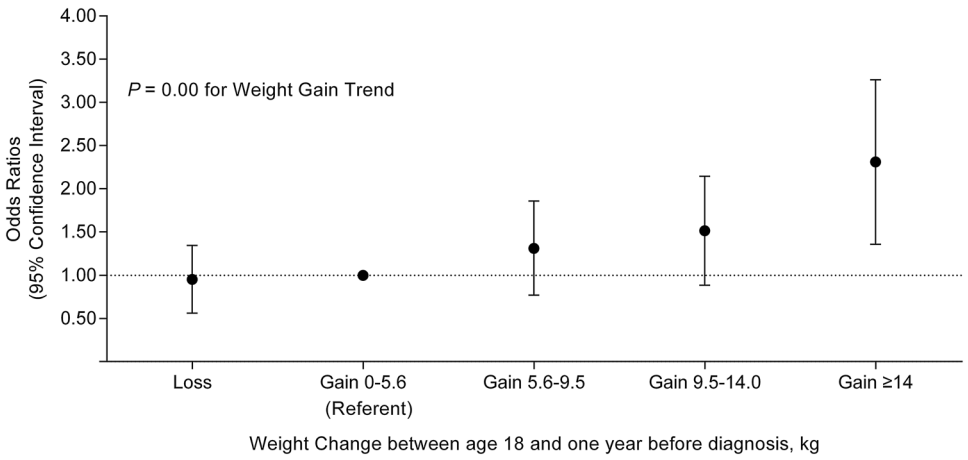

Fig. 1 Risk of Postmenopausal breast cancer according to weight change between age 18 and 1 year before diagnosis

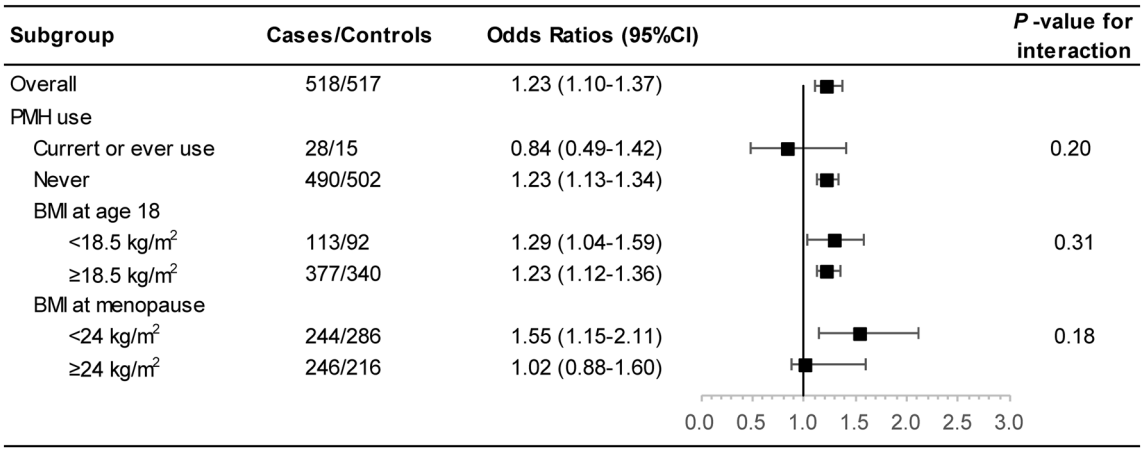

Fig. 2 Risk of Postmenopausal breast cancer among women who have never used HRT according to a 5-kg increase in weight change between age 18 and one year before diagnosis, stratified by BMI at age 18 and menopause

had not gained or who had lost weight during study period. All models were adjusted for age (years), education (illiterate and primary, middle and high school, university and above), age at menarche (years), age at first birth (years), parity (0, 1, 2, or ≥ 3), age at menopause (years), family history of breast cancer (yes: first-degree relative, or no), history of benign breast disease (yes: included lactation mastitis, plasma cell mastitis, cyclomastopathy, fibroadenoma of breast, galactocele, or no), use of HRT (yes: included current use and ever use, or no), use of oral contraceptives (yes: included current use and ever use, or no), alcohol consumption (yes: ≥ 3 day/week, or no), physical activity (MET-hours/week), height (cm), weight at age 18 (kg). The *P* value for trend was determined by the *P* value of the coefficient of the continuous exposure variable, adjusted for covariates and excluding the group of women who had not gained or lost weight. The interaction was calculated using the likelihood ratio test by comparing models with or without an interaction term.

All subjects were included in the primary weight-change analysis, with the missing weight data imputed by using the fully conditional specification Multivariate Imputation by Chained Equations method. In the secondary analysis, the patterns of changes in weight over time were analyzed using mixed-effects linear models with time as a fixed effect and individuals as a random effect. Imputation was not performed for the mixed model because it failed to reach significance by using only completers.

All statistical analyses were conducted using R version 3.3.1 (The R Project for Statistical Computing, China; http://www.r-project.org/). All P values quoted were 2-sided, and less than or equal to 5% were considered as statistically significant.

Results

From November 2013 to November 2014, a total of 1410 newly diagnosed breast cancer cases were identified in Wuxi City, and 818 of them were recruited in this study. A total of 1072 controls were matched to the cases and 935 of them participated in the survey. 46 cases and 56 controls were excluded because of missing information on adjusting covariant variables (Supplemental Fig. 1). No significant difference of the possible covariates was found between the excluded participants and the remained ones. The final results presented here were based on 772 cases and 879 controls who have complete information on all covariates included for adjustment.

The details of the study population have been published previously [18]. Some related demographic characteristics and anthropometric measures of the subjects stratified by menopausal status are presented in Table 1. Among premenopausal participants, the anthropometric measures were not statistically different between cases and controls, with the exception of waist circumference ($P = 0.00$). No difference of weight gain since age 18 was noted between premenopausal cases and controls ($P = 0.88$). Furthermore, we examined premenopausal breast cancer risk associated with the BMI 1 year before diagnosis and weight gain between age 18 and 1 year before diagnosis, and showed no associated risk with the adjusted ORs of 1.14 (95% CI 0.67–1.95, *P* for trend = 0.39 for women in the highest quartile of BMI (> 25.64 kg/m^2) vs. the lowest quartile of BMI (< 21.49 kg/m^2)), and 1.31 (95% CI 0.74–2.33, *P* for trend = 0.18 for women in the highest quartile of the weight gain (> 14 kg) versus women who gained between 0 and 4.6 kg) (Supplement Table 1). Because the association of risk with weight gain was not found among

Table 1 Descriptive characteristics of cases and controls (mean ± standard deviation), stratified by menopausal status

	Premenopausal women ($n=616$)			Postmenopausal women[a] ($n=1035$)		
	Case ($n=254$)	Control ($n=362$)	*P* value	Case ($n=518$)	Control ($n=517$)	*P* value
Age (years)	44.74 ± 5.91	44.96 ± 6.47	0.67	59.78 ± 9.25	61.64 ± 8.39	0.01
Age at menarche (years)	14.95 ± 1.72	14.95 ± 1.66	0.99	15.99 ± 1.85	16.16 ± 1.91	0.16
Age at first live birth (years)	24.26 ± 2.45	24.41 ± 2.07	0.42	24.80 ± 2.84	24.66 ± 2.70	0.41
Parity	1.23 ± 0.46	1.19 ± 0.45	0.21	1.70 ± 0.74	1.78 ± 0.75	0.13
Age at menopause	–	–	–	49.32 ± 4.28	49.57 ± 4.86	0.40
Height (cm)	158.13 ± 5.20	158.70 ± 5.43	0.19	156.31 ± 5.18	155.27 ± 5.24	0.00
Waist circumference (cm)	83.14 ± 9.58	79.80 ± 8.95	0.00	89.52 ± 10.16	85.39 ± 9.70	0.00
BMI 1 year ago (kg/m^2)[b]	23.43 ± 3.08	23.06 ± 2.84	0.13	24.56 ± 3.48	24.06 ± 3.12	0.01
BMI at age 18 (kg/m^2)[b]	20.56 ± 2.66	20.29 ± 3.04	0.25	20.91 ± 3.24	21.14 ± 3.09	0.24
Weight at interview (kg)	60.93 ± 9.67	59.79 ± 8.44	0.12	61.67 ± 8.97	58.91 ± 8.17	0.00
Weight 1 year before diagnosis (kg)	59.18 ± 8.56	58.55 ± 7.72	0.34	60.72 ± 9.10	58.80 ± 8.31	0.00
Weight at age 18 (kg)	52.07 ± 7.34	51.54 ± 8.08	0.41	52.18 ± 8.25	52.38 ± 8.07	0.69
Weight gain since age 18 (kg)	7.11 ± 8.78	7.00 ± 8.62	0.88	8.54 ± 9.78	6.42 ± 9.98	0.00
Breast cancer family history (yes)	13.0%	6.1%	0.00	10.2%	3.9%	0.00
Breast benign disease history (yes)	50.0%	45.9%	0.31	34.6%	23.0%	0.00
Current or ever use of HRT (yes)	5.1%	4.7%	0.81	5.4%	2.9%	0.04
Current or ever of OC (yes)	20.1%	17.1%	0.35	19.9%	18.0%	0.44
Alcohol consumption (yes)	9.4%	13.0%	0.18	6.8%	6.6%	0.91
Physical activity (MET-hours/week)	13.58 ± 12.06	12.93 ± 12.02	0.51	15.20 ± 14.61	15.82 ± 13.64	0.49

BMI body mass index, *METs* metabolic equivalents, *HRT* hormone replacement therapy, *OC* oral contraceptives

[a]Natural menopause or bilateral oophorectomy

[b]Calculated as weight in kilograms divided by height in meters squared

premenopausal women, further analyses were restricted only to the postmenopausal participants.

Selected anthropometric measures of postmenopausal subjects are also shown in Table 1. Generally, anthropometric measures in early adult life, including weight at age 18, and BMI at 18, were not statistically different between cases and controls. However, for the measures in later adulthood, we found positive associations of postmenopausal breast cancer risk with the weight 1 year before diagnosis, and weight and waist circumference at interview. Besides, the correlations between BMI and weight change in different time periods were also examined, and the BMI 1 year before diagnosis was found to be correlated with weight change between age 18 and 1 year before diagnosis, with the correlation coefficients of 0.62 for both indicators (cases and controls).

The risks associated with weight change between age 18 and 1 year before diagnosis for postmenopausal breast cancer are shown in Table 2. An increased risk of breast cancer was found for postmenopausal women who gained more than 14 kg compared with those who gained between 0 and 5.6 kg (OR 2.18; 95% CI 1.43–3.32; for the top quartile vs. the bottom quartile; *P* for trend = 0.00), even after adjusting for weight at age 18. A risk increase of 23% was estimated by every 5 kg increase in the weight between age 18 and 1 year before diagnosis (OR 1.23; 95% CI 1.10–1.37).

In addition, weight changes stratified by the key time points with biological relevance to breast cancer were examined. We found a significant higher positive association of breast cancer risk with weight gain between menopause and 1 year before diagnosis (OR 1.65; 95% CI 1.28–2.14 for each 5 kg increase; $P=0.00$ for trend) than that between age 18 and menopause (OR 1.14; 95% CI 1.02–1.28 a 5-kg increase; $P=0.04$ for trend).

The ORs for risk associated with weight gain between age 18 and 1 year before diagnosis, stratified by the categories defined by the median of waist circumference were also calculated (Table 3). The adult weight gain and central body fat were correlated with each other ($r=0.40$, $P<0.00$). More weight gain was observed for both cases and controls among those with higher central body fat. Adult weight gain was associated with increased risk of breast cancer only among women with waist circumference above the median (OR 1.81; 95% CI 1.01–3.26; for the top quartile vs. the bottom quartile). There was an obvious monotonic risk increase of the breast cancer in the group of women with waist circumference above the median ($P=0.04$ for trend), while no association was found between breast cancer risk and those

Table 2 Risk of postmenopausal breast cancer according to weight change during key time periods with and without adjustment for weight at age 18 for adult lifetime weight gain

	Cases (%)	Controls (%)	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Weight change: from age 18 to 1 year before diagnosis ($n=518$ for cases; $n=517$ for controls)				
≤0	94 (18.1)	133 (25.7)	0.95 (0.63–1.42)	0.90 (0.59–1.37)
0–5.6	82 (15.8)	102 (19.7)	1.00	1.00
5.7–9.5	90 (17.4)	94 (18.2)	1.22 (0.80–1.85)	1.24 (0.81–1.89)
9.6–14.0	102 (19.7)	95 (18.4)	1.38 (0.91–2.10)	1.43 (0.93–2.18)
>14.0	150 (29.0)	93 (18.0)	2.05 (1.37–3.06)	2.18 (1.43–3.32)
P trend[c]			0.00	0.00
Per 5 kg			1.21 (1.10–1.34)	1.23 (1.10–1.37)
Weight change: from age 18 to menopause ($n=518$ for cases; $n=517$ for controls)				
≤0	109 (10.5)	141 (27.3)	0.93 (0.64–1.35)	0.93 (0.63–1.38)
0–5.0	112 (21.6)	122 (23.6)	1.00	1.00
5.1–8.0	59 (11.4)	58 (11.2)	1.16 (0.73–1.84)	1.16 (0.73–1.84)
8.1–13.0	115 (22.2)	95 (18.4)	1.39 (0.94–2.04)	1.38 (0.94–2.05)
>13.0	123 (23.7)	101 (19.5)	1.47 (1.00-2.16)	1.47 (0.99–2.18)
P trend[c]			0.03	0.04
Per 5 kg			1.15 (1.03–1.28)	1.14 (1.02–1.28)
Weight change: from age menopause to 1 year before diagnosis ($n=518$ for cases; $n=517$ for controls)				
≤0	239 (46.1)	280 (54.2)	0.89 (0.61–1.29)	0.88 (0.61–1.28)
0–2.0	75 (14.5)	76 (14.7)	1.00	1.00
2.1–4.0	56 (10.8)	72 (13.9)	0.70 (0.43–1.14)	0.70 (0.43–1.14)
4.1–6.0	57 (11.0)	52 (10.1)	1.06 (0.64–1.76)	1.07 (0.64–1.78)
>6.0	91 (17.6)	37 (7.2)	2.35 (1.40–3.93)	2.38 (1.43–3.98)
P trend[c]			0.00	0.00
Per 5 kg			1.70 (1.31–2.19)	1.65 (1.28–2.14)

[a]Adjusted for age, education, age at menarche, age at first birth, parity, age at menopause, family history of breast cancer, previous benign breast disease, use of hormone replacement therapy, use of oral contraceptives, alcohol consumption, physical activity, height

[b]Adjusted for all of above plus weight at age 18

[c]Excluding the group of women who had lost weight

with waist circumference below the median (P)($P=0.79$ for trend).

Finally, we evaluated whether the association of weight gain with risk was different in women receiving HRT (Table 3). While the weight change was not associated with breast cancer risk among women who current or ever received of HRT, the adult weight gain was strongly associated with increased risk of breast cancer among women who never use of HRT ($P=0.00$).

For women who had never received HRT, the breast cancer risk associated with each 5 kg gain between age 18 and one year before diagnosis was significant among women who were lean at age 18 (BMI < 18.5; OR 1.29; 95% CI 1.04–1.59). Although the interaction between BMI at age 18 and the later weight change was not significant ($P=0.31$), the weight gain still significantly associated with higher risk of breast cancer among heavier women with a BMI≥ 18.5 at age 18 (OR 1.23; 95% CI 1.21–1.36). Moreover, we found a stronger association between weight gain and breast cancer risk among women who were leaner at menopause with BMI < 24 (OR 1.55; 95% CI 1.15–2.11), while there was no association among those with BMI≥24 (OR 1.02; 95% CI 0.88–1.60).

The secondary analysis based on linear mixed-effects regression models showed similar results with the primary weight-change analysis. A long-term weight gain from age 18–1 year before diagnosis was associated with postmenopausal breast cancer risk ($P=0.01$). Moreover, the Liner mixed model output illustrated that the growth rate of weight gain in the case group was significantly higher than that in the control group (Supplement Table 2).

Discussion

In this case–control study in Chinese women, we found that increased risk of breast cancer was associated with the adulthood weight gain among postmenopausal women, and there was a tendency of a stronger association for those with central obesity, or with weight gain during periods of hormonal

Table 3 Risk of Postmenopausal breast cancer according to weight change between age 18 and 1 year before diagnosis, stratified by waist circumference and HRT use

Weight change (kg)	Below median (< 88 cm)[c]			Below median (≥88 cm)[c]		
	Cases (%)	Controls (%)	Adjusted OR[a] (95% CI)	Cases (%)	Controls (%)	Adjusted OR[a] (95% CI)
≤0	44 (26.7)	92 (35.1)	0.88 (0.48–1.60)	48 (13.9)	41 (16.1)	1.40 (0.72–2.73)
0-5.6	38 (23.0)	58 (22.1)	1.00	44 (12.8)	44 (17.3)	1.00
5.7–9.5	35 (21.2)	46 (17.6)	1.11 (0.59–2.09)	53 (15.4)	48 (18.8)	1.00 (0.55–1.84)
9.6–14	29 (17.6)	42 (16.0)	0.98 (0.51–1.91)	71 (20.6)	53 (20.8)	1.36 (0.75–2.47)
> 14	19 (11.5)	24 (9.2)	1.05 (0.48–2.32)	129 (37.4)	69 (27.1)	1.81 (1.01–3.26)
P trend[b]			0.79			0.04
Per 5 kg			1.11 (0.88–1.39)			1.14 (0.99–1.31)
Weight change (kg)	Current or ever use of HRT[d]			Never use of HRT[d]		
	Cases (%)	Controls (%)	Adjusted OR[a] (95% CI)	Cases (%)	Controls (%)	Adjusted OR[a] (95% CI)
≤0	7 (25.0)	4 (26.7)	2.11 (0.11–39.98)	87 (17.8)	129 (25.7)	0.90 (0.58–1.39)
0–5.6	7 (25.0)	3 (20.0)	1.00	75 (15.3)	99 (19.7)	1.00
5.7–9.5	5 (17.9)	3 (20.0)	3.70 (0.08–163.07)	85 (17.3)	91 (18.1)	1.26 (0.82–1.95)
9.6–14	4 (14.3)	2 (13.3)	0.43 (0.03–7.32)	98 (20.0)	93 (18.5)	1.48 (0.96–2.28)
> 14	5 (17.9)	3 (20.0)	1.74 (0.10–30.12)	145 (29.6)	90 (17.9)	2.29 (1.49–3.53)
P trend[b]			0.95			0.00
Per 5 kg			0.80 (0.30–2.13)			1.24 (1.11–1.39)

[a]Adjusted for age, education, age at menarche, age at first birth, parity, age at menopause, family history of breast cancer, previous benign breast disease, use of hormone replacement therapy, use of oral contraceptives, alcohol consumption, physical activity, height, weight at age 18

[b]Excluding the group of women who had lost weight

[c]$P = 0.08$ for interaction waist circumference * weight change between age 18 and one year before diagnosis

[d]$P = 0.20$ for HRT use * weight change between age 18 and 1 year before diagnosis

change. Among women who never used HRT, stronger associations with risk were found in those who were lean at early adult life or at menopause. And a secondary analysis based on mixed-effects linear models as a cross validation with our primary analysis indicated that the growth rate of weight gain between cases and the controls was significantly different in adulthood.

The observed increased risk associated with weight gain since age 18 year among all postmenopausal women in our study was consistent with previously reported cohort or case–control studies [2, 7, 11, 16]. Our findings of significant increased risks with weight gains both before and after menopause were also in line with other studies with time-period analyses [16, 17].

Considering that BMI does not distinguish fat mass from lean body mass or apple- from pear-shaped body, adult weight gain could be a better indicator for reflecting amount and distribution of adiposity and be a more sensitive predictor of disease risk [4]. We found a statistically significant linear trend persisted for adult weight gain but not for BMI, which suggested that adult weight gain might lead to a higher risk beyond attained adiposity. The better predictability of adult weight gain compared with BMI also suggested that the excess adiposity may exert a continuous and cumulative influence on carcinogenesis throughout the adulthood for women [4].

The biological mechanism of the risks of these cancers affected by excess adiposity may involve several factors, such as estrogens, insulin, and bioavailable insulin resistance and the insulin-like growth factor (IGF)-1 system [19]. Excess adiposity, particularly abdominal adiposity, could result in hormonal and metabolic perturbations by producing estrogen (estrone) through the aromatization of androgen (androstenedione) and inducing insulin resistance, the resulting hyperinsulinemia of which suppresses hepatic production of hormonal binding proteins (e.g., SHBG, IGFBP) [20]. Thus, the net consequences of excess adiposity might involve the increased circulating concentrations of total/bioavailable estrogens, insulin, and bioavailable IGF-I [20]. Thus, insulin and bioavailable IGF-1 promote carcinogenesis by enhancing proliferation of the tissues and inhibiting apoptosis.

With regard to the effects of menopausal status on breast cancer risks, the null finding for premenopausal breast cancer might be explained by the following biological mechanisms: in the premenopausal period when the ovaries are a predominant site of estrogen synthesis, additional contribution of adipocytes to the circulating pool of estrogens (i.e.,

estrone, estradiol, estriol) may be negligible. Not only the amount of estrogens from adipocytes is far smaller, but also the form of estrogens (i.e., estrone rather than estradiol) is less biologically potent [21].

The timing of weight gain may have different effects on the location of fat disposition [17]. However, timing of weight gain has not been generally addressed adequately in previous studies on the association between weight change and breast cancer. Our results suggested that such timing may provide a clue on etiologic role of adult weigh gain in relation to breast cancer risk. There was evidence which suggested that menopause-related changes in fat distribution caused fats redistribution toward the abdominal region with a preferential increase in visceral fat after menopause [22]. As the hormonal and metabolic perturbations could be induced by abdominal adiposity [20], the adverse effect of adult weight gain on breast cancer may be much weaker during the premenopausal period than that in the postmenopausal period. These lines of evidence could support our finding of a stronger positive association with risk for weight gain during the time periods of post-menopause in this study.

In addition, greater central adiposity may also reflect differences in steroid hormones including testosterone in women [23, 24]. We performed a stratified analysis of central obesity and found that only among women with greater central adipose the weight gain was associated with the increased breast cancer risk, which indicated that central adipose tissue is more metabolically active than peripheral adipose [25].Our findings are consistent with most previously published studies of central adiposity and postmenopausal breast cancer risks [26–29], but not all studies had similar conclusions [1, 30]. In addition, Waist–hip ratio was commonly used for the measurement of central adiposity, but some recent studies used waist circumference instead and found that waist circumference might be a stronger predictor of breast cancer risk than waist-to-hip ratio [25, 26]. However, the mechanism for these findings is not very clearly known; weight gain may be an indicator of hormonal environment and affect energy balance at the key time point.

For breast cancer, the observed heterogeneity of risks affected by menopausal status and HRT use was particularly important, as it hinted at relative contributions of estrogens, progesterone, insulin, and IFG-1 in mediating the association. Similar to other studies [16, 31], we found that weight gain was only associated with breast cancer risk among women who had never used HRT. During the postmenopausal period, estrogens appear to be a dominant driver of breast cancer risk. In the absence of excess estrogens from the ovaries and HRT, variation in estrogen levels because of difference in the amount of adipocytes may be sufficient enough to differentiate the risk of breast cancer. In contrast, for HRT users, the HRT use itself could be an independent risk factor for breast cancer [31, 32]; exogenous estrogens from HRT may raise plasma estrogens to the extent that endogenous estrogens from adipocytes have little incremental effect [33]. Thus, the association between weight change and breast cancer could not be clearly observed in women who received HRT.

Furthermore, among women who never use HRT, we observed stronger associations of breast cancer risk with weight gain in both time periods among women who were lean at age 18 and at menopause. The hypothesis was that weight during young adulthood may influence breast cancer risk after menopause, possibly due to slower pubertal growth or a greater likelihood of irregular menstrual cycles and ovulatory infertility in adulthood [34], which were also supported by several epidemiological studies [10–12, 30, 35]. The interaction between BMI at age 18 and weight change likely reflects the fact that women who were lean at age 18 do not benefit from earlier weight that is ultimately protective [36, 37]. The increased association with breast cancer risk among leaner women at menopause may partially be explained by the declining of ovarian hormone production after menopause and adipose tissue becomes the primary estrogen source by aromatization of adrenal androgens [38, 39]. Compared with normal weight postmenopausal women, those with higher BMI have twofold higher circulating estrogens [14, 23, 40, 41] and lower sex hormone–binding globulin levels [23, 42], and thus more bioavailable estrogens. However, associations did not vary across levels of BMI in a few other studies [2, 43].

Strengths of our population-based case–control study included that the determination of postmenopausal status and the assessment of adult weight change at key time periods of the subjects. We were able to assess various indicators of weight change and central adiposity, especially the hormonal changes during different periods in a woman's life, and to assess effect modification of this association by stratifying the use of HRT. Although weight can reflect both lean body mass and adipose tissue, weight gain after young adulthood is more likely to reflect a gain in adipose tissue [44].

Several limitations of this work should be noted. Firstly, the self-reported weight may be affected by recall and response bias. But since the cases and the controls were not aware of the specific objectives of the collection of these information and the possible link between weight change and breast cancer risk, these bias may not be significant. Secondly, we were concerned that for cases the current measured weight might be affected by their disease or the treatment. However, the reported weight one year before diagnosis showed a high correlation with measured weight at the time of interview (0.92 and 0.91 for cases and controls, respectively). In addition, our study involved women in a single area of China, which may limit the generalization of the findings. Therefore, more studies are needed to corroborate our findings before the firm conclusions can be drawn.

This study found that an increased risk of breast cancer was associated with adult weight gain among postmenopausal women, and there was a stronger association for those with higher waist circumference, who never used HRT, or with weight gain during periods of hormonal change. The timing of adult weight gain was found to be of importance in relation to breast cancer risk. However, the interplay between times of hormonal changes and the central adiposity appears to be complex, which should be further evaluated in other research settings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This study was approved by the ethical review committee of the Jiangsu Center for DiseaseControl and Prevention (Jiangsu, China).

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