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► **To cite this version:**

Alina Vrieling, Katharina Buck, Rudolf Kaaks, Jenny Chang-Claude. Adult weight gain in relation to breast cancer risk by estrogen and progesterone receptor status: a meta-analysis. *Breast Cancer Research and Treatment*, 2010, 123 (3), pp.641-649. 10.1007/s10549-010-1116-4 . hal-00565900

HAL Id: hal-00565900

<https://hal.science/hal-00565900>

Submitted on 15 Feb 2011

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**Adult Weight Gain in Relation to Breast Cancer Risk by Estrogen and Progesterone Receptor Status:
a Meta-Analysis**

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Key words: adult weight gain; breast cancer; estrogen receptor; progesterone receptor; meta-analysis

Word count abstract: 250
Word count text: 2824

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ABSTRACT

Purpose: Adult weight gain is positively associated with postmenopausal breast cancer and inversely associated with premenopausal breast cancer risk. To date, no meta-analysis has been conducted to assess this association by estrogen receptor (ER) and progesterone receptor (PR) status.

Methods: We searched PubMed for relevant studies published through March 2010. Summarized risk estimates (RE) with 95% confidence intervals (CIs) were calculated using random effects or fixed effects models.

Results: We retrieved nine articles on weight gain from adulthood to reference age and ER and/or PR defined breast cancer risk, reporting on three prospective cohort studies and eight case-control studies. Comparing the highest versus the lowest categories of adult weight gain, risk was increased for ER⁺PR⁺ and ER⁺ tumors combined (11 studies; RE = 2.03, 95% CI = 1.62, 2.45). Statistically significant heterogeneity ($p_{\text{heterogeneity}} = 0.002$) was shown between risk estimates for a mixed population of pre- and postmenopausal women combined (4 studies; RE = 1.54, 95% CI = 0.86, 2.22) and for postmenopausal women only (7 studies; RE = 2.33; 95% CI = 2.05, 2.60). Risk for ER⁻PR⁻ tumors among postmenopausal women was also slightly increased (7 studies, RE = 1.34, 95% CI = 1.06, 1.63), but statistically significantly different from risk for ER⁺PR⁺ tumors ($p_{\text{heterogeneity}} < 0.0001$). No associations were observed for ER⁺PR⁻ tumors whereas risk for ER⁻PR⁺ tumors could not be assessed.

Conclusion: The association between adult weight gain and postmenopausal breast cancer risk is heterogeneous according to ER/PR status and stronger for ER⁺PR⁺ than for ER⁻PR⁻ tumors.

INTRODUCTION

Body weight is an established risk factor for postmenopausal breast cancer whereas it is inversely associated with premenopausal breast cancer risk (1). This may be due to differential effects of obesity on circulating endogenous estrogen levels according to menopausal status [2]. In postmenopausal women, estrogen is mainly synthesized by adipose tissue. Fatter women have larger adipose stores than leaner women, resulting in higher circulating levels of estrogen and lower levels of sex hormone-binding globulin (SHBG). In premenopausal women, estrogens mainly originate from ovarian synthesis, and levels are much higher than after menopause. However, overweight or obese premenopausal women are more likely to have anovulatory cycles and a greater clearance rate of estrogens by the liver compared to normal-weight women, resulting in lower levels of circulating estrogen and progesterone.

A recent meta-analysis has shown that the association between body mass index (BMI) and breast cancer risk is also heterogeneous according to estrogen receptor (ER) and progesterone receptor (PR) status [3]. Higher BMI was associated with higher risk for ER⁺PR⁺ tumors in postmenopausal women but had a protective effect on ER⁺PR⁺ tumors in premenopausal women. By contrast, no associations were observed for ER⁻PR⁻ tumors.

Adult weight gain is thought to be a better measure to assess adiposity and its metabolic consequences than BMI [4]. BMI reflects both lean and fat mass whereas adult weight gain largely reflects an increase in body fat independent of BMI [4]. Several studies examining both adult weight gain and adult BMI in the same study population have found weight gain to be an equivalent [5, 6] or stronger [4, 7-10]

predictor of postmenopausal breast cancer risk than recent BMI. Adult weight gain has been inversely associated with premenopausal breast cancer risk [11].

Ten studies have investigated the association between adult weight gain and breast cancer risk according to ER/PR status of the tumor [12-21], and no systematic review or meta-analysis has been conducted thus far. Results of these studies were inconsistent, however, a limitation was that the number of non-ER⁺PR⁺ tumors in individual studies was mostly small and comparisons for these groups were likely to be underpowered. Therefore, the aim of this meta-analysis was to investigate whether the association between adult weight gain and breast cancer risk differed according to ER/PR status of the tumor.

MATERIALS AND METHODS

Selection of studies

A systematic PUBMED search was performed to identify epidemiologic studies published through March 2010 that reported on the association between adult weight gain and risk for breast cancer defined by ER/PR status. We used a combination of the Medical Subject Headings (i.e., breast neoplasms, body weight, body mass index, estrogen receptors, progesterone receptors) and also searched for related key words in title and abstract. The query retrieved 899 articles. In addition, cited references in retrieved articles were reviewed to identify possible further articles that may have been missed in this search. Eligible publications were assessed independently by two reviewers (AV, KB). Studies were included in the meta-analysis if they presented data from a prospective cohort or case-control study on the association between adult weight gain and ER and/or PR defined breast

cancer risk. Studies that did not provide risk estimates (REs) for quantiles of adult weight gain were excluded.

Data extraction and classification

From each publication, we extracted the following information: the name of the first author, the year of publication, the country where the study was conducted, the major ER/PR assay, the name of the cohort study / the type of case-control study, years of follow-up (cohort studies), years of data collection (case-control studies), the number of overall cases, the study size (cohort studies), the number of controls (case-control studies), age, menopausal status, the weight gain categories studied, the effect estimates, and the adjusted factors. Relative risks or odds ratios and 95% confidence intervals (CI) from regression models were extracted and used for the subsequent analyses. The most fully adjusted risk estimates (REs) and confidence intervals for the highest quantile compared to the lowest quantile from each study were used for the meta-analyses. From the REs, the standard error of the estimate (SEE) was directly derived as $SEE = [\log(95\% \text{ CI, upper limit}) - \log(95\% \text{ CI, lower limit})] / 3.92$ and was employed in the calculation of the pooled estimates.

Statistical analysis

All analyses were carried out using the “meta” and “rmeta” packages of the statistical software environment R (version 2.7.1) [22]. The statistical analyses included a test of heterogeneity to determine whether the study results (of groups) were significantly heterogeneous. The correct model for the combination of single study results to a common pooled estimate could thereby be determined. Several

statistical and quantifying measurements were used to assess heterogeneity of a set of point estimates together with the respective standard errors, i.e., the τ^2 heterogeneity estimator, the Q statistic yielding a (two-sided) p-value for heterogeneity, and the I^2 index [23].

Weighting was performed by the inverse variance method [24] based on two commonly used models: the fixed effects model [25] and the random effects model [26]. In the prior model, one assumes that the effects are all in the same direction and of the same magnitude and are thus results of a common pooled effect. In the latter model, by contrast, there is no assumption that the effects are of identical direction and magnitude. Thus, in the random effects model the study results are combined in a more independent way by allowing variability within and heterogeneity between studies, respectively. Fixed effects models were used when heterogeneity was low (p-value > 0.1). Otherwise, random effects models were used. The individual study results as well as the combined pooled estimates were illustrated in forest plots. We calculated a pooled estimate for prospective cohort studies, case-control studies, and all studies combined. We initially included studies defined by joint ER/PR status and ER status only, and studies in mixed populations (pre- and postmenopausal women combined) and in postmenopausal women. Subsequently, we performed sensitivity analyses including only studies defined by joint ER/PR status or studies restricted to mixed populations or postmenopausal women, separately. For subgroup analyses, differences between the pooled REs were determined by the Q statistic.

In addition, a sensitivity analysis was conducted to investigate publication bias of the included studies. This was visualized using a funnel plot [27, 28] and quantified using weighted linear regression of the effect estimate on its SEE [29].

RESULTS

Characteristics of studies

We retrieved 10 articles on adult weight gain and risk of breast cancer by ER/PR status [12-21]. One article did not provide risk estimates for quantiles of adult weight gain, and was therefore excluded [21]. In total, 9 articles (including 11 studies) on adult weight gain (10 from early adulthood, 1 from age 50 to reference age) and risk of breast cancer by ER/PR status were included in the meta-analysis (**Table 1**). Three of these studies were prospective cohort studies [12-14], and eight were population-based case-control studies [15-20]. Three case-control studies defined breast tumours by ER status only [18, 20], and nine studies by joint ER/PR status [12-17, 19]. Four studies were conducted in a mixed population of pre- and postmenopausal women [16, 20], there were no studies that included only premenopausal women, and seven studies included only postmenopausal women [12-15, 17-19]. All studies were conducted in the US, except for one study that was conducted in Sweden [19]. The number of cases with known ER/PR status ranged from 170 to 651 among the prospective cohort studies, and from 210 (ER⁺PR⁺ and ER⁻PR⁻ only) to 1,001 among the case-control studies.

ER⁺PR⁺ tumors

Random effects models were used to assess the association between adult weight gain and ER-positive breast cancer risk. Adult weight gain was associated with an increased risk for ER⁺PR⁺ and ER⁺ tumors combined (11 studies; RE = 2.03, 95% CI = 1.62, 2.45, $p_{\text{heterogeneity}} < 0.0001$) (**Figure 1, Table 2**). Restricting our analyses to ER⁺PR⁺ tumors slightly increased the risk estimate (8 studies; RE = 2.22; 95% CI = 1.83, 2.61, $p_{\text{heterogeneity}} < 0.0001$).

When comparing results for a mixed population of pre- and postmenopausal women combined and for postmenopausal women only, we found statistically significant heterogeneity ($p_{\text{heterogeneity}} = 0.002$) between risk estimates for the mixed population (4 studies; RE = 1.54, 95% CI = 0.86, 2.22, $p_{\text{heterogeneity}} < 0.0001$) and for postmenopausal women only (7 studies; RE = 2.33; 95% CI = 2.05, 2.60, $p_{\text{heterogeneity}} = 0.0024$).

ER⁻PR⁻ tumors

Fixed effects models were used to assess the association between adult weight gain and ER-negative breast cancer risk. Adult weight gain was associated with an increased risk for ER⁻PR⁻ and ER⁻ tumors combined (11 studies; RE = 1.36, 95% CI = 1.14, 1.58, $p_{\text{heterogeneity}} = 0.14$) (**Figure 2, Table 2**).

Results were not statistically significantly heterogeneous ($p_{\text{heterogeneity}} = 0.92$) for the mixed population of pre- and postmenopausal women combined (4 studies; RE = 1.32, 95% CI = 0.74, 1.89, $p_{\text{heterogeneity}} = 0.06$) and for postmenopausal women only (7 studies; RE = 1.34; 95% CI = 1.06, 1.63, $p_{\text{heterogeneity}} = 0.30$).

ER⁺PR⁺ versus ER⁻PR⁻ tumors

Although risk among postmenopausal women was statistically significantly increased for both ER⁺PR⁺ and ER⁻PR⁻ tumors, adult weight gain was associated with a statistically significantly greater risk for ER⁺PR⁺ than ER⁻PR⁻ tumors ($p_{\text{heterogeneity}} < 0.0001$).

ER⁺PR⁻ and ER⁻PR⁺ tumors

The association between adult weight gain and risk for ER⁺PR⁻ breast tumors was only assessed in postmenopausal women. Fixed effects models were used and no statistically significant association was found (4 studies; RE = 1.04, 95% CI = 0.68, 1.40, $p_{\text{heterogeneity}} = 0.81$). Associations for ER⁻PR⁺ tumors could not be assessed due to the small number of studies and the limited number of cases (3 studies).

Publication bias

Funnel plots were relatively symmetrical (data not shown) and no evidence for publication bias was found for ER⁺PR⁺, ER⁻PR⁻ and ER⁺PR⁻ tumors (Egger's test: $p = 0.96$, $p = 0.19$, and $p = 0.30$, respectively).

DISCUSSION

This meta-analysis shows that the association between adult weight gain and postmenopausal breast cancer risk is heterogeneous according to ER/PR status of the tumor. Higher adult weight gain was associated with higher risk for ER⁺PR⁺ postmenopausal breast cancer and risk for ER⁻PR⁻ postmenopausal breast cancer was only slightly increased. No association with ER⁺PR⁻ postmenopausal breast cancer risk was observed.

A previous meta-analysis on BMI found that higher BMI was associated with higher risk for ER⁺PR⁺ tumors in postmenopausal women, but not with risk for ER⁻PR⁻ tumors [3]. In our current meta-analysis, adult weight gain was associated with higher risk for both ER⁺PR⁺ and ER⁻PR⁻ postmenopausal breast cancer, although risk was statistically significantly higher for ER⁺PR⁺ compared to ER⁻PR⁻ tumors. Both BMI [3] and adult weight gain were not associated with ER⁺PR⁻

postmenopausal breast cancer risk. The association of BMI [3] and adult weight gain with ER⁻PR⁺ postmenopausal breast cancer could not be reliably assessed due to the limited number of studies. No studies were available on adult weight gain and risk of premenopausal breast cancer by ER/PR status, and therefore this association could not be independently assessed.

BMI is the most commonly used anthropometric measure to define obesity, and has been consistently associated with increased postmenopausal breast cancer risk [1]. However, adult weight gain is thought to be a better measure to assess adiposity and its metabolic consequences than BMI. Whereas BMI reflects both lean body mass and adipose mass, weight gain in adult life is generally a gain of body fat and thus potentially represents the age-related metabolic change that may be important in breast cancer development [4]. Several studies examining both adult weight gain and adult BMI in the same study population have found weight gain to be an equivalent [5, 6] or stronger [4, 7-10] predictor of postmenopausal breast cancer risk than recent BMI.

In postmenopausal women, obesity has been associated with hyperinsulinaemia and insulin resistance, and with elevated estradiol and lower SHBG levels [30]. Similar associations have been found for adult weight gain [31]. Hyperinsulinaemia and insulin resistance, among other factors, may promote both ER⁺PR⁺ and ER⁻PR⁻ breast tumors in postmenopausal women. The stronger associations found for adult weight gain in relation to risk for ER⁺PR⁺ compared with ER⁻PR⁻ postmenopausal breast cancer may be explained by an additional promoting effect of higher free estradiol levels on ER⁺PR⁺ breast tumors, specifically.

Although this meta-analysis shows that adult weight gain is clearly associated with increased risk for ER⁺PR⁺ breast cancer and to a lesser extent with increased

risk for ER⁻PR⁻ breast cancer in postmenopausal women, we observed large heterogeneity between the study-specific risk estimates, in particular for ER⁺PR⁺ breast tumors. One possible explanation for this heterogeneity may be differences in the definition of quantiles between studies, which preclude relating risk for ER⁺PR⁺ or ER⁻PR⁻ breast tumors to specific cut-off measurements of adult weight change. However, the heterogeneity between studies may be due to several other reasons.

Studies were performed in different age groups and adult weight gain has been previously shown to be differentially related to premenopausal and postmenopausal breast cancer risk [11]. Indeed, restricting the studies to those conducted in postmenopausal women reduced heterogeneity.

Further, there is a potential for measurement error from self-reported weight and recall of weight during early adulthood. However, correlations between measured and self-reported weight typically are >0.95 [11], and correlations between recalled weight over several decades and measured weight have been between 0.80 and 0.87 in several studies [32].

The assay methods for the measurement of ER/PR status and cutoff points for ER/PR status were not available for all studies and also varied across/within studies. This may have led to misclassification of the tumor subtypes and in consequence to attenuation of the observed risk estimates. Some studies only reported on ER and PR status separately whereas other studies considered joint ER/PR status. The combination of ER and PR status is reflective of true tumor estrogen dependence, since tumors will be both ER and PR positive if expression of the PR gene is induced by the presence of a normally functioning ER-estradiol-binding system [33]. Restricting our meta-analyses to studies measuring joint ER/PR status increased the risk estimates.

Current use of hormone replacement therapy increases circulating estrogen levels and may obscure the effect of adult weight gain on postmenopausal breast cancer risk. Some studies restricted their study population of postmenopausal women to non-users of postmenopausal hormones [12-14, 19] while other studies adjusted for postmenopausal hormone use [15, 17, 18]. However, results for adult weight gain and postmenopausal breast cancer risk did not appear to differ between the two types of studies.

Associations may be different for different ethnic groups. In black women, adult weight gain was not statistically significantly associated with ER⁺PR⁺ postmenopausal breast cancer risk [14]. It may also be possible that it was more difficult to detect this association in black women due to the smaller study population and the lower proportion of breast carcinomas that are ER⁺, PR⁺, or both.

To account for baseline differences in body size, some studies adjusted the analyses for baseline weight and height or BMI [13, 14, 16, 17]. The other studies either adjusted for recent BMI [18, 19], or did not perform any adjustment for body size [12, 15, 20]. However, results did not appear differ for studies with or without adjustment. Finally, unknown or residual confounding may be present.

The relation between adult weight gain and ER/PR defined breast cancer risk has not yet been fully clarified. To the best of our knowledge, no studies have been conducted in premenopausal women only. Future studies should investigate whether adult weight gain has a differential effect on ER⁺PR⁺ premenopausal breast cancer risk, as is suggested by the lower risk estimates in the mixed population of pre- and postmenopausal women combined compared to those in postmenopausal women.

Further, it is unclear whether adult weight gain throughout the entire adulthood lifespan or weight gain during specific life stages is most relevant for the

observed increase in ER⁺PR⁺ defined postmenopausal breast cancer risk. Weight gain during pubertal years is distributed primarily on the hips and buttocks. During later adult life fat accumulates preferentially around the waist. Only few studies have addressed the effect of adult weight gain during multiple life stages with respect to overall postmenopausal breast cancer risk. Three prospective cohort studies and one case-control study showed that both adult weight gain before and after menopause were associated with postmenopausal breast cancer risk [13, 18, 34, 35] whereas in one case-control study an increase in risk was only evident for adult weight gain after menopause [17]. None of these studies investigated whether these associations differed by ER/PR status of the tumor.

In conclusion, the association between adult weight gain and postmenopausal breast cancer risk is heterogeneous according to ER/PR status of the tumor, with higher risk estimates for ER⁺PR⁺ than for ER⁻PR⁻ tumors. The association of adult weight gain with ER/PR defined premenopausal breast cancer risk could not be independently assessed. These findings suggest that control of body weight may prevent ER⁺PR⁺ tumors, and to a lesser extent ER⁻PR⁻ tumors, after menopause.

ACKNOWLEDGEMENTS

This work was funded by the Deutsche Krebshilfe, project number 108253. The authors had no conflict of interest.

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Table 1 Characteristics of prospective cohort and case-control studies on weight gain from age 15, 18, 20 or 50 to referent age and breast cancer incidence by ER/PR status

Author, year, country, major ERPR assay [ref]	Design (study name), follow-up / yr-data collection, no. of overall cases and (study size) / controls	Age and menopausal status	Type of tumor	ER/PR defined cases number (approximate % known receptor)	Exposure measurement (kg unless otherwise stated)	Effect estimates	Adjusted factors
<i>Prospective cohort studies</i>							
Feigelson, 2006, US, N.A. [12]	Prospective coh (CPS-II), 1992-2001, 1,200 cases (44,161)	50-74 yr Post	ER+PR+ ER+PR-/ ER-PR+	445 cases (68%) 108 cases (17%) 98 cases (15%)	>27.3 vs. -2.3 to 9.1 from age 18 >27.3 vs. -2.3 to 9.1 from age 18 >27.3 vs. -2.3 to 9.1 from age 18	2.42 (1.82, 3.23) 1.32 (0.70, 2.49) 1.78 (0.98, 3.23)	Age, age at menarche, age at menopause, number of live births, age at first live birth, use of OC, family history of breast cancer, history of breast cysts, history of mammography, height, education, physical activity, alcohol intake, aspirin use, race (excluded PMH user).
Ahn, 2007, US, N.A. [13]	Prospective coh (AARP), 1996-2000, 2,111 cases (99,039)	50-71 yr Post	ER+PR+ ER+PR-/ ER-PR+	202 cases (66%) 44 cases (14%) 10 cases (3%) 53 cases (17%)	≥30 vs. -2.0 to 9.9 from age 18 ≥30 vs. -2.0 to 9.9 from age 18 ≥30 vs. -2.0 to 9.9 from age 18 ≥30 vs. -2.0 to 9.9 from age 18	2.69 (1.74, 4.17) 1.28 (0.47, 3.48) - 0.61 (0.21, 1.82)	Age, age at menarche, age at menopause, age at first live birth, parity, smoking, education, race, family history of breast cancer, fat intake, alcohol intake, oophorectomy, physical activity, weight at age 18, height (excluded PMH user).
Palmer, 2007, US, N.A. [14]	Prospective coh (BWHS), 1995-2005, 442 cases (9,542)	25-79 yr Post	ER+PR+ ER+PR-/ ER-PR+	82 cases (48%) 36 cases (21%) 52 cases (31%)	≥25 vs. <15 from age 18 ≥25 vs. <15 from age 18 ≥25 vs. <15 from age 18	1.29 (0.73, 2.28) 0.31 (0.13, 0.77) 1.03 (0.52, 2.05)	Age, age at menarche, parity, age at first birth, age at menopause, vigorous activity, education, family history of breast cancer, BMI at age 18 (excluded PMH user).
<i>Case-control studies</i>							
Enger, 2000, US, DCC [15]	Population-based cc 1987-1989 760 cases 1,091 controls	55-64 yr Post	ER+PR+ ER+PR-/ ER-PR+	450 cases (59%) 159 cases (21%) 24 cases (3%) 127 cases (17%)	≥29.2 vs. ≤0 % from age 18 ≥29.2 vs. ≤0 % from age 18 - ≥29.2 vs. ≤0 % from age 18	2.32 (1.58, 3.41) 0.99 (0.58, 1.78) - 1.75 (0.91, 3.38)	Age at reference year (matched), socioeconomic status (matched), number of full term pregnancy, breast feeding, age at menopause, use of PMH, family history of breast cancer, alcohol intake, physical activity.
Wenten, 2002, US, N.A. [16]	Population-based cc 1992-1994 694 cases 813 controls	30-74yr Mixed NHW Hispanic	ER+PR+ ER-PR- ER+PR+ ER-PR-	133 cases 77 cases 133 cases 77 cases	>14 vs. <4 from age 18 >14 vs. <4 from age 18 >14 vs. <4 from age 18 >14 vs. <4 from age 18	1.05 (0.60, 1.84) 0.93 (0.42, 2.05) 3.04 (1.47, 6.26) 1.73 (0.71, 4.25)	Age, family history of breast cancer, total METS, parity, use of OC, breast feeding, age at first birth, use of PMH, menopausal status, weight at age 18.
Eng, 2005, US, N.A. [17]	Population-based cc 1996-1997 990 cases 1,006 controls	20-98 yr Post	ER+PR+ ER+PR-/ ER-PR+	387 cases (58%) 121 cases (18%) 30 cases (4%) 132 cases (20%)	≥11.3 vs. 0 from age 50 ≥11.3 vs. 0 from age 50 ≥11.3 vs. 0 from age 50 ≥11.3 vs. 0 from age 50	2.17 (1.38, 3.42) 1.25 (0.57, 2.74) 1.54 (0.38, 6.35) 1.50 (0.72, 3.13)	Age at reference date, number of pregnancy, use of PMH, family history of breast cancer, history of benign breast disease, BMI at age 50 yr.
Han, 2006, US, DCC/IHC [18]	Population-based cc 1996-2001	35-79 yr Post	ER+ ER- PR+	510 cases (79%) 136 cases (21%) 389 cases (60%)	>27.3 vs. >0 to 9.1 from age 20 >27.3 vs. >0 to 9.1 from age 20	2.42 (1.62, 3.61) 1.19 (0.58, 2.43) 3.14 (1.96, 5.04)	Age, education, age at menarche, age at first birth, previous benign breast disease, family history of breast cancer, age at menopause,

	841 cases 1,495 controls		PR-	257 cases (40%)	>27.3 vs. >0 to 9.1 from age 20 >27.3 vs. >0 to 9.1 from age 20	1.21 (0.73, 2.01)	BMI residuals, use of PMH.
Rosenberg, 2006, Sweden, EIA [19]	Population-based cc 1993-1995 2,643 cases 3,065 controls	50-74 yr Post	ER+PR+ ER+PR- ER-PR+ ER-PR-	622 cases (62%) 156 cases (16%) 34 cases (3%) 189 cases (19%)	≥ 30 vs. 0-9.5 from age 18 ≥ 30 vs. 0-9.5 from age 18 ≥ 30 vs. 0-9.5 from age 18 ≥ 30 vs. 0-9.5 from age 18	2.7 (1.9, 3.8) 0.8 (0.4, 1.7) 2.1 (0.6, 6.8) 1.0 (0.5, 2.1)	Age, recent BMI, age at first birth (excluded PMH user).
Slattery, 2007, US, N.A. [20]	Population-based cc 1999-2004 2,325 cases 2,525 controls	25-79 yr Mixed NHW Hispanic	ER+ ER- ER+ ER-	801 cases (80%) 195 cases (20%) 379 cases (74%) 130 cases (26%)	>25 vs. ≤ 5 from age 15 >25 vs. ≤ 5 from age 15 >25 vs. ≤ 5 from age 15 >25 vs. ≤ 5 from age 15	1.13 (0.85, 1.50) 1.81 (1.07, 3.08) 1.17 (0.73, 1.86) 0.72 (0.35, 1.49)	Age (matched), height, physical activity, energy intake, parity, alcohol consumption, age at first pregnancy, age at menopause, menopausal status, estrogen status, center.

AARP = National Institutes of Health – AARP cohort, BMI = body mass index, BWHS = Black Women’s Health Study, cc = case-control study, coh = cohort study, CPS-II = the American Cancer Society’s Prevention Study II, DCC = dextran-coated charcoal assay / biochemical, EIA = enzyme linked immunoassay, IHC = immunohistochemistry method / immunoperoxidase, mixed = pre- and postmenopausal, N.A. = not available, NHS I = Nurses’ Health Study I, NHW = non-Hispanic white, OC = oral contraceptives, PMH = postmenopausal hormone, post = postmenopausal, US = United States

Table 2 Results of the meta-analysis for adult weight gain and ER⁺PR⁺ and ER⁻PR⁻ breast cancer risk

Group	No. of studies	τ^2^a	$p_{\text{heterogeneity}}$^b	I^2^c	Model used	Pooled estimate (95% CI)
<i>Adult weight change, ER+PR+</i>						
All studies	11	0.44	<0.0001	91%	REM	2.03 (1.62, 2.45)
Mixed	4	0.42	<0.0001	88%	REM	1.54 (0.86, 2.22)
Postmenopausal	7	0.10	0.0024	71%	REM	2.33 (2.05, 2.60)
<i>Adult weight change, ER-PR-</i>						
All studies	11	0.07	0.14	32%	FEM	1.36 (1.14, 1.58)
Mixed	4	0.20	0.06	60%	REM	1.32 (0.74, 1.89)
Postmenopausal	7	0.03	0.30	17%	FEM	1.34 (1.06, 1.63)

^a τ^2 is an estimator of between-studies variance.

^b p-values (two-sided) were based on the Q statistic of heterogeneity.

^c I^2 quantifies the percentage of variation across studies that is due to heterogeneity rather than chance.

FEM = fixed effects model, mixed = pre- and postmenopausal women combined,

REM = random effects model.

Figure 1 Association between adult weight gain and ER⁺PR⁺ breast cancer risk

Figure 2 Association between adult weight gain and ER⁻PR⁻ breast cancer risk

Footnote to Figures:

Relative samples sizes are represented by size of symbols. Horizontal lines indicate 95% CI for the respective RE. Pooled REs are illustrated by diamonds. Cut-off values ranged from 11.3 to 30 kg for the highest quantiles and 0 to 15 kg for the lowest quantiles, respectively. Mixed = pre- and postmenopausal combined, post = postmenopausal.



