



Published in final edited form as:

Int J Cancer. 2020 September 01; 147(5): 1306–1314. doi:10.1002/ijc.32892.

Adult weight change and premenopausal breast cancer risk: a prospective pooled analysis of data from 628,463 women

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Author disclosure

Since 1 January 2019, Elisabete Weiderpass has been a staff member of the International Agency for Research on Cancer. Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization (E Weiderpass, L Dossus), the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

Conflict of interest

None of the authors declared a conflict of interest with regard to this paper.

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Abstract

Early-adulthood body size is strongly inversely associated with risk of premenopausal breast cancer. It is unclear whether subsequent changes in weight affect risk. We pooled individual-level data from 17 prospective studies to investigate the association of weight change with premenopausal breast cancer risk, considering strata of initial weight, timing of weight change, other breast cancer risk factors, and breast cancer subtype. Hazard ratios (HR) and 95% confidence intervals (CI) were obtained using Cox regression. Among 628,463 women, 10,886 were diagnosed with breast cancer before menopause. Models adjusted for initial weight at ages 18–24 years and other breast cancer risk factors showed that weight gain from ages 18–24 to 35–44 or to 45–54 years was inversely associated with breast cancer overall (e.g. HR per 5kg to ages 45–54: 0.96, 95% CI: 0.95–0.98) and with oestrogen-receptor(ER)-positive breast cancer (HR per 5kg to ages 45–54: 0.96, 95% CI: 0.94–0.98). Weight gain from ages 25–34 was inversely associated with ER-positive breast cancer only and weight gain from ages 35–44 was not associated with risk. None of these weight gains were associated with ER-negative breast cancer. Weight *loss* was not consistently associated with overall or ER-specific risk after adjusting for initial weight. Weight increase from early-adulthood to ages 45–54 years is associated with a reduced premenopausal breast cancer risk independently of early-adulthood weight. Biological explanations are needed to account for these two separate factors.

Keywords

breast neoplasms; premenopause; body weight changes; risk factors; cohort studies

Introduction

The influence of obesity on breast cancer risk varies by life-stage. Adiposity before menopause is inversely associated with risk, whereas adiposity during the postmenopausal years is positively associated with risk^{1–3}. The inverse association with premenopausal adiposity is particularly strong for adiposity in early adulthood, i.e. ages 18–24 years⁴, and it is likely that the origin of this association lies in childhood^{5, 6}.

It is not clear whether changes in weight after early adulthood further affect risk of premenopausal breast cancer. The role of weight gain in adulthood is of interest because increases in body weight during adulthood mostly reflect accumulation of adipose rather than lean tissue, and therefore any change might reflect body fatness better than adult weight itself, and because of its association with intra-abdominal fat deposition, which is more metabolically active than peripheral adiposity⁷. Timing of weight change might additionally be relevant in that weight change at different stages of life, e.g. during periods of hormonal change such as during pregnancy, might have different biological effects, and differentially affect breast cancer risk⁸.

Due to the relatively low incidence of premenopausal breast cancer, past studies have had limited numbers of cases to investigate the association of weight change with risk by timing of weight change, to examine the effect of weight loss or of weight gain, or to analyse these associations by participant or tumour characteristics. Additionally, past studies have often only used proxies for menopausal status, such as status at study entry or attained age, rather than time-updated menopausal status.

We pooled individual-level data from prospective studies to investigate the association of weight change and its timing with premenopausal breast cancer risk, overall and by breast cancer characteristics.

Materials and methods

We used data from 17 of the 22 cohort studies in the Premenopausal Breast Cancer Collaborative Group⁹ that had participants' weight available at a minimum of two time points before women were age 55 years and had at least 100 breast cancer cases diagnosed before age 55 years. Individual-level data were pooled from cohorts in North America (n=9), Europe (n=6), Asia (n=1) and Australia (n=1), with participants recruited between 1963–2013. Data from 1–16 questionnaire rounds per study were harmonised to a common protocol. Women provided historical information on their weight prior to study entry on the baseline questionnaire and their current bodyweight was provided or measured at baseline and on follow-up questionnaires (if available). This work was approved by the relevant institutional review boards and women provided informed consent to partake.

Women were included in the analysis if they were breast cancer-free and premenopausal at study entry, and had premenopausal weight available for at least two age categories (defined below). Premenopausal follow-up time was determined from menopause information obtained from multiple questionnaire rounds, and, if missing, assumptions based on attained age using age 50 as cut-off (see supplement).

The main analytical endpoint was diagnosis with invasive or *in-situ* premenopausal breast cancer combined. We also conducted analyses of invasive and *in-situ* outcomes separately, as well outcomes by hormone-receptor status and a clinicopathological surrogate definition of intrinsic breast cancer subtypes (see supplement).

Analyses were conducted using STATA 14.2¹⁰. Data on weight was available at 2–13 time points per study. We first investigated weight patterns across time with longitudinal trajectory models at a selected number of time points¹¹ (Figure S1–S2). These models resulted in trajectories of weight gain delineated by initial weight, but did not delineate women with weight loss as a separate group. We therefore instead constructed variables for weight change between the age categories 18–24, 25–34, 35–44 and 45–54 years, to be able to use data from all the studies with varying numbers of time points and to examine the association of weight loss with risk. Weight at ages 18–24 was derived, for the great majority of subjects, from weight at age 18 or 20 (depending on the study) retrospectively reported on the baseline questionnaire. Weight at other ages was usually reported or measured at or after recruitment to the study.

Follow-up for breast cancer began at the second weight assessment, that was used to compute weight change, or at recruitment, whichever was later. Follow-up ended with the first of the following events: breast cancer diagnosis, menopause, last follow-up, death or age 55 years. Hazard ratios (HR) and 95% confidence intervals (CI) representing estimates of relative risk of breast cancer were derived from Cox proportional hazards models with attained age as the underlying time scale¹². Models were adjusted for cohort; year of birth; age at menarche; parity; age at first birth; time since most recent birth; adult height at recruitment; and family history of breast cancer. Covariate information was updated over follow-up, where available. In the main analyses, we analysed weight change in categories of 5.0 kg increments and as linear trends in risk per 5.0 kg of weight gain. We also obtained results in finer strata of 2.5kg increments (supplement). We obtained HRs for weight change with and without adjustment for starting weight to investigate whether starting weight was a confounder, but presented results adjusted for starting weight unless otherwise stated.

Tests for effect modification of weight change by cohort, starting weight, other available breast cancer risk factors, and time since weight change were conducted using log-likelihood ratio tests¹³. We estimated separate risk-factor associations for breast cancer type-specific outcomes using an augmentation method¹⁴.

We conducted sensitivity analyses by (i) excluding the first two years of follow-up to reduce the chance of reverse causation by preclinical disease; (ii) restricting analyses to reported, rather than assumed, premenopausal follow-up time; (iii) repeating the analyses excluding one study at a time; (iv) additionally adjusting for the number of years between weight

assessments; (v) in analyses restricted to subjects with weight at ages 18–24 available, adjusting for weight at ages 18–24 rather than weight at the start of the age category; (vi) restricting analyses to the 5 cohorts contributing to analyses of weight change at all of the six age groups (vii) repeating analyses for subjects with non-missing covariate information (viii) for subjects with available data, additionally adjusting one at a time for variables only available for some cohorts: race/ethnicity, cigarette smoking, alcohol consumption, physical activity level, polycystic ovary syndrome, childhood somatotype and mammographic screening history as at the most recent questionnaire round.

We additionally analysed the average annual weight change assuming a linear trajectory as a risk factor, rather than absolute increase in weight.

Data availability

Research data will be made available upon reasonable request due to privacy/ethical restrictions.

Results

The analyses included 628,463 women, whose median age at recruitment was 39.4 (interquartile range 33.8–44.0) years and who were followed for a median of 10.1 (interquartile range 5.9–15.5) years from recruitment during which 10,886 breast cancer cases (8,509 invasive) were diagnosed. Oestrogen-receptor (ER) status was known for 6,994 (72.5% of invasive and 43.5% of *in-situ*) breast cancer patients; ER, progesterone-receptor (PR) and HER2-status was available for 3,425 (37.2% invasive, 13.9% *in-situ*) breast cancer patients.

Most women were white (85.7%), from North America (56.6%), or Europe (41.1%) (Table 1). Women in the weight loss group were on average heavier at the onset than women who gained weight. Most women were parous at recruitment (80.7%) and 12.4% had a family history of breast cancer. The age-specific weight change variables were available for 5–14 cohorts per variable, representing weight change over median time intervals of 6.1–28.2 years and median follow-up for breast cancer of 4.2–17.2 years (Table S1 & S2). For all follow-up periods, the majority (80.3–90.4%) of women gained weight.

Figure 1 shows HRs in relation to weight change without (left) and with (right) adjustment for starting weight. There was an inverse U-shaped association with risk (Figure 1 & Figure S3, left), with women who lost weight and those who gained weight having lower HRs than women whose weight remained constant (within ± 5.0 kg), in particular for weight change from ages 18–24 years. Women who lost 5 kg since ages 18–24 years had a statistically significantly lower breast cancer risk than those whose weight remained constant. However, after additionally adjusting for starting weight (Figure 1 & Figure S3, right), which was on average greater for women with weight loss than for those who gained weight, the inverse HRs for weight loss were attenuated and no longer associated with risk. Weight gain from ages 18–24 to 35–44 years or from ages 18–24 to 45–54 years was associated with lower breast cancer risk, and HRs were not appreciably attenuated with adjustment for starting weight. Linear inverse trends in risk per 5 kg gain over these time periods remained

statistically significant (HRs: 0.97, 95% CI: 0.96–0.98 for ages 18–24 to 35–44 and 0.96, 95% CI: 0.95–0.98 for 18–24 to 45–54 years). The association of starting weight with risk remained statistically significant in these models.

Patterns of risk with weight change from later ages (i.e. from 25–34 or 35–44 years) were less clear, with no association with weight loss and linear trends with weight gain not being statistically significantly associated with risk after adjustment for starting weight.

In analyses by breast cancer invasiveness, the inverse associations of weight gain with breast cancer risk tended to be stronger for *in-situ* than for invasive breast cancer, but only significantly so for weight gain between ages 18–24 and 25–34 years (p-interaction=0.007) (Table S3). Stronger associations for *in-situ* than invasive breast cancer were also observed when we repeated the analyses among subjects with a previous history of mammographic screening only.

Associations of weight gain from young ages tended to be stronger for ER-positive than ER-negative (Table 2) or for ER+/PR+ than ER– and PR– breast cancer (Table S4). The difference in hazard ratios between these subgroups were only strongly statistically significant for one weight change group, however.

In analysis by breast cancer intrinsic subtype, weight gain from ages 18–24 onwards was inversely associated with Luminal A-like (ER+PR+HER2–) breast cancer and weight gain from ages 18–24 to 35–44 and to 45–54 years additionally with luminal B-like (ER+PR– or ER–PR+) breast cancer risk (Figure S4). For some of the age groups, there was evidence of a positive association with non-luminal (ER–PR–) breast cancer risk, in particular HER2-enriched breast cancer, whereas there was no association with triple-negative breast cancer risk.

There was evidence for effect modification by starting weight for the linear effect of weight change at two age groups, ages 18–24 years to 45–54 years (p-interaction=0.02) and 25–34 to 35–44 years (p-interaction=0.006), but in opposite directions and some of the results were based on small numbers of cases (Table S5). We observed no statistically significant evidence for effect modification in the linear association of weight change with risk by other breast cancer risk factors considered (childhood body shape or weight, adult height, age at menarche, parity, age at first birth, number of births, family history of breast cancer, and race/ethnicity, see Table S6) or by time since weight change (Table S7).

The main findings did not materially differ in the sensitivity analyses conducted (see methods and Table S8 & Table S9 for selected results) except that the inverse associations with weight gain were somewhat stronger when a stricter definition of menopausal status was applied. When analysing risk in relation to average annual weight change, rather than absolute amount of weight change, conclusions were similar, with the strongest inverse association with risk observed for weight change over the longest interval, from ages 18–24 to 45–54 years (HR=0.82, 95% CI: 0.75–0.89 per kg/yr), reflecting the largest absolute weight gains (Figure S5).

Conclusions

We observed that both weight loss ≥ 5 kg and weight gain of 10–15 kg since early adulthood were inversely associated with premenopausal breast cancer risk, but that degree of weight change was associated with initial weight, and that only weight gain was associated with risk after controlling for early adult weight. Early adulthood weight remained significant in such models, indicating that both starting weight and weight gain are associated with risk. There was weak and inconsistent evidence that the effect of weight gain depended on starting weight, and no evidence that the association varied by other investigated breast cancer risk factors. We captured weight change between ages 18–24 and 35–44 years, when most parous women had their pregnancies, but did not find statistical evidence that the association of weight change with risk differed between parous and nulliparous women. Weight change from later ages, age 35 years onwards, was not associated with risk.

Our pooling project incorporates data from most^{15–22}, although not all^{23–28}, published prospective studies on long-term weight change and premenopausal breast cancer risk, and additionally includes previously unpublished data. It consequently had enhanced statistical power based on its large sample size. Few past studies reported on weight loss separately; those that did reported null associations or non-significant inverse associations with weight loss since age 18 or 20 years compared with women whose weight remained stable^{15, 21–23, 26}, and not all adjusted for starting weight. In relation to weight gain, the majority of prospective studies have reported null or non-statistically significant inverse linear trends^{15, 18–28}, except for two reporting positive associations, but with no clear dose-response relationship^{16, 20}.

There was a tendency for inverse associations with risk to be somewhat stronger for *in-situ* than invasive breast cancer; this might reflect stage-specific aetiology or could be artefactual, e.g. a deficit of *in-situ* diagnoses could occur if increasing weight made women less likely to attend breast screening or if they presented later because breast self-examination and lump detection is more difficult²⁹. Stronger associations for *in-situ* than invasive cancer were also observed among women who had previously had a screening mammogram, suggesting that it is not explained by past breast screening attendance, but unfortunately we did not have data on mode of detection of breast cancer.

We observed stronger inverse associations of weight gain with ER+ than ER– breast cancer, or with ER+/PR+ than ER–PR– breast cancer. This agrees with our previous finding that BMI at ages over 25 years is inversely associated with risk of hormone-receptor-positive breast cancer only⁴. In augmentation analyses by intrinsic subtype, however, we observed somewhat contradictory findings, with some weight change variables being positively associated with HER2-enriched breast cancer and nonluminal breast cancer overall. These analyses were conducted on somewhat different subsets of the data and some of them on small numbers. Whether there is an association of weight change with non-luminal subtypes remains therefore uncertain.

It is of interest that we observed the strongest inverse associations with risk for weight change from early adulthood and no significant association of risk with absolute or rate of weight gain from ages 35–44 years onwards. Weight gain soon after age 18, if not followed by later weight loss, would lead to the greatest cumulative exposure to adiposity. It is possible that it is cumulative exposure to excess weight that is inversely associated with risk or that late weight gain is outside the susceptibility window for premenopausal breast cancer e.g. because there is a lag time between weight gain and an effect on risk. Our analyses by time since weight since did not suggest the latter is the case. The lack of association with later (i.e. 35 years) weight gain appears discordant with the results from two previous studies. The EPIC-PANACEA study reported a positive association of rate of weight gain over four years with breast cancer diagnosed at age <50 years, based on 283 cases³⁰. Women were premenopausal or perimenopausal at study entry (median age 40.7 years, M Emaus, personal communication) but no information on menopausal status at the second weight assessment was available; it is therefore possible that for some of the women postmenopausal weight gain was assessed. The Nurses' Health Study reported a positive association of weight gain over four years among initially premenopausal women with breast cancer risk over the subsequent 2 years (HR: 1.38, 95% CI: 1.13–1.69 for 15 vs. <5 lbs, n=736 cases)³¹. In our study, weight change was assessed over longer periods but the reason for the disparity in results is unclear.

The strong inverse association of breast cancer risk with early adult body size⁴ may originate in early life, or in childhood/adolescence^{5, 6}. It has been hypothesized to be due to greater differentiation of breast tissue during puberty^{2, 32}, altered oestrogen metabolism³³, lower adult mammographic density^{34, 35} and/or lower circulating IGF-1 levels³⁶ in heavier girls. Additional weight gain is associated with a reduction in mammographic density³⁷ and substantial weight gain leading to obesity suppresses ovarian function^{38, 39}, with a consequent reduction in endogenous sex hormone, in particular, progesterone, exposure³⁸. Weight gain might affect risk through changes in hormone profile because young women with high BMI have been reported to have lower levels of sex-hormone binding globulin (SHBG), oestradiol and progesterone, and higher levels of free testosterone than women with lower BMI⁴⁰. Oestrogens and testosterone have been associated with premenopausal breast cancer risk⁴¹, although less clearly than for postmenopausal breast cancer, but the evidence for an association of risk with progesterone is inconsistent, however⁴¹. A recent study reported lower breast cell proliferation in heavier compared with leaner premenopausal women, and the reverse in postmenopausal women, which might be hormone-related⁴².

Strengths of our study include its prospective design, its large number of cases, and therefore its ability to investigate associations according to breast cancer characteristics, multiple time-points of weight assessments, and the use of time-updated covariates. Limitations include that weight at ages 18–24 years was ascertained by recall for most participants, but recalled weight at age 18 years has been shown to correlate well with measured weight⁴³, and that we did not consider central adiposity measures. We studied weight change over six, some overlapping, age categories, using data of somewhat different populations, but a sensitivity analyses restricting to the five cohorts that contributed to all age categories showed similar results. There were too few women contributing to consecutive non-

overlapping time periods of weight change to investigate the role timing of weight change in a single model. In analyses by breast cancer subtype, numbers of subtype-specific breast cancers were modest for some of the weight change variables. Furthermore, our data set was not well-suited to investigate Asian women. We did not observe effect modification by ethnicity/race, but the study included relatively few women of Asian descent. It has been suggested that among Asian women, there is a positive association between BMI and premenopausal breast cancer risk⁴⁴, but prospective studies of weight *gain* in Asian women have, so far, shown an inverse or null association with premenopausal breast cancer risk overall^{24, 26, 45}.

Our results may contribute to the understanding of breast cancer causation and aid in risk stratification. However, weight gain would not provide a strategy for long-term risk reduction because weight and weight gain are positively associated with risks of postmenopausal breast cancer, several other types of cancer, and other adverse health outcomes^{46, 47}. Additionally, obese women diagnosed with breast cancer tend to have worse outcomes than leaner women, independent of their menopausal status⁴⁸.

In conclusion, we have observed that both body size in early adulthood and subsequent weight gain are independently associated with reductions in premenopausal breast cancer risk. There is a need to understand mechanisms underlying this finding, which may provide a means for breast cancer prevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the National Cancer Institute Cohort Consortium for facilitating this collaboration. We thank Melissa House MS (WestStat Inc, MD, USA); Mustapha Abubakar MBBS PhD (National Cancer Institute, MD, USA); Niclas Håkansson PhD (Karolinska Institute, Stockholm, Sweden); Jane Sullivan-Halley BS (Beckman Research Institute of City of Hope, Duarte, CA, USA); Allison Iwan BS, Diane Kampa BS (University of Minnesota, MN, USA); Jerry Reid PHD (American Registry of Radiologic Technologists, MN, USA); Jeffrey Yu MPH (Slone Epidemiology Center at Boston University, Boston, MA, USA) for contributions to acquisition, analysis or interpretation of data. They received no compensation for their contributions other than their salaries.

We wish to acknowledge all study participants, staff, and participating cancer registries. The Nurses' Health Study (NHS) and Nurses' Health Study 2 (NHS2) would like to thank the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required.

Funding/support

Support for this research comes, in part, from Breast Cancer Now; The Institute of Cancer Research, London; the Avon Foundation (02-2014-080); the United States National Center for Advancing Translational Sciences (KL2-TR001109); Karolinska Institutet Distinguished Professor Award Dnr: 2368/10-221; the United States National Institutes of Health, National Institute of Environmental Health Sciences (Z01 ES044005, P30 ES000260, P30 CA016087), National Cancer Institute (UM1 CA176726, UM1 CA186107, UM1 CA182876, UM1 CA182934, UM1 CA164974, R01 CA058420, R01 CA092447, CA144034), the National Program of Cancer Registries of the Centers for Disease Control and Prevention, and the Department of Energy; The Dahod Breast Cancer Research Program at Boston University School of Medicine; the State of Maryland, the Maryland Cigarette Restitution Fund; VicHealth, Cancer Council Victoria and the Australian National Health and Medical Research Council (209057, 396414 and 1074383); the Breast Cancer Research Foundation (BCRF-17-138); the Swedish Research Council and

Swedish Cancer Foundation; the Japanese Ministry of Health, Labor and Welfare; the Hellenic Health Foundation. The California Teachers Study is supported by R01 CA77398 and U01 CA199277. The coordination of the European Prospective Investigation in Cancer is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF), Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany); the Hellenic Health Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Swedish Cancer Society, Swedish Research Council and County Councils of Skane and Västerbotten (Sweden); Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPIC-Oxford; United Kingdom). The Institute of Cancer Research, London, acknowledges National Health Service funding to the Royal Marsden/ICR NIHR Biomedical Research Centre.

List of abbreviations:

BMI	body mass index
CI	confidence interval
ER	oestrogen-receptor
HR	hazard ratio
PR	progesterone-receptor
SHBG	sex-hormone binding globulin

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Novelty and impact:

Body weight in childhood and early adulthood is inversely associated with breast cancer risk diagnosed before the menopause. We investigated the role of subsequent changes in weight on breast cancer risk among 628 463 premenopausal women from 17 prospective studies. The results show, for the first time, that weight gain from early adulthood is inversely associated with risk of premenopausal breast cancer, providing further evidence of adiposity as a fundamental determinant of breast cancer risk.

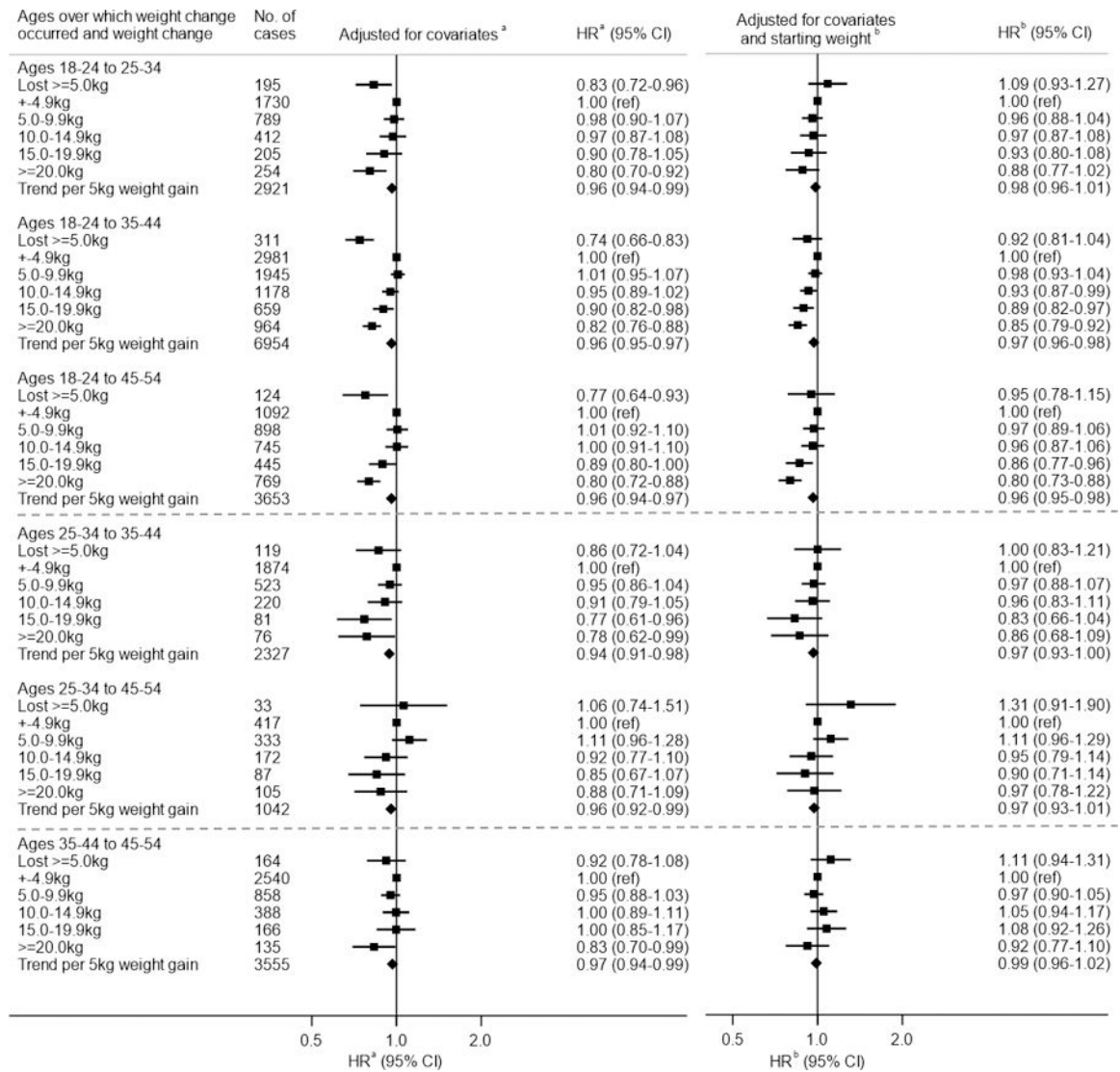


Figure 1: Relative risk of premenopausal breast cancer in relation to weight change between various ages

Footnotes:

Abbreviations: HR, hazard ratio; CI, confidence interval

(a) Adjusted for attained age, cohort, year of birth, adult height, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer

(b) Adjusted for covariates in (a) plus weight at start of age range

Table 1:

Characteristics of women included in the analyses, by degree of weight change between earliest available weight and weight at or close to recruitment to the study

Factor ^(b)		Weight change category ^(a)					Overall	
		Loss 5kg	Stable (± 4.9 kg)	Gain 5–9.9kg	Gain 10–14.9kg	Gain 15–19.9kg		Gain 20kg
Height (cms)	Mean	165.0	164.4	164.9	165.0	165.2	165.6	164.8
Age at first weight ^(c)	Mean	19.9	22.1	20.1	19.5	19.3	19.1	20.6
First weight (kg)	Mean	71.4	57.5	56.4	56.7	57.8	60.5	58.2
First BMI (kg/m ²)	Mean	26.2	21.3	20.7	20.8	21.2	22.0	21.4
Age at recruitment (years)	Mean	37.9	37.6	38.8	39.8	40.2	40.4	39.3
Recruitment weight (kg)	Mean	60.6	58.5	63.6	68.8	74.8	89.2	65.7
Recruitment BMI (kg/m ²)	Mean	22.2	21.7	23.4	25.3	27.4	32.5	24.2
Change in weight between starting age and recruitment (kg)	Mean	–10.8	1.0	7.2	12.1	17.0	28.7	7.5
	Median	–8.7	1.4	7.0	12.0	17.0	26.0	5.9
Rate of weight change between starting age and recruitment (kg/yr)	Mean	–0.8	0.1	0.5	0.7	0.9	1.5	0.4
	Median	–0.5	0.1	0.4	0.6	0.8	1.3	0.3
Race/ethnicity								
White	%	90.0	90.4	87.7	84.4	79.6	70.5	85.7
Black	%	6.0	5.3	8.6	12.3	17.5	27.3	10.6
Asian	%	1.9	2.8	2.1	1.8	1.2	0.5	2.0
Other	%	2.1	1.6	1.6	1.6	1.7	1.7	1.6
Continent of residence								
North America	%	63.2	57.4	53.2	51.6	55.0	65.6	56.6
Europe	%	35.3	40.8	44.9	46.1	42.6	32.1	41.4
Australia	%	0.8	0.7	1.3	1.8	2.2	2.2	1.3
Asia	%	0.7	1.1	0.7	0.5	0.3	0.09	0.7
All participants	Total	32726	253164	140227	86632	48297	67417	628463

^(a)Weight change was computed between earliest available weight and first weight available at or after recruitment, with the exception of a small number of subjects for whom weight change was computed from two retrospectively assessed weights before recruitment because weight at or after recruitment was not available.

^(b)Frequency-distributions for non-missing values only

^(c)Weight was retrospectively assessed at age 18 or 20 for the majority of studies.

Table 2: Risk of premenopausal breast cancer in relation to weight change between various ages, by oestrogen-receptor status of breast cancer

Ages at weight change	Median weight change, kg (25–75 th percentile)	ER status	No. of cases	Weight gain category, kg										Trend per 5kg gain (b)	P int-trend		
				Loss 5.0kg	Stable ± 4.9kg	Gain 5.0–9.9kg	Gain 10.0–14.9kg	Gain 15.0–19.9kg	Gain 20.0kg	HR (95% CI) (a)	HR (95% CI) (a)	HR (95% CI) (a)	HR (95% CI) (a)			HR (95% CI) (a)	HR (95% CI) (a)
				HR (95% CI) (a)	HR (a)	HR (95% CI) (a)	HR (95% CI) (a)	HR (95% CI) (a)	HR (95% CI) (a)	HR (95% CI) (a)	HR (95% CI) (a)	HR (95% CI) (a)	HR (95% CI) (a)			HR (95% CI) (a)	P -int
Ages 18–24 to 25–34	4.5 (0.4–9.6)	ER+	1834	1.00 (0.80–1.25)	1.00 (ref)	0.89 (0.79–1.01)	0.96 (0.83–1.12)	0.87 (0.71–1.07)	0.85 (0.70–1.02)	0.98 (0.95–1.01)							
Ages 18–24 to 35–44	6.9 (2.3–13.6)	ER–	591	1.24 (0.86–1.79)	1.00 (ref)	1.10 (0.90–1.36)	1.06 (0.82–1.38)	0.85 (0.59–1.24)	1.12 (0.83–1.50)	1.01 (0.96–1.07)							0.24
Ages 18–24 to 45–54	10.0 (4.5–18.2)	ER+	3976	0.92 (0.78–1.09)	1.00 (ref)	1.00 (0.92–1.08)	0.96 (0.87–1.05)	0.88 (0.78–0.99)	0.77 (0.69–0.86)	0.95 (0.93–0.97)							
Ages 18–24 to 45–54	10.0 (4.5–18.2)	ER–	1268	0.85 (0.62–1.18)	1.00 (ref)	1.07 (0.93–1.24)	1.11 (0.94–1.31)	1.11 (0.90–1.35)	1.01 (0.85–1.21)	1.01 (0.98–1.04)							0.0009
Ages 25–34 to 35–44	3.2 (0–7.3)	ER+	1547	0.99 (0.77–1.28)	1.00 (ref)	0.99 (0.86–1.13)	0.99 (0.81–1.20)	0.71 (0.50–0.99)	0.72 (0.50–1.03)	0.94 (0.89–0.99)							
Ages 25–34 to 45–54	7.3 (3.1–13.6)	ER–	466	0.74 (0.44–1.24)	1.00 (ref)	1.04 (0.82–1.33)	1.13 (0.81–1.57)	0.85 (0.49–1.49)	1.08 (0.64–1.83)	1.03 (0.96–1.10)							0.03
Ages 35–44 to 45–54	3.2 (0–7.7)	ER+	2575	1.15 (0.94–1.41)	1.00 (ref)	1.10 (0.92–1.32)	0.91 (0.73–1.15)	0.86 (0.64–1.16)	0.90 (0.68–1.19)	0.95 (0.90–1.00)							
Ages 35–44 to 45–54	3.2 (0–7.7)	ER–	670	0.77 (0.48–1.22)	1.00 (ref)	1.07 (0.74–1.54)	0.91 (0.58–1.43)	0.98 (0.56–1.71)	0.69 (0.37–1.28)	0.95 (0.86–1.04)							1.00

Abbreviations: CI, confidence interval; ER, oestrogen-receptor; HR, hazard ratio; P-int, p-value for interaction test

(a) HRs are adjusted for attained age, cohort, year of birth, adult height, weight at start of age range, age at menarche, age at first birth, number of births, time since last birth and family history of breast cancer

Including subjects with weight gain only
(?)

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