Adult Weight Change and Risk of Postmenopausal Breast Cancer

A. Heather Eliassen, ScD
Graham A. Colditz, MD, DrPH
Bernard Rosner, PhD
Walter C. Willett, MD, DrPH
Susan E. Hankinson, ScD

Context Endogenous hormones are a primary cause of breast cancer. Adiposity affects circulating hormones, particularly in postmenopausal women, and may be a modifiable risk factor for breast cancer.

Objective To assess the associations of adult weight change since age 18 years and since menopause with the risk of breast cancer among postmenopausal women.

Design, Setting, and Participants Prospective cohort study within the Nurses’ Health Study. A total of 87,143 postmenopausal women, aged 30 to 55 years and free of cancer, were followed up for up to 26 years (1976-2002) to assess weight change since age 18 years. Weight change since menopause was assessed among 49,514 women who were followed up for up to 24 years.

Main Outcome Measure Incidence of invasive breast cancer.

Results Overall, 4393 cases of invasive breast cancer were documented. Compared with those who maintained weight, women who gained 25.0 kg or more since age 18 years were at an increased risk of breast cancer (relative risk [RR], 1.45; 95% confidence interval [CI], 1.27-1.66; P<.001 for trend), with a stronger association among women who had never taken postmenopausal hormones (RR, 1.98; 95% CI, 1.55-2.53). Compared with weight maintenance, women who gained 10.0 kg or more since menopause were at an increased risk of breast cancer (RR, 1.18; 95% CI, 1.03-1.35; P=.002 for trend). Women who had never used postmenopausal hormones, lost 10.0 kg or more since menopause, and kept the weight off were at a lower risk than those who maintained weight (RR, 0.43; 95% CI, 0.21-0.86; P=.01 for weight loss trend). Overall, 15.0% (95% CI, 12.8%-17.4%) of breast cancer cases in this population may be attributable to weight gain of 2.0 kg or more since age 18 years and 4.4% (95% CI, 3.6%-5.5%) attributable to weight gain of 2.0 kg or more since menopause. Among those who did not use postmenopausal hormones, the population attributable risks are 24.2% (95% CI, 19.8%-29.1%) for a weight gain since age 18 years and 7.6% (95% CI, 5.9%-9.7%) for weight gain since menopause.

Conclusions These data suggest that weight gain during adult life, specifically since menopause, increases the risk of breast cancer among postmenopausal women, whereas weight loss after menopause is associated with a decreased risk of breast cancer. Thus, in addition to other known benefits of healthy weight, our results provide another reason for women approaching menopause to maintain or lose weight, as appropriate.

JAMA. 2006;296:193-201

©2006 American Medical Association. All rights reserved.

Author Affiliations: Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School and Departments of Epidemiology (Drs Eliassen, Colditz, and Hankinson), Biostatistics (Dr Rosner), and Nutrition (Dr Willett) Harvard School of Public Health, Boston, Mass.

Corresponding Author: A. Heather Eliassen, ScD, Channing Laboratory, Brigham and Women’s Hospital, 181 Longwood Ave, Boston, MA 02115 (heather.eliasen@channing.harvard.edu).
examine the associations of weight gain and loss, both since age 18 years and since menopause, with postmenopausal breast cancer risk.

METHODS

In 1976, 121,700 female, married, registered nurses, ages 30 to 55 years, were enrolled in the Nurses' Health Study.\textsuperscript{11,21,22} Information on lifestyle factors, including many breast cancer risk factors, and new disease diagnoses was collected by biennial mailed questionnaires. Follow-up data through June 2002 are available for 95% of the study population. This analysis expands on a previous analysis of adult weight change within the Nurses' Health Study,\textsuperscript{11} with an additional 10 years of follow-up and nearly 3 times the number of postmenopausal breast cancer cases. This study was approved by the Committee on the Use of Human Subjects in Research at the Brigham and Women's Hospital (Boston, Mass); completion of the self-administered questionnaire was considered to imply informed consent.

Study Population

We assessed weight change for 2 different periods: since age 18 years and since menopause. The analysis of change since age 18 years included women who were either postmenopausal at the start of follow-up in 1976 or became postmenopausal during follow-up. After excluding women with a history of cancer, other than nonmelanoma skin cancer, 87,143 women (1,245,416 person-years) contributed to the analysis. The analysis of change since menopause was restricted to women who were premenopausal in 1976 and had either natural menopause or bilateral oophorectomy during follow-up and therefore reported their weight at menopause. Women joined the study population as they became postmenopausal during follow-up. After excluding women with a history of cancer, other than nonmelanoma skin cancer, 49,514 women (649,061 person-years) were included.

Weight Change Assessment

Weight at age 18 years was queried in 1980. Recall of weight at age 18 years has been validated previously in the Nurses' Health Study II cohort, with a correlation of 0.87 between recalled weight and weight recorded on college or nursing school records at age 18 years (mean difference, −1.4 kg [recalled−measured]).\textsuperscript{23} With adjustment for current weight, a similar correlation was observed, suggesting minimal systematic bias. Current weight was queried biennially; self-reported weight in this cohort was validated previously, with a correlation of 0.97 between reported and measured weight (mean difference, −1.5 kg [reported−measured]).\textsuperscript{24} Weight at menopause was defined as the weight reported one questionnaire cycle prior to the first report of natural menopause or bilateral oophorectomy.

Weight change since age 18 years was calculated as the difference between current weight and weight at age 18 years. The primary analyses used updated weight change for each questionnaire cycle, categorized into 9 groups. Cut points for weight change categories are comparable with those used in previous literature.\textsuperscript{10,11,14,15,20} To capture the impact of maintaining a stable weight, we used a more restricted definition in secondary analyses. Women were categorized as having lost, gained, or maintained weight since age 18 years and their weight was considered stable if they remained in the same category at the next questionnaire cycle. Thus, a woman who gained weight in one cycle and lost weight in the next was not considered stable until she maintained the loss in the following cycle. Within the stable groups, women were categorized further by the amount of weight change.

Weight change since menopause was calculated as the difference between current postmenopausal weight and weight at menopause and was categorized into 7 groups. The primary and secondary analyses were similar to those described above, with a simple update in the primary analyses and restriction to stable change in the secondary analyses.

Breast Cancer Case Ascertainment

Cases of invasive breast cancer, diagnosed from the start of follow-up in 1976 through May 2002, were identified on biennial questionnaires; the National Death Index was searched for those who did not nonrespond. To confirm cancer reports and abstract information on invasiveness and hormone receptor status, medical records were reviewed by investigators blinded to exposure status. Records were unavailable for 241 (5.5%) of 4,393 cases. Given that pathology reports confirmed 99% of the reported cases, diagnoses confirmed by the participant but missing medical record confirmation were included as cases in this analysis. The observed incidence of breast cancer in the total Nurses' Health Study cohort is comparable with the expected incidence based on the Surveillance, Epidemiology, and End Results (SEER) rates\textsuperscript{25} for white women, 1988-1992 (O/E, 1.0; 95% confidence interval [CI], 0.98-1.03).

Covariate Assessment

Age was calculated from birth date to questionnaire return date. Age at menarche, height, and age at first birth were queried in 1976. Information on parity and oral contraceptive use was collected biennially from 1976 until 1984. Diagnosis of benign breast disease was assessed biennially. History of breast cancer in the participants' mothers and sisters was queried in 1976, 1982, and every 4 years since 1988. Alcohol consumption was assessed with a semiquantitative food frequency questionnaire in 1980, 1984, 1986, 1990, 1994, and 1998. Physical activity data were collected in 1980, 1982, 1986, 1988, and biennially since 1994.

Menopausal status, age at menopause, and PMH use were assessed biennially. Women were classified as postmenopausal at the first report of natural menopause or surgery with bilateral oophorectomy. Accuracy and reproducibility of self-report of natural menopause and ovarian surgery in this cohort has been previously validated.\textsuperscript{20} Women who reported hysterectomy without...
bilateral oophorectomy or whose type of menopause was unknown were not classified as postmenopausal until they reached the age at which 90% of the cohort had reached natural menopause (54 years for current smokers, 56 years for nonsmokers).

**Statistical Analysis**

We calculated person-years from the baseline questionnaire return date to the first date of diagnosis of breast or other cancer (except nonmelanoma skin cancer), death, or June 1, 2002. Cox proportional hazards models, stratified jointly by age in months and calendar year of follow-up at the beginning of each 2-year questionnaire cycle, were used to calculate adjusted relative risks (RRs) and 95% CIs. Multivariate models controlled for several breast cancer risk factors.

Tests for trend were performed using the medians of weight change categories, modeled continuously; tests for trend across weight loss were restricted to women who maintained or lost weight. To assess whether the associations between weight change and breast cancer varied across levels of other risk factors, we tested interaction terms between weight change and the potential modifier in multivariate models using the Wald test. To test whether associations differed by estrogen and progesterone receptor (ER/PR) status of the tumor, we used polytomous logistic regression with 3 endpoints (ER+/PR−, ER−/PR+, and no breast cancer). We used a likelihood ratio test to compare a model with separate weight-change slopes in each case group to a model with a common slope. We calculated incidence rates for categories of weight change using the incidence rate in women who maintained weight and the RR estimates from the multivariate analyses. To estimate the absolute risk of breast cancer by category of weight change, we applied the multivariate RRs to the number of expected cases in the referent group of weight maintenance obtained from the incidence rates. We calculated the population attributable risk conferred by weight gain (≥2 kg) to estimate the percentage of cases of invasive breast cancer in our cohort that, theoretically, would not have occurred if women had maintained or lost weight, assuming a causal relationship between weight gain and breast cancer incidence, holding all other risk-factor distributions constant. These calculations use multivariate-adjusted RRs and take into account the joint distribution of weight change along with the other risk factors included in the multivariate model. Variance estimates account for the variability in both the estimated RRs as well as in the joint prevalences of the risk factors. All analyses were conducted using SAS software, version 8 (SAS Institute Inc, Cary, NC). All P values were based on 2-sided tests and were considered statistically significant at P ≤ .05.

**RESULTS**

We documented 4393 cases of invasive breast cancer among postmenopausal women from 1976 through 2002; the analysis of weight change since menopause, among women with known age at menopause, included 2376 cases from 1978 through 2002. Women gained an average of 12 kg since age 18 years and 3 kg since menopause (mean years since menopause, 11). Compared with women who maintained their weight (lost or gained <2.0 kg) since age 18 years, those who gained...
weight had a higher body mass index (BMI), calculated as weight in kilograms divided by height in meters squared, through follow-up and a lower daily alcohol intake (Table 1). They were also less likely to exercise and to use PMH for more than 5 years. Women who lost weight since age 18 years were heavier at that age, more likely to have had their first birth after age 30 years, less likely to have used PMH long-term, and less likely to have a history of benign breast disease than those who maintained weight. Among women included in the analysis of weight change since menopause, characteristics by change since menopause were similar to those noted in Table 1, with the exception that women who gained weight were more likely to have used PMH long-term than women who maintained weight (data not shown).

Weight change since age 18 years was associated with breast cancer risk among all postmenopausal women (P < .001 for trend; Table 2). Compared with women who maintained weight, women who gained 25.0 kg or more were at increased risk (multivariate-adjusted RR, 1.45; 95% CI, 1.27-1.66). The association varied by PMH use; for women who had a 25.0-kg or more weight gain and who had ever used PMH, the multivariate-adjusted RR was 1.20 (95% CI, 1.01-1.43) vs 1.98 (95% CI, 1.55-2.53) among those who never used it (P < .001 for interaction). Weight loss was associated with a decreased breast cancer risk among all postmenopausal women (P = .02 for trend), and among women who had ever used PMH (P = .04 for trend). Restricting the analyses to those with stable change since age 18 years yielded similar results.

Analyses of weight change since age 18 years among those who never used PMH were further stratified by BMI at age 18 years (<21 vs ≥21) and by receptor status of the tumor. The association with a weight gain of 25.0 kg or more was stronger among leaner women (multivariate-adjusted RR, 2.39; 95% CI, 1.62-3.54) than among heavier women (multivariate-adjusted RR, 1.66;
WEIGHT CHANGE AND POSTMENOPAUSAL BREAST CANCER

95% CI, 1.19-2.32; P = .05 for interaction). The association with a weight gain of 25.0 kg or more was apparent among ER+/PR+ cases (multivariate-adjusted RR, 2.97; 95% CI, 1.93-4.58) but not among ER+/PR- cases (multivariate-adjusted RR, 1.20; 95% CI, 0.65-2.20; P = .01 for heterogeneity).

Weight change since menopause was also associated with breast cancer risk (P = .002 for trend; Table 3). Among all postmenopausal women, a weight gain of 10.0 kg or more was associated with an increased risk (multivariate-adjusted RR, 1.18; 95% CI, 1.03-1.35) compared with women who had maintained weight since menopause. Weight loss of 10.0 kg or more since menopause was associated with a suggested decreased breast cancer risk (multivariate-adjusted RR, 0.77; 95% CI, 0.56-1.08), although there was not a clear trend across categories of weight loss. Results were similar when the analysis was restricted to women who maintained a stable change since menopause. The association again varied by PMH use, although the interaction was not significant (P = .13). Among women who had ever used PMH, weight change since menopause was not associated with breast cancer risk (P = .22 for trend). Among those who never used PMH, the association with weight gain was similar to the overall results but the association with weight loss was stronger; for a weight loss of 10.0 kg or more, the multivariate-adjusted RR was 0.63 (95% CI, 0.38-1.05; P = .04 for weight loss trend; Figure). Among those who had never used PMH and who maintained stable change since menopause, the association with a 10.0 kg or more weight loss was even stronger (multivariate-adjusted RR, 0.43; 95% CI, 0.21-0.86; P = .01 for weight loss trend; Table 3).

Analyses of weight change since menopause among women who had never used PMH were further stratified by BMI at menopause (<25 vs ≥25) and by receptor status of the tumor. We observed a stronger association with weight gain among women who were leaner at menopause (multivariate-adjusted RR, 1.34; 95% CI, 0.94-1.90 for a weight gain of ≥10.0 kg) and a stronger association with weight loss among heavier women (multivariate-adjusted RR, 0.54; 95% CI, 0.30-0.97 for a weight loss of ≥10.0 kg), although the interaction was nonsignificant (P = .23). The associations were stronger for ER+/PR+ than for ER-/PR- tumors (P = .02 for heterogeneity). For ER+/PR+ tumors, a weight gain of 10.0 kg or more was associated with an increased risk (multivariate-adjusted RR, 1.52; 95% CI, 1.07-2.15) and a weight loss of 2.0 kg or more was suggested inversely associated with risk (multivariate-adjusted RR, 0.79; 95% CI, 0.55-1.15). For ER-/PR+ tumors, neither a weight gain of 10.0 kg or more (age-adjusted RR, 0.88; 95% CI, 0.47-

Table 3. Relative Risk of Postmenopausal Breast Cancer According to Weight Change Since Menopause

<table>
<thead>
<tr>
<th>Weight Change Since Menopause, kg</th>
<th>No. of Cases</th>
<th>Simple Update*</th>
<th>MV-Adjusted RR (95% CI)$</th>
<th>Stable Change†</th>
<th>No. of Cases</th>
<th>MV-Adjusted RR (95% CI)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td><strong>.000</strong></td>
<td></td>
<td><strong>.000</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss</td>
<td>≥10.0</td>
<td>41</td>
<td>0.73</td>
<td>0.87 (0.66-1.11)</td>
<td>29</td>
<td>0.70 (0.47-1.04)</td>
</tr>
<tr>
<td></td>
<td>5.0-9.9</td>
<td>113</td>
<td>1.06</td>
<td>1.12 (0.91-1.37)</td>
<td>66</td>
<td>1.00 (0.76-1.30)</td>
</tr>
<tr>
<td></td>
<td>2.0-4.9</td>
<td>184</td>
<td>0.89</td>
<td>0.91 (0.77-1.08)</td>
<td>77</td>
<td>0.77 (0.60-0.99)</td>
</tr>
<tr>
<td>Loss or gain &lt;2.0</td>
<td>642</td>
<td>1.00</td>
<td>1.00</td>
<td>348</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Gain</td>
<td>≥10.0</td>
<td>552</td>
<td>1.00</td>
<td>1.01 (0.90-1.14)</td>
<td>303</td>
<td>0.94 (0.80-1.10)</td>
</tr>
<tr>
<td></td>
<td>5.0-9.9</td>
<td>486</td>
<td>1.03</td>
<td>1.06 (0.96-1.22)</td>
<td>397</td>
<td>1.02 (0.88-1.18)</td>
</tr>
<tr>
<td></td>
<td>≥10.0</td>
<td>358</td>
<td>1.04</td>
<td>1.18 (1.03-1.35)</td>
<td>334</td>
<td>1.12 (0.96-1.32)</td>
</tr>
<tr>
<td>P for trend¶</td>
<td>.07</td>
<td>.002</td>
<td><strong>.001</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for weight loss trend¶</td>
<td>.09</td>
<td>.38</td>
<td>.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Even used PMH# Loss</td>
<td>≥10.0</td>
<td>18</td>
<td>0.66</td>
<td>0.81 (0.50-1.33)</td>
<td>15</td>
<td>0.81 (0.47-1.41)</td>
</tr>
<tr>
<td></td>
<td>5.0-9.9</td>
<td>64</td>
<td>1.13</td>
<td>1.25 (0.95-1.64)</td>
<td>36</td>
<td>1.02 (0.71-1.47)</td>
</tr>
<tr>
<td></td>
<td>2.0-4.9</td>
<td>106</td>
<td>0.93</td>
<td>0.98 (0.79-1.22)</td>
<td>43</td>
<td>0.78 (0.56-1.09)</td>
</tr>
<tr>
<td>Loss or gain &lt;2.0</td>
<td>379</td>
<td>1.00</td>
<td>1.00</td>
<td>227</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Gain</td>
<td>≥10.0</td>
<td>327</td>
<td>0.99</td>
<td>1.02 (0.87-1.18)</td>
<td>190</td>
<td>0.92 (0.75-1.12)</td>
</tr>
<tr>
<td></td>
<td>5.0-9.9</td>
<td>279</td>
<td>0.94</td>
<td>1.03 (0.88-1.21)</td>
<td>232</td>
<td>0.92 (0.76-1.11)</td>
</tr>
<tr>
<td></td>
<td>≥10.0</td>
<td>206</td>
<td>0.95</td>
<td>1.15 (0.96-1.38)</td>
<td>196</td>
<td>1.03 (0.86-1.29)</td>
</tr>
<tr>
<td>P for trend¶</td>
<td>.93</td>
<td>.22</td>
<td><strong>.001</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for weight loss trend¶</td>
<td>.31</td>
<td>.85</td>
<td>.42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never used PMH# Loss</td>
<td>≥10.0</td>
<td>18</td>
<td>0.80</td>
<td>0.83 (0.58-1.21)</td>
<td>9</td>
<td>0.43 (0.21-0.88)</td>
</tr>
<tr>
<td></td>
<td>5.0-9.9</td>
<td>40</td>
<td>0.97</td>
<td>0.89 (0.63-1.26)</td>
<td>24</td>
<td>0.85 (0.54-1.33)</td>
</tr>
<tr>
<td></td>
<td>2.0-4.9</td>
<td>73</td>
<td>0.95</td>
<td>0.90 (0.69-1.18)</td>
<td>32</td>
<td>0.85 (0.57-1.27)</td>
</tr>
<tr>
<td>Loss or gain &lt;2.0</td>
<td>238</td>
<td>1.00</td>
<td>1.00</td>
<td>111</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Gain</td>
<td>2.0-4.9</td>
<td>205</td>
<td>1.05</td>
<td>1.04 (0.86-1.26)</td>
<td>94</td>
<td>0.87 (0.66-1.16)</td>
</tr>
<tr>
<td></td>
<td>5.0-9.9</td>
<td>180</td>
<td>1.19</td>
<td>1.17 (0.95-1.43)</td>
<td>141</td>
<td>1.12 (0.87-1.45)</td>
</tr>
<tr>
<td></td>
<td>≥10.0</td>
<td>122</td>
<td>1.18</td>
<td>1.19 (0.94-1.50)</td>
<td>111</td>
<td>1.13 (0.88-1.50)</td>
</tr>
<tr>
<td>P for trend¶</td>
<td>.02</td>
<td>.002</td>
<td><strong>.001</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P for weight loss trend¶</td>
<td>.02</td>
<td>.04</td>
<td>.01</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MV, multivariate; PMH, postmenopausal hormone; RR, relative risk.

*Simple update uses weight change as of current questionnaire cycle.
†Weight change defined as gain, no change, or loss for at least 2 consecutive questionnaire cycles.
‡Multivariate adjustments include all factors listed in the footnotes in Table 2 plus weight at menopause (continuous).
§Excludes women who switched between gain, no change, or loss categories since previous questionnaire cycle.
*Calculated using medians of categories.
¶Calculated using medians of loss and loss or gain <2.0 kg categories.
©2006 American Medical Association. All rights reserved.
1.67) nor a weight loss of 2.0 kg or more (age-adjusted RR, 1.11; 95% CI, 0.66-1.86) was associated with risk.

To more thoroughly examine timing of weight change through adult life, we analyzed the associations of 5-kg increases in weight from age 18 years to menopause and since menopause with breast cancer risk in the same statistical model (Table 4). Among all postmenopausal women, breast cancer risk increased with gains during both periods (18 years to menopause multivariate-adjusted RR, 1.04 per 5 kg; 95% CI, 1.01-1.06; since menopause multivariate-adjusted RR, 1.06 per 5 kg; 95% CI, 1.02-1.09). Among those who had ever used PMH, no association was observed with gain between age 18 years and menopause, although there was a suggested, but nonsignificant, association after menopause. Among women who never used PMH, the risk before menopause was stronger (multivariate-adjusted RR, 1.12; 95% CI, 1.08-1.16) but the risk after menopause was similar to the overall risk (multivariate-adjusted RR, 1.07; 95% CI, 1.01-1.13). When women who had never used PMH were stratified by BMI, the results were again stronger among women who were leaner at age 18 years (BMI <21; multivariate-adjusted RR, 1.18; 95% CI, 1.12-1.24, for a 5-kg increase between age 18 years and menopause). Although the interaction between BMI at age 18 years and weight gain was significant ($P = .04$), weight gain remained significantly associated with risk among women heavier at age 18 years (BMI ≥21; multivariate-adjusted RR, 1.08; 95% CI, 1.03-1.13). The association with each 5-kg gain since menopause was stronger among women who were lean at menopause (BMI <25; multivariate-adjusted RR, 1.17; 95% CI, 1.06-1.30) while there was no association among heavier women (multivariate-adjusted RR, 1.02; 95% CI, 0.95-1.09; $P = .08$ for interaction).

We did not include physical activity as a covariate in our analyses because our primary interest was weight change, regardless of how weight change occurred. However, adding physical activity to the models did not alter the results. Including past oral contraceptive use in our model also did not alter the results. To ensure that our results were not dependent on the weight-change categories chosen, we repeated the trend test analyses using continuous weight change instead of using the medians of the categories; results were unchanged. Analyses of weight gain as a percentage of baseline weight produced results similar to the primary analyses; this also was true when stratified by baseline BMI. To ensure that weight change due to preclinical disease did not induce a spurious association, we repeated the analyses using weight change from either 2 or 4 years before the questionnaire cycle in which the cases were diagnosed; results were essentially unchanged.

To assess the implications of our findings in terms of absolute rates, we calculated incidence rates for categories of weight change, using the incidence rate in women who maintained weight and the RR estimates from our multivariate analyses. Overall, incidence rates for women who maintained weight and women who gained 25.0 kg or more since age 18 years were 296 and 429 cases per 100 000 person-years, respectively (228 and 451 per 100 000 person-years among women who had never used PMH, respectively). The incidence rates for women who maintained weight since menopause and women who gained 10.0 kg

---

**Table 4.** Relative Risk of Postmenopausal Breast Cancer According to a 5-kg Increase in Weight From Age 18 Years to Menopause and Since Menopause

<table>
<thead>
<tr>
<th>Age 18 Years to Menopause</th>
<th>Since Menopause</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Cases</strong></td>
<td><strong>Age-Adjusted RR</strong></td>
</tr>
<tr>
<td><strong>BMI at age 18 y</strong></td>
<td><strong>BMI at menopause</strong></td>
</tr>
<tr>
<td>&lt;21 at age 18 y</td>
<td>421</td>
</tr>
<tr>
<td>≥21 at age 18 y</td>
<td>388</td>
</tr>
<tr>
<td>&lt;25 at menopause</td>
<td>398</td>
</tr>
<tr>
<td>≥25 at menopause</td>
<td>411</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; MV, multivariate; NA, not applicable; PMH, postmenopausal hormones; RR, relative risk.

†Multivariate adjustments include all factors listed in the footnotes in Table 2 plus weight gain at menopause (continuous).

‡Body mass index is calculated as weight in kilograms divided by height in meters squared. $P = .04$ for interaction of body mass index at age 18 years × weight change from age 18 years to menopause; $P = .08$ for interaction of body mass index at menopause × weight change since menopause.
or more since menopause were 339 and 400 per 100 000 person-years, respectively (281 and 334 cases per 100 000 person-years, respectively, among women who had never used PMH). Among women who had never used PMH, the rates were 177 cases per 100 000 person-years for women who lost 10.0 kg or more since menopause and 121 cases per 100 000 person-years among women who lost weight and kept it off. Applying these rates over 5 years to 100 000 women who had not used PMH translates into 1145 cases among women who maintained weight since age 18 years and an excess of 1122 cases (2267 total) among women who gained 25.0 kg or more since age 18 years. For weight change since menopause, the numbers of cases would be 1392 among those who maintained their weight and an excess of 265 cases (1637 total) among women who gained 10.0 kg or more since menopause. For those who lost weight since menopause, 515 cases would be avoided among women who lost 10.0 kg or more; 793 cases would be avoided among women who lost 10.0 kg or more and kept it off. In addition, we estimated that 15.0% (95% CI, 12.8%-17.4%) of postmenopausal breast cancer cases in our population may be attributable to weight gain of 2.0 kg or more since age 18 years, and 4.4% (95% CI, 3.6%-5.5%) attributable to weight gain of 2.0 kg or more since menopause. Among women who had not used PMH, the population attributable risks are 24.2% (95% CI, 19.8%-29.1%) for gain since age 18 years and 7.6% (95% CI, 5.9%-9.7%) for gain since menopause.

COMMENT

In this large, prospective cohort study of postmenopausal women, weight gains since age 18 years and since menopause were associated with increased breast cancer risk. Weight loss since menopause was associated with a decreased risk among women who never used PMH, with stronger associations among women who lost and kept off weight and among those who were heavier at menopause. When weight changes in each time period were included in the same statistical model, gains both before and after menopause were associated with increased risk.

Hormones are directly related to breast cancer risk.6-8 and weight likely affects risk, at least in part, through a hormonal pathway. Higher weight at younger ages (ie, before age 18 years) decreases breast cancer risk for both premenopausal and postmenopausal women, possibly due to slower pubertal growth or a greater likelihood of irregular menstrual cycles and ovulatory infertility in adulthood.31-34 Although the ovaries produce endogenous hormones in premenopausal women, ovarian hormone production declines after menopause and adipose tissue becomes the primary estrogen source by aromatization of adrenal androgens.35-37 Compared with normal weight postmenopausal women, those with higher BMI have 2-fold higher circulating estrogens38-41 and lower sex hormone–binding globulin levels.39,42 and thus more bioavailable estrogens. Weight reduction in postmenopausal women decreases circulating estrogen levels3 and increases sex hormone–binding globulin levels.43

The observed increased risk associated with weight gain since age 18 years among all postmenopausal women is consistent with many cohort15 and case-control28,30,44-52 studies. Similar to the results of other studies,11,12,14,15 we observed no association among women who had ever used PMH. Stronger associations among never or past users have been observed in prior studies,11,12,14,15 with RRs ranging from 1.5215 to 2.1314 in the highest categories of weight gain, similar to the 2-fold increased risk that we observed among those who never used PMH. This interaction between weight change and PMH use is likely because exogenous hormones increase circulating estrogen levels among all women, regardless of adiposity, and thus obscure the gradient due to adipose tissue alone.38,33,34 Thus, an association between weight change and breast cancer is most clearly observed in women who have never used PMH.

To our knowledge, this prospective study is the largest to date to examine the effect of recent weight gain among postmenopausal women. The observed significant risk associated with increasing weight gain confirms results of prior studies.11,12,17-19,45 Our findings of significant increased risks with gains both before and since menopause are consistent with 2 other studies with time-period analyses.17,19 Regardless of whether weight gain occurs before or after menopause, adipose tissue produces hormones after menopause; thus, women should be advised to avoid weight gain both before and after menopause to decrease their postmenopausal breast cancer risk.

We observed stronger associations with weight gain in both time periods among women who were leaner at age 18 years or at menopause. Results of a few other studies showed stronger associations among leaner women, although the interactions were not significant.11,18 However, associations did not vary across levels of BMI in a few other studies.5,15,30 The interaction between BMI at age 18 years and weight change likely reflects the fact that women who were lean at age 18 years do not benefit from earlier weight that is ultimately protective. The stronger association among women leaner at menopause suggests that the effect of weight gain may be more pronounced with the initial addition of adipose tissue. The plateau of the BMI and breast cancer association in higher BMI categories53 and the lack of association between PMH and breast cancer in obese women56-58 support this.

While null1,44,45,47 or weak, nonsignificant inverse10,15,16,40,48-50 associations with weight loss since early adulthood have been observed in most studies, significant decreased risks were observed in 3 case-control studies.17,20,32 In the context of these suggestive studies, we observed a significant trend of decreased breast cancer risk with weight loss since age 18 years among all postmenopausal women.
Weight loss in later life has not been extensively studied, with a few studies reporting null\textsuperscript{17,20} or nonsignificant inverse\textsuperscript{19} associations. To our knowledge, ours is the first study to show a significant decreased risk with weight loss after menopause for women who maintained their loss. Although there were few cases in the highest weight loss category, the trend of decreasing risk with more weight lost also was statistically significant. Given the low prevalence of weight loss after menopause in this study and the modest results of and low adherence to weight loss programs,\textsuperscript{29} women should avoid weight gain throughout adult life rather than count on losing weight after menopause.

While weight loss was not an aim of the recently published Women’s Health Initiative Dietary Modification Trial,\textsuperscript{30} women in the intervention group, who had a nearly significant breast cancer risk reduction (RR, 0.91; 95% CI, 0.83-1.01), experienced significantly greater weight loss over 6 years than the control group by about 1.4 kg (estimated by the mean of group differences in weight change at years 1, 3, and 6). Although the trial was designed to assess the low-fat intervention, the 9% reduction in risk is compatible with the greater weight loss in the intervention group, as each 1.4-kg loss after menopause in our data was associated with a 4% reduction in risk among women who had never used PMH and an 8% risk reduction among those who kept weight off.

Our absolute risk and population attributable risk calculations suggest that weight gain since age 18 years and since menopause contributes substantially to the incidence of breast cancer, and many cases could be avoided by maintaining weight throughout adult life. Importantly, many breast cancer cases also could be avoided by weight loss after menopause.

This study has several strengths, including the cohort size and length of follow-up. Validated, updated weight information allowed us to calculate change in weight. Although weight reflects both lean body mass and adipose tissue, weight gain after young adulthood more likely reflects a gain in adipose tissue.\textsuperscript{43} With biennially adjusted weight and menopausal status, we were able to determine weight at menopause and assess postmenopausal weight change. Biennial information also allowed for the identification of women with stable gain or loss since age 18 years and since menopause. There are also limitations, including recalled weight at age 18 years. However, the recall is likely quite accurate given its previous validation study.\textsuperscript{23} Although exposure was assessed by self-reported weight, reliability of self-reported anthropometric measures in this population is high and does not vary substantially by BMI.\textsuperscript{24} Another limitation is that relatively few women lose weight, particularly after menopause. Although we were able to assess weight loss in a few categories and stratify the analyses by PMH use and BMI, more follow-up is needed to confirm our findings and characterize the benefits more precisely. Although the homogeneity of the study population is a potential limitation, it is unlikely that the observed association between weight change and breast cancer differs substantially from the general population. However, these findings will need to be confirmed in other populations.

In summary, our results confirm the direct association between weight gain since age 18 years and postmenopausal breast cancer, particularly among women who had never used PMH. In addition, our data suggest that weight gain in adult life increases postmenopausal breast cancer risk, regardless of whether the gain occurs before or after menopause. An important finding from this study is that weight loss may reduce breast cancer risk, even if weight is not lost until after menopause. Although weight loss leads to several short-term benefits, these data provide another reason women should be advised to avoid weight gain and counseled on the potential benefit of weight loss after menopause. Although these data suggest that it is never too late to lose weight to decrease risk, given the difficulty in losing weight, the emphasis must also remain on weight maintenance throughout adult life.

**Author Contributions:** Dr Eliassen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Eliassen, Colditz, Willett, Hankinson.

**Acquisition of data:** Colditz, Willett, Hankinson.

**Analysis and interpretation of data:** Eliassen, Colditz, Rosner, Willett, Hankinson.

**Drafting of the manuscript:** Eliassen.

**Critical revision of the manuscript for important intellectual content:** Eliassen, Colditz, Rosner, Willett, Hankinson.

**Statistical analysis:** Eliassen, Rosner.

**Obtained funding:** Colditz, Hankinson.

**Analysis and interpretation of data:** Eliassen, Colditz, Willett, Hankinson.

**Statistical analysis:** Eliassen, Rosner.

**Study supervision:** Colditz, Hankinson.

**Financial Disclosures:** None reported.

**Funding/Support:** This study was supported by research grant CA87969 from the National Cancer Institute. Dr Eliassen was supported by training grant DAMD17-00-1-0165 from the Department of Defense and Cancer Education and Career Development grant R25 CA098566-02 from the National Cancer Institute. Dr Colditz was supported in part by a Cissy Hornig Clinical Research Professorship from the American Cancer Society.

**Role of the Sponsor:** The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

**Acknowledgment:** We gratefully acknowledge the Nurses’ Health Study participants for their continuing cooperation.

**REFERENCES**


Diet and Cancer Study.


