Cancer Biol Med 2024. doi: 10.20892/j.issn.2095-3941.2024.0172

LETTER

Weight gain after 35 years of age is associated with increased breast cancer risk: findings from a large prospective cohort study

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Adiposity affects lifetime estrogen exposure, which is a key factor in breast carcinogenesis. However, adiposity effects, often assessed as the body mass index (BMI), on pre- and post-menopausal breast cancer risk are paradoxical. Body weight gain may reflect body fat mass accumulation during adulthood better than the BMI, potentially representing age-related metabolic changes[1]. Therefore, weight gain at specific hormone-related stages given by early or late reproductive and menopausal years may have different effects on breast cancer risk. However, research on whether the timing of weight gain influences the relationship between body fat and breast cancer risk is limited, inconclusive, and most often based on Western populations. Therefore, we conducted a prospective study to evaluate the association between weight change throughout distinct lifetime periods and breast cancer risk stratified by menopausal status.

During a median follow-up duration of 9.2 years, we prospectively followed 73,192 Korean women (40–69 years of age) from the 2004–2013 population-based Health Examinees-Gem Study (HEXA-G)[2]. Weight at recruitment and self-reported weights at 18–20, 35, and 50 years of age were used to calculate weight change across 5 lifetime periods based on data availability. Weight change was assessed with respect to absolute total weight and calculated by subtracting the weight at the earlier age from the weight at the later age. Additionally, the annual average weight change rate was calculated. Cox regression was used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for breast cancer risk using age as the time scale. The follow-up evaluations were completed for all participants until 31 December 2018. The study flow chart, study population, breast cancer ascertainment, and statistical analysis methods are detailed in the **Supplementary material**.

The study protocol and procedures were approved by the Institutional Review Board (IRB) of the Seoul National University Hospital in Seoul, Korea (IRB No. E-2009-117-1159) and the Korea National Institute of Health (IRB No. 2014-08-02-3C-A). Written informed consent was obtained from all participants. The approved research was performed in accordance with relevant guidelines and regulations established by the Ethics Committee of the Korean National Institute of Health and the Helsinki Declaration of the World Medical Association.

Weight gain after 35 years of age

Among 66,870 women (611,139 person-years) with information on weight at 35 years of age, 790 new breast cancer cases were identified. Of the 66,870 women, 10.72% had weight loss, 32.68%

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Received May 15, 2024; accepted August 1, 2024.
Available at www.cancerbiomed.org

maintained a stable weight, and 35.92% gained > 5.0 kg. Women who gained more weight since middle adulthood tended to give birth earlier, were more likely to breastfeed, had a higher proportion of ever-smokers, were less physically active, and consumed more total calories per day compared to women in the lowest weight gain group (**Table S1**).

Women who gained > 10 kg after 35 years of age was associated with an increased risk of breast cancer compared to women with stable weight [± 2.5 kg] (HR, 1.41; 95% CI, 1.02–1.96; P_{trend} = 0.02; **Figure 1**). Gaining 5–9.9 kg after 35 years of age increased the risk of breast cancer among premenopausal women by 89% (HR, 1.89; 95% CI, 1.35–2.67) and gaining ≥ 10 kg increased the risk of breast cancer among premenopausal women by 2.23-fold (HR, 2.23; 95% CI, 1.27–3.91) with a dose-response effect (P_{trend} < 0.01; **Figure 2** and **Table S2**).

When a linear weight increment was assumed, women who gained > 0.75 kg per year after 35 years of age had a 35% higher risk of breast cancer (HR, 1.35; 95% CI, 1.01–1.82; P_{trend} = 0.02), but no associations were detected based on menopausal status (**Table S3**). However, a V-shaped relationship was observed between weight change rate after 35 years of age and premenopausal breast cancer risk, with the highest risk occurring in women who gained weight at a rate of 0.25–0.49 kg/year (HR, 1.29; 95% CI, 0.94–1.77; $P_{non\text{-}linear}$ = 0.03; **Table S3**). Although the rate of weight gain was associated with an overall increased breast cancer risk, it was not directly linked to increased premenopausal breast cancer. However, the association should not be disregarded. While absolute values showed the actual amount of weight gain, the average weight change rate assumed linearity and allowed time comparisons. Therefore, the timeframe studied influenced the average weight change rate, which may mask notable weight fluctuations and cause non-linear changes. The absence of a clear association suggests that the relationship between weight over time and breast cancer is complex, involving multiple factors. Conversely, the positive correlation between total weight change and cancer risk emphasizes the relevance of long-term weight variation, potentially through cumulative effects on biological processes.

Thirty-five years of age was considered a cut-off point for late reproductive years because evidence worldwide suggests that women who become pregnant after this age are at an increased risk of complications during pregnancy, even in healthy individuals. Women who had their first pregnancy after 25 years of age and gained weight had an increased risk of breast cancer (HR, 1.93; 95% CI, 1.26–2.93; $P_{trend} \leq 0.01$; **Table S4**). Although the median age for the first pregnancy was 25 years in this cohort, by 35 years of age most women may have experienced pregnancy, motherhood, marriage, or cohabiting, all of which potentially influence weight

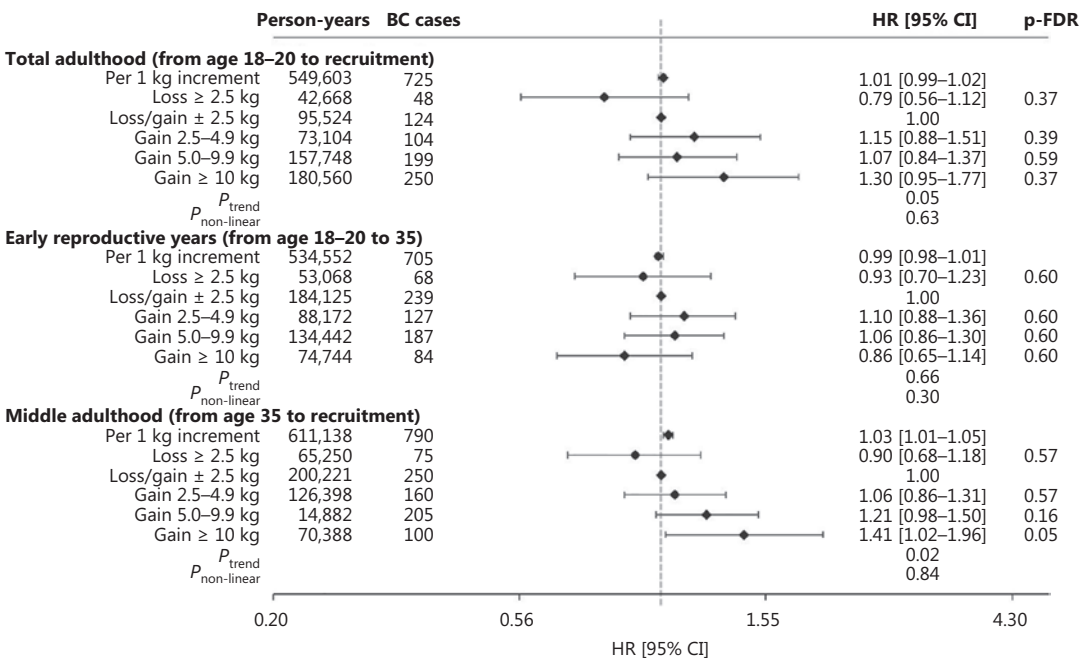

Figure 1 Weight change and breast cancer risk.

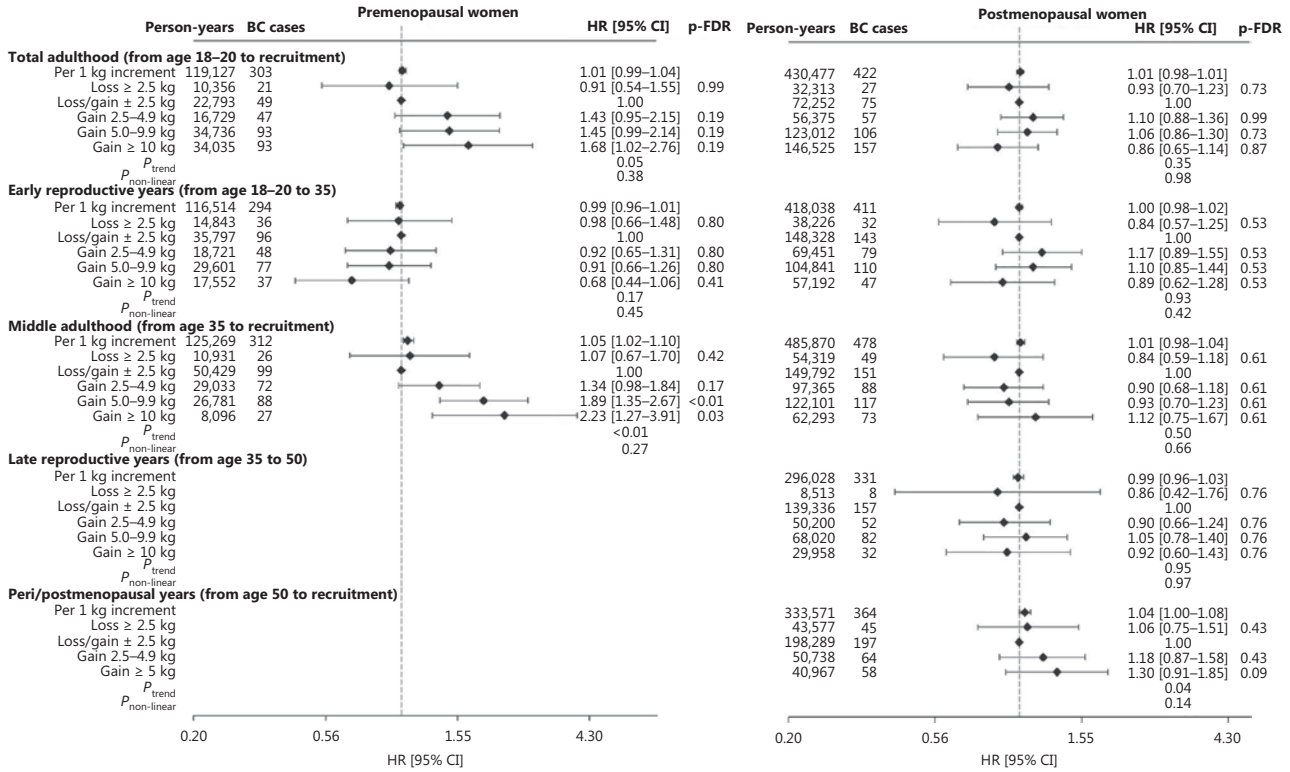

Figure 2 Weight change by menopausal status.

fluctuations[3]. We also noted that breast cancer risk with increased weight was higher in lean women in their 30s (HR, 1.85; 95% CI, 1.27–2.70; P_{trend} = 0.01) and in women with abdominal obesity (HR, 2.09; 95% CI, 1.33–3.29; P_{trend} < 0.01) and high daily calorie intake (HR, 2.67; 95% CI, 1.69–4.22; P_{trend} < 0.01; **Table S4**). These findings suggest the importance of fat distribution and the harmful effects of weight gain, especially in lean women. Women store fat in subcutaneous and gluteo-femoral regions during the reproductive years. However, as women age, there is a shift towards visceral adipose tissue accumulation, leading to metabolic disturbances and the creation of a low-grade inflammatory microenvironment[4]. Adipose tissue in premenopausal women produces and stores active estrogens, with estrone being more prominent in fat deposits. Estrone has been linked to adiposity-related inflammation and function in conjunction with nuclear factor-κB (NFκB) to trigger an inflammatory pathway, highlighting the impact of estrone and estradiol balance on breast cancer development[5]. While being overweight or obese during childhood and adolescence may reduce breast cancer risk by promoting early breast tissue differentiation and increased tumor suppressor gene expression, hormonal changes that might begin in regularly menstruating women after their mid-30s, including erratically higher estradiol levels, decreased progesterone levels, a shortened luteal phase, anovulatory cycles, and disrupted ovarian-pituitary-hypothalamic feedback[6], along with the role of adipose-derived estrogens, may increase breast cancer risk. Although evidence supports an inverse association between being overweight/obese and premenopausal breast cancer[7], this protective effect has mainly been observed in premenopausal Caucasian women[8-10]. However, being overweight or obese remained a risk factor for premenopausal breast cancer among Asian women[8,10]. This finding suggests that excess adiposity may have different effects on women of Asian ethnicities.

Our findings align with previous studies. The European EPIC-PANACEA study showed a positive association between weight gain in middle adulthood and breast cancer diagnosed at ≤ 50 years of age (HR, 1.37; 95% CI, 1.02–1.85)[11]. The Nurses' Health Study reported a positive association between short-term (4 y) weight gain and breast cancer for premenopausal women [relative risk (RR), 1.38; 95% CI, 1.13–1.69][12]. Inconclusive findings were reported from the Premenopausal

Breast Cancer Collaborative Group for weight gain between 35–44 and 45–54 years of age (HR, 0.92; 95% CI, 0.77–1.10)[13]. Inconsistent findings were attributed to methodologic differences, time intervals between weight assessments, age ranges, and cohort heterogeneity. Further research is warranted to replicate our findings and elucidate the mechanisms behind the association between weight gain during this period and breast cancer risk.

Weight gain after 50 years of age

The current study, which included 37,909 women (333,571 person-years) with 364 recorded cases of breast cancer, showed a positive trend association between weight gain in the peri- and post-menopausal age and postmenopausal breast cancer (P_{trend} = 0.04; **Figure 2** and **Table S2**). Postmenopausal women who gained > 0.75 kg/year after 50 years of age had a 42% increased risk of breast cancer (HR, 1.42; 95% CI, 1.01–2.00; P_{trend} = 0.04; **Table S2**) and those women who also had abdominal obesity (HR, 1.54; 95% CI, 1.05–2.26; P_{trend} = 0.02) were at a higher risk (**Table S5**). This finding aligns with previous research in Western populations[14-16]. Adipose-derived estrogens become more important in estrogen production as gonadal estrogen declines during the peri- and postmenopausal period. Excess adipose tissue triggers aromatase production, leading to an imbalance in adipokines, increased inflammatory cytokines, and dysregulation of estrogen signaling. These disruptions can lead to DNA damage, genome instability, and apoptosis inhibition[17].

Despite the large sample size from a large prospective cohort, accurate cancer diagnoses, a follow-up duration of nearly 10 years, and weight information over time, we acknowledge some limitations to the current study. Recall bias and misclassification may have occurred due to self-reported weight and the lack of information on menopausal status at the time of breast cancer diagnosis. However, these limitations were addressed by sensitivity analysis, such as the exclusion of extreme weight values and daily calorie intake, by varying the definition of pre- and post-menopausal status, and by excluding individuals with < 2 y of follow-up evaluations. These analyses yielded similar associations with breast cancer as observed overall (**Tables S6-S9**). Information on breast cancer subtypes, intentional weight loss, and changes in lifestyle factors over time were not available. Despite controlling for various variables, some residual confounding may still be present. Furthermore, although there may be some indications of trends or associations between weight gain in certain age groups and breast cancer risk, some of these associations were marginally significant and some were not consistently signifi cant across different periods and menopausal statuses. This inconsistency suggests that there may not be enough robust data to firmly establish a clear link between weight change in some lifetime periods and breast cancer risk. Additionally, our findings are specific to Korean women and may not apply to other populations. Further research with larger and more diverse samples is needed to replicate and determine the generalizability of these results.

Overall, our findings suggest that weight gain in women in their 30s and 50s could have a significant role in breast cancer prevention. It is important to consider the current changing trends in delaying childbearing, which may influence the timing of weight gain, potentially impacting breast cancer incidence in the ensuing years. Therefore, additional studies focusing on these specific periods are warranted to better understand the potential relationship. Our findings suggest a lag period between weight gain and the effect on breast cancer risk and emphasize the need for weight management starting in early mid-adulthood to reduce breast cancer risk. The implications of these findings may influence public health recommendations and programs, promoting weight loss in overweight and obese young women and weight maintenance in young and lean women for breast cancer prevention.

Grant support

This work was supported by the Research Program funded by the Korea Centers for Disease Control and Prevention (Grant Nos. 2004-E71004-00; 2005-E71011-00; 2005-E71009-00; 2006-E71001-00; 2006-E71004-00; 2006-E71010-00; 2006E71003-00; 2007-E71004-00; 2007-E71006-00; 2008-E7100600; 2008-E71008-00; 2009-E71009-00; 2010-E71006-00; 2011E71006-00; 2012-E71001-00; 2013-E71009-00).

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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Data availability statement

Raw data for this study came from the Health Examinees (HEXA) study as part of the Korean Genome and Epidemiology Study (KoGES), conducted by the Korea Disease Control and Prevention Agency (KDCA; formerly Korea Centers for Disease Control and Prevention), Republic of Korea. The Korea Central Cancer Registry (KCCR) data is provisioned by the KDCA in cooperation with the National Cancer Center of Korea as a part of the KoGES. The dataset used for the analysis in this study is maintained and managed by the Division of Population Health Research at the National Institute of Health, which is a part of the Korea Disease Control and Prevention Agency. The Health Examinees Study dataset has been merged with the cancer registry data provided by National Cancer Center of Korea in a collaborative agreement. The data generated in this study are not publicly available due to the inclusion of personal data that may potentially be sensitive to the patients, even though researchers are provided with an anonymized dataset that excludes resident registration numbers. Derived data supporting the findings of this study are available from the corresponding author upon request.

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Cite this article as: De la Torre K, Shin W, Lee H, Huang D, Min S, Shin A, et al. Weight gain after 35 years of age is associated with increased breast cancer risk: findings from a large prospective cohort study. Cancer Biol Med. 2024; 21: 651-655. doi: 10.20892/j.issn.2095-3941.2024.0172