To examine effects of body size change on postmenopausal breast cancer, the authors conducted a population-based case-control study among 990 cases and 1,006 controls participating in the Long Island Breast Cancer Study Project in 1996–1997. Women who had gained more than 15 kg (33 pounds) since age 20 years were at a 1.6-fold increased risk of breast cancer (95% confidence interval (CI): 1.11, 2.26) relative to their counterparts with stable (±3 kg) weight. Subjects who had gained more than 11 kg (24 pounds) during the peri- and postmenopausal years (since age 50 years) had 1.62 times the risk of breast cancer of those whose weight remained unchanged during this time period. This effect of peri- and postmenopausal body size gain was present only among never users of hormone replacement therapy (odds ratio (OR) = 2.02 (95% CI: 1.35, 3.02) as opposed to 0.81 (95% CI: 0.43, 1.53) for ever users; multiplicative interaction: p < 0.01) and was more pronounced among women with estrogen receptor-positive/progesterone receptor-positive breast cancer (OR = 2.17, 95% CI: 1.38, 3.42).

Weight loss over the lifetime was associated with decreased risk of postmenopausal breast cancer (OR = 0.55, 95% CI: 0.32, 0.96). These results add to the literature by focusing on the perimenopausal weight trajectory and support efforts urging women to avoid weight gain as they age.

Many of the known estrogen-related risk factors for breast cancer, such as menstrual (1, 2) or childbearing (3, 4) characteristics, are not easily changed by an individual, making the primary prevention of breast cancer difficult. One factor emerging in recent years as possibly affecting breast cancer risk is weight gain in adulthood, hypothesized to increase a woman’s risk of postmenopausal breast cancer (5). This factor is tantalizing from a prevention point of view because it is potentially modifiable by individuals.

Body weight reflects both lean mass and fat mass, whereas weight gain in adulthood has been shown to represent an increase in adipose or fat tissue only (6). Estrogens derived from aromatization of androstenedione in peripheral fat may account for the increased risk of breast cancer observed among postmenopausal obese women (7). Additionally, overweight and obesity have been linked with increased insulin levels and insulin resistance (8). In vitro, insulin has a mitogenic effect on breast epithelium (9), and in vivo, insulin probably stimulates cellular proliferation via the mediator insulin-like growth factor 1 (10). Defects in insulin and insulin-like growth factors have been observed in human breast cancer cell lines, the overall effect of which has been increased cellular proliferation (11).
In the current analysis, we made use of data from a large population-based case-control study to characterize the relation between changes in body size and breast cancer. Because weight exerts different effects according to menopausal status, we restricted the analysis to postmenopausal women. Changes in weight and relative weight during three particular time periods in adulthood were investigated for their effects on postmenopausal breast cancer risk, as were patterns of body size change throughout the lifetime. We paid particular attention to evaluation of the perimenopausal weight trajectory in order to address the question “How do body size changes later in life affect breast cancer risk?” This is a critical question that remains largely unanswered, despite the wide availability of papers describing anthropometry’s role in the development of breast neoplasms.

**MATERIALS AND METHODS**

The Long Island Breast Cancer Study Project (LIBCSP) was a collaborative, population-based case-control study conducted primarily to identify environmental risk factors for breast cancer among women residing in Nassau and Suffolk counties on Long Island, New York. Details of the study methods have been published previously (12).

**Study population**

English-speaking female residents of Nassau and Suffolk counties in New York State were eligible to participate in the LIBCSP. Cases were women diagnosed with first primary in-situ or invasive breast cancer between August 1, 1996, and July 31, 1997. Population-based control subjects were frequency-matched to cases by 5-year age group, with those under age 65 years being identified using random digit dialing procedures (13) and those aged 65 and over being randomly selected from Health Care Financing Administration rosters.

Subjects’ ages ranged from 20 years to 98 years. The questionnaire component of the LIBCSP was completed by 1,508 (82.1 percent) eligible cases and 1,556 (62.7 percent) eligible controls. Primary reasons for nonresponse among cases and controls included refusal or break-off and being too ill, cognitively impaired, or deceased.

**Data collection**

Written informed consent was obtained from each participant before any component of data collection was conducted. The main interview was administered by a trained interviewer in the respondent’s home; details on the LIBCSP questionnaire have been previously published (12). Factors associated with increased breast cancer risk among participants included lower parity, later age at first birth, little or no breastfeeding, and family history of breast cancer (12). Similar associations were observed when the population was restricted to postmenopausal subjects (data not shown).

As part of the Main Questionnaire, subjects reported height to the nearest inch and weight to the nearest pound at age 20 years and at 1 year prior to the reference date, which was the date of diagnosis for cases and the date of identification for controls. Subjects also reported their weight in each relevant decade of age throughout their lives, from the 20s to the 70s.

Participants were invited to self-administer a previously validated modification of the Block food frequency questionnaire (14), from which estimates of daily fat intake and total calories were derived. The reference period for dietary intake was the year prior to interview.

**Variable definitions**

**Menopausal status.** Menopausal status was derived using information provided on the Main Questionnaire and the Specimen Checklist, which was filled out at the time of biologic specimen donation. Data on the last menstrual period and gynecologic surgeries were combined with information on pregnancy, lactation, and use of hormone replacement therapy. Subjects reporting a last menstrual period more than 6 months prior to the reference date who were not currently pregnant or lactating were classified as postmenopausal if they reported natural menopause without surgery, total oophorectomy, or partial oophorectomy. For persons with missing data on the date of the last menstrual period, surgical data were consulted; subjects reporting a bilateral oophorectomy were classified as postmenopausal. If surgical data were not available, the last menstrual period on the Specimen Checklist was consulted; if the date of the last menstrual period was within 6 months of the reference date, subjects were coded as premenopausal. If, after the above algorithm had been used, any subjects were still missing data on menopausal status, menopausal status was assigned to these subjects on the basis of their age at the reference date, using the 90th percentile for natural menopause among controls, by smoking status, for comparison. Using these substitutions, 1,996 subjects (1,006 cases and 990 controls) were classified as postmenopausal. Analyses for the current study compared all postmenopausal control women with all postmenopausal women with breast cancer.

**Body size data.** Body mass index (weight (kg)/height (m)\(^2\)) was calculated for each relevant decade of life from the 20s to the 70s, as well as for the year preceding the reference date. Height and weight at age 20 years, 1 year prior to the reference date, and through the relevant decades of life were also examined. The aforementioned variables will be collectively referred to as static body size variables.

Changes in weight during three time periods were calculated: from the 20s to the 30s, to approximate change in early adulthood; from the 20s to 1 year prior to the reference date, to approximate change throughout all of adulthood; and from the 50s to 1 year prior to the reference date, to approximate change during the peri- and postmenopausal years. To adjust for residual confounding by obesity, these weight changes were also examined as a percentage of body size at age 20 years and as a percentage of body size at age 50 years. Models were also adjusted for body mass index at the beginning of the change interval, to account for any residual confounding by body size at the beginning of the interval. The aforementioned variables will be collectively referred to as dynamic body size variables.

To explore the effect of patterns of body size change throughout the entire lifetime on postmenopausal breast cancer risk, we categorized body size change into two groups: static or dynamic (squares and diamonds, respectively) and dynamic or static (circles and triangles, respectively). The categories were based on the change in body size for the years 1950–1960 and 1961–1970 (squares) and 1971–1980 and 1981–1990 (diamonds), and the change in body size for the years 1950–1960 and 1961–1970 (circles) and 1971–1980 and 1981–1990 (triangles). The dynamic patterns were those in which body size changed, whereas the static patterns were those in which body size remained stable. For each decade of adulthood, we evaluated the effects of static and dynamic patterns of body size change on breast cancer risk, as well as the effects of static patterns of body size change on breast cancer risk, as well as the effects of static patterns of body size change on breast cancer risk, as well as the effects of static patterns of body size change on breast cancer risk.
cancer risk, we classified subjects as high (greater than or equal to the control median) or low (less than the control median) with respect to weight for the following decades of life: the 20s, to approximate body size in early adulthood; the 30s, to approximate body size in early mid-adulthood; the 50s, to approximate body size during the perimenopausal years; and 1 year prior to study interview, to approximate body size during the postmenopausal years.

**Statistical methods**

An unpaired Student’s *t* test (15) was used to compare mean values for static and dynamic body size variables between cases and controls. Unconditional logistic regression (16) was used to estimate odds ratios and 95 percent confidence intervals for breast cancer, with adjustment made for potential confounders and covariates. All models were adjusted for the frequency matching factor of age at reference date. Additional factors included in the models were based on the known epidemiology of breast cancer. Any subject with a missing value for a particular covariate was eliminated from any analyses that included that covariate.

Covariates considered independently in logistic regression models included variables related to demographic factors (race, education, marital status, Latina ethnicity, religion), reproduction (gravidity, parity, age at first livebirth, breastfeeding), and menstrual cycle (age at menarche). Additionally, we investigated use of exogenous hormones (oral contraceptives, hormone replacement therapy), medical history (history of biopsy-proven benign breast disease, fertility problems, or breast cancer in a mother, sister, or daughter), and lifestyle factors (alcohol consumption, dietary fat intake, total caloric intake, active cigarette smoking, and regular participation in recreational physical activity).

A covariate was considered a confounder if it caused at least a 10 percent change in the regression coefficient when it was added to the model versus a model without the covariate (16). To identify the most parsimonious multivariate model, we conducted backward elimination from a saturated model (17). We examined interactions on a multiplicative scale between categorical body size variables and other covariates using stratified analyses and also using chi-squared tests of the difference in the log-likelihood between models with and without the cross-product terms (18). Covariates investigated as potential effect modifiers on the basis of previous literature included use of hormone replacement therapy, race, and history of breast cancer in a first-degree relative. The tumor characteristics of estrogen receptor/progesterone receptor status and stage were also tested as effect modifiers.

**RESULTS**

**Static body size variables**

No relation was observed between height at age 20 years and postmenopausal breast cancer risk (table 1). Cases had marginally lower body sizes at age 20 years than controls (data not shown), but there were no significant associations between weight at age 20 years and postmenopausal breast cancer, as table 1 shows (for the highest quartile of weight at age 20 years, odds ratio (OR) = 1.04, 95 percent confidence interval (CI): 0.80, 1.37). Greater weight during the year preceding the reference date was associated with increased risk of postmenopausal breast cancer in a dose-dependent manner (*p*-trend = 0.0001).

**Dynamic body size variables**

**Body size gain in early adulthood.** There were no marked differences between case and control mean values for weight change in early adulthood (data not shown). Greater gains in weight in early adulthood were not associated with increased risk of breast cancer (table 2).

**Body size gain throughout adulthood.** Greater gains in weight throughout adulthood conferred increased risks of postmenopausal breast cancer (table 2). Compared with women who stayed within 3 kg of their age 20 weight, those who had gained 15 or more kg (≥33 pounds) between age 20 years and the year preceding the reference date had a 58 percent greater risk of postmenopausal breast cancer, even when results were controlled for any residual confounding by body mass index at the beginning of the change interval, at age 20 years (OR = 1.58, 95 percent CI: 1.11, 2.26). Accounting for a woman’s baseline body size by examining gains as a percentage of body size at age 20 also did not yield materially altered risk estimates (data not shown).

**Body size gain during the peri- and postmenopausal years.** Change in body size during the peri- and postmenopausal years, defined as change occurring from age 50 to 1 year prior to the reference date, was strongly associated with postmenopausal breast cancer (table 2). With adjustment for body mass index at the beginning of the change interval, at age 50 years, women in the highest quartile of weight gain during this time period had a multivariate-adjusted odds ratio for postmenopausal breast cancer of 1.62 (95 percent CI: 1.14, 2.30) compared with women whose weight did not change during this time period. Controlling for residual confounding from obesity by considering a woman’s baseline body size at age 20 did not materially change these risk estimates (data not shown).

**Timing of body size gain.** Since weight change during the peri- and postmenopausal years was a component of weight change over the lifetime, we determined whether peri- and postmenopausal change was largely responsible for the statistically significant association between weight gain over the lifetime and postmenopausal breast cancer by separating weight change over the lifetime into its component changes (data not shown). We then determined the time period in which weight change had most affected postmenopausal breast cancer risk. This analysis indicated that body size gain during the peri- and postmenopausal years showed the strongest association with risk of postmenopausal breast cancer. Women in the highest quartile of weight gain from age 50 years to 1 year prior to the reference date had an odds ratio for postmenopausal breast cancer of 1.64 (95 percent CI: 1.19, 2.25) as compared with women who stayed within 2 kg of their age 50 weight; the corresponding risks for women in the highest quartile of weight gain from age 20 to age 30, from age 30 to age 40, and from age 40 to age 50 were 1.05, 1.05, and 1.37, respectively.
Modifiers of peri- and postmenopausal body size gain. The odds ratio for postmenopausal breast cancer for the highest quartile of body size gain between age 50 and 1 year prior to the reference date was significantly increased by 102 percent among never users of hormone replacement therapy, whereas it was decreased by 19 percent among women who had ever used hormone replacement therapy (table 3). The odds ratio for estrogen receptor-positive/progesterone receptor-positive (ER$^+$/PR$^+$) postmenopausal breast cancer was significantly increased twofold in relation to the highest quartile of body size gain between age 50 and the year preceding the reference date (table 4). Odds ratios for postmenopausal breast cancer were not found to differ by race or first-degree family history of breast cancer (data not shown). Comparison of in-situ cases with controls and invasive cases with controls yielded similar results (data not shown).

Effects of body size loss. Women who lost weight in early adulthood had a 34 percent decreased risk of postmenopausal breast cancer compared with women whose body size remained the same during this time period (table 2). This inverse association of weight loss with breast cancer risk was slightly more pronounced for decrease over the entire lifetime (for weight loss from age 20 years to 1 year prior to the reference date, OR = 0.55, 95 percent CI: 0.32, 0.96). In contrast, a decrease in body size during the peri- and postmenopausal years was associated with nonsignificantly increased risk of postmenopausal breast cancer (for weight loss, OR = 1.19, 95 percent CI: 0.85, 1.67) in comparison with women whose body size remained the same throughout that time interval.

Patterns of body size cycling throughout life

Results from exploratory analyses of body size patterns throughout the lifetime were consistent with those from analyses of dynamic body size variables (table 5). Subjects who were consistently at or above the control median for weight when they were 20, 30, and 50 years old and 1 year prior to the reference date were at 22–52 percent increased risk of postmenopausal breast cancer compared with those remaining below the control median. Women who switched at menopause from being below the control median body size to above the control median had higher risks of breast cancer than women whose body size remained low throughout adulthood (OR for weight = 1.52), but the 95 percent confidence interval for this estimate included the null value. In addition,

### Table 1. Age-adjusted and multivariate-adjusted odds ratios for postmenopausal breast cancer in relation to static body size variables, Long Island Breast Cancer Study Project, 1996–1997

<table>
<thead>
<tr>
<th>Body size variable</th>
<th>Cases</th>
<th>Controls</th>
<th>Age-adjusted</th>
<th>Multivariate$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Height (m) at age 20 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.21–1.57</td>
<td>308</td>
<td>31</td>
<td>316</td>
<td>32</td>
</tr>
<tr>
<td>1.58–1.62</td>
<td>274</td>
<td>27</td>
<td>261</td>
<td>27</td>
</tr>
<tr>
<td>1.63–1.67</td>
<td>118</td>
<td>12</td>
<td>122</td>
<td>12</td>
</tr>
<tr>
<td>1.68–1.88</td>
<td>302</td>
<td>30</td>
<td>283</td>
<td>29</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg) at age 20 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36.29–49.88</td>
<td>289</td>
<td>29</td>
<td>301</td>
<td>31</td>
</tr>
<tr>
<td>49.89–54.42</td>
<td>185</td>
<td>19</td>
<td>154</td>
<td>16</td>
</tr>
<tr>
<td>54.43–58.95</td>
<td>298</td>
<td>30</td>
<td>294</td>
<td>30</td>
</tr>
<tr>
<td>58.96–106.14</td>
<td>214</td>
<td>22</td>
<td>228</td>
<td>23</td>
</tr>
<tr>
<td>Unknown</td>
<td>20</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg) 1 year prior to reference date</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36.29–58.97</td>
<td>182</td>
<td>18</td>
<td>224</td>
<td>23</td>
</tr>
<tr>
<td>58.98–67.59</td>
<td>275</td>
<td>27</td>
<td>271</td>
<td>28</td>
</tr>
<tr>
<td>67.60–77.11</td>
<td>260</td>
<td>26</td>
<td>266</td>
<td>26</td>
</tr>
<tr>
<td>77.12–170.55</td>
<td>285</td>
<td>29</td>
<td>224</td>
<td>23</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age at reference date, number of pregnancies, months of hormone replacement therapy, history of breast cancer in a mother, sister, or daughter, and history of benign breast disease.
† OR, odds ratio; CI, confidence interval.
an increase in postmenopausal breast cancer risk of 111 percent was observed among those women who exhibited a fluctuating pattern of body size throughout adulthood, although these results were not statistically significant.

**DISCUSSION**

Results from this large case-control study of postmenopausal women support the hypothesis that greater gains in weight over the lifetime, particularly during the peri- and postmenopausal years, elevate a woman’s risk of postmenopausal breast cancer. Adjusting for residual confounding from obesity by examining weight change as a percentage of age 20 weight did not materially alter our findings, nor did consideration of caloric intake or dietary fat intake. Controlling for any confounding by body mass index at the beginning of the change interval also did not alter our results. Relative to women whose weight remained stable over the

<table>
<thead>
<tr>
<th>Body size variable</th>
<th>Cases No.</th>
<th>%</th>
<th>Controls No.</th>
<th>%</th>
<th>Age-adjusted OR*</th>
<th>95% CI*</th>
<th>Multivariate OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight change (kg) from age 20 years to age 30 years†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>–36.29 to –0.01</td>
<td>60</td>
<td>6</td>
<td>81</td>
<td>8</td>
<td>0.72</td>
<td>0.50, 1.06</td>
<td>0.66</td>
<td>0.43, 1.02</td>
</tr>
<tr>
<td>0.00</td>
<td>271</td>
<td>28</td>
<td>259</td>
<td>27</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>0.01 to 2.26</td>
<td>219</td>
<td>22</td>
<td>182</td>
<td>19</td>
<td>1.17</td>
<td>0.90, 1.52</td>
<td>1.20</td>
<td>0.90, 1.60</td>
</tr>
<tr>
<td>2.27 to 4.53</td>
<td>187</td>
<td>19</td>
<td>179</td>
<td>18</td>
<td>1.04</td>
<td>0.80, 1.37</td>
<td>1.09</td>
<td>0.82, 1.47</td>
</tr>
<tr>
<td>4.54 to 7.70</td>
<td>102</td>
<td>11</td>
<td>116</td>
<td>12</td>
<td>0.87</td>
<td>0.63, 1.19</td>
<td>0.88</td>
<td>0.62, 1.24</td>
</tr>
<tr>
<td>7.71 to 51.16</td>
<td>138</td>
<td>14</td>
<td>149</td>
<td>16</td>
<td>0.95</td>
<td>0.71, 1.27</td>
<td>1.05</td>
<td>0.76, 1.45</td>
</tr>
<tr>
<td>Unknown</td>
<td>29</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Weight change (kg) from age 20 years to 1 year prior to reference date†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>–44.91 to –3.01</td>
<td>36</td>
<td>4</td>
<td>61</td>
<td>6</td>
<td>0.64</td>
<td>0.39, 1.05</td>
<td>0.55</td>
<td>0.32, 0.96</td>
</tr>
<tr>
<td>–3.00 to 3.00</td>
<td>103</td>
<td>11</td>
<td>119</td>
<td>12</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>3.01 to 7.71</td>
<td>141</td>
<td>14</td>
<td>156</td>
<td>16</td>
<td>1.06</td>
<td>0.74, 1.50</td>
<td>1.03</td>
<td>0.70, 1.50</td>
</tr>
<tr>
<td>7.72 to 8.15</td>
<td>241</td>
<td>24</td>
<td>228</td>
<td>24</td>
<td>1.25</td>
<td>0.90, 1.72</td>
<td>1.18</td>
<td>0.83, 1.68</td>
</tr>
<tr>
<td>8.16 to 14.96</td>
<td>209</td>
<td>21</td>
<td>206</td>
<td>21</td>
<td>1.20</td>
<td>0.87, 1.67</td>
<td>1.21</td>
<td>0.84, 1.74</td>
</tr>
<tr>
<td>14.97 to 87.09</td>
<td>256</td>
<td>26</td>
<td>204</td>
<td>21</td>
<td>1.51</td>
<td>1.09, 2.08</td>
<td>1.58</td>
<td>1.11, 2.26</td>
</tr>
<tr>
<td>Unknown</td>
<td>33</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>Weight change (kg) from age 50 years to 1 year prior to reference date‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>–68.04 to –0.01</td>
<td>157</td>
<td>17</td>
<td>170</td>
<td>18</td>
<td>1.00</td>
<td>0.74, 1.37</td>
<td>1.19</td>
<td>0.85, 1.67</td>
</tr>
<tr>
<td>0.00</td>
<td>167</td>
<td>18</td>
<td>197</td>
<td>21</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>0.01 to 2.71</td>
<td>133</td>
<td>14</td>
<td>136</td>
<td>15</td>
<td>1.11</td>
<td>0.81, 1.53</td>
<td>1.19</td>
<td>0.84, 1.69</td>
</tr>
<tr>
<td>2.72 to 4.98</td>
<td>124</td>
<td>13</td>
<td>146</td>
<td>16</td>
<td>0.94</td>
<td>0.68, 1.30</td>
<td>0.96</td>
<td>0.68, 1.37</td>
</tr>
<tr>
<td>4.99 to 11.33</td>
<td>195</td>
<td>20</td>
<td>148</td>
<td>16</td>
<td>1.45</td>
<td>1.07, 1.97</td>
<td>1.58</td>
<td>1.14, 2.23</td>
</tr>
<tr>
<td>11.34 to 62.14</td>
<td>171</td>
<td>18</td>
<td>125</td>
<td>14</td>
<td>1.49</td>
<td>1.08, 2.05</td>
<td>1.62</td>
<td>1.14, 2.30</td>
</tr>
<tr>
<td>Unknown</td>
<td>59</td>
<td>68</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
<td></td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval.
† Multivariate odds ratio was adjusted for age at reference date, number of pregnancies, months of hormone replacement therapy, history of breast cancer in a mother, sister, or daughter, history of benign breast disease, and body mass index at age 20 years.
‡ Multivariate odds ratio was adjusted for age at reference date, number of pregnancies, months of hormone replacement therapy, history of breast cancer in a mother, sister, or daughter, history of benign breast disease, and body mass index at age 50 years.
lifetime, those who had gained more than 15 kg (33 pounds) since age 20 years were at a 58 percent increased risk of breast cancer. Subjects who had gained more than 11 kg (24 pounds) since age 50 years had 1.62-fold the breast cancer risk of those whose weight remained the same during this time period. Weight loss over the lifetime, defined as loss during the period from age 20 years to 1 year prior to the reference date, was associated with a 45 percent decrease in postmenopausal breast cancer risk.

Our observation of a 50–60 percent increased risk of postmenopausal breast cancer with greater weight gain over the lifetime is consistent with most (6, 19–36), but not all (37–39), other investigations that have examined change in body size throughout adulthood. The current study’s finding of a 1.6-fold increased risk of postmenopausal breast cancer related to greater body size gain in the peri- and postmenopausal years is consistent with the two other US case-control studies (26, 40) that have examined gain in later adulthood. Our finding of a reduced odds ratio of 0.55 in relation to lifetime weight loss confirms results of an earlier report (25) but has not been replicated by other investigators (6, 24, 26, 28, 39).

Our finding that peri- and postmenopausal weight gain increased the risk of postmenopausal breast cancer only among women who reported never using hormone replacement therapy supports the hypothesis that among ever users of hormone replacement therapy, plasma estrogen levels are elevated by exogenous hormones even among lean women; this may mask any effect of adiposity on breast cancer risk, since the increases in estrogen levels brought about by pharmacologic doses are usually higher than those associated with obesity alone (20, 41). Thus, only among women who had never used hormone replacement therapy was a clear positive association between body size gain and

<table>
<thead>
<tr>
<th>Weight change (kg) from age 50 years to 1 year prior to reference date</th>
<th>Use of hormone replacement therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never (680 cases, 670 controls)</td>
</tr>
<tr>
<td>Weight change (kg) from age 50 years to 1 year prior to reference date</td>
<td>OR†</td>
</tr>
<tr>
<td>-68.04 to -0.01</td>
<td>1.10</td>
</tr>
<tr>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.01 to 2.71</td>
<td>1.22</td>
</tr>
<tr>
<td>2.72 to 4.98</td>
<td>0.99</td>
</tr>
<tr>
<td>4.99 to 11.33</td>
<td>1.89</td>
</tr>
<tr>
<td>11.34 to 62.14</td>
<td>2.02</td>
</tr>
</tbody>
</table>

* Adjusted for age at reference date, number of pregnancies, months of hormone replacement therapy, history of breast cancer in a mother, sister, or daughter, history of benign breast disease, and body mass index at age 50 years.
† OR, odds ratio; CI, confidence interval.

Our finding of a reduced odds ratio of 0.55 in relation to lifetime weight loss confirms results of an earlier report (25) but has not been replicated by other investigators (6, 24, 26, 28, 39).

Our finding that peri- and postmenopausal weight gain increased the risk of postmenopausal breast cancer only among women who reported never using hormone replacement therapy supports the hypothesis that among ever users of hormone replacement therapy, plasma estrogen levels are elevated by exogenous hormones even among lean women; this may mask any effect of adiposity on breast cancer risk, since the increases in estrogen levels brought about by pharmacologic doses are usually higher than those associated with obesity alone (20, 41). Thus, only among women who had never used hormone replacement therapy was a clear positive association between body size gain and

<table>
<thead>
<tr>
<th>Weight change (kg) from age 50 years to 1 year prior to reference date</th>
<th>Estrogen receptor (ER)/progesterone receptor (PR) status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ER+/PR+ (387 cases, 990 controls)</td>
</tr>
<tr>
<td>Weight change (kg) from age 50 years to 1 year prior to reference date</td>
<td>OR†</td>
</tr>
<tr>
<td>-68.04 to -0.01</td>
<td>1.27</td>
</tr>
<tr>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>0.01 to 2.71</td>
<td>1.45</td>
</tr>
<tr>
<td>2.72 to 4.98</td>
<td>1.00</td>
</tr>
<tr>
<td>4.99 to 11.33</td>
<td>1.54</td>
</tr>
<tr>
<td>11.34 to 62.14</td>
<td>2.17</td>
</tr>
</tbody>
</table>

* Adjusted for age at reference date, number of pregnancies, months of hormone replacement therapy, history of breast cancer in a mother, sister, or daughter, history of benign breast disease, and body mass index at age 50 years.
† OR, odds ratio; CI, confidence interval.
Greater weight gain was associated with a twofold increase in risk of ER+/PR+/postmenopausal breast cancer. This finding suggests that body size gain later in life may preferentially lead to ER+/PR+/ tumors among postmenopausal women, which supports the hypothesis that hormone receptor status defines biologically unique cancers with different etiologic pathways (42). However, cell sizes were particularly small for non-ER+/PR+/ cases in comparison with ER+/PR+/ cases, making it possible that comparisons within these groups were underpowered. These results are similar to those from the two studies that examined the relation of body size change to postmenopausal breast cancer risk according to estrogen receptor/progesterone receptor status (29, 43).

Patterns of weight cycling throughout the lifetime were examined in an exploratory fashion in our study. The referent group for pattern analyses was women who remained consistently below the median control body size across all four time periods examined. Women who were consistently above the control median weight were at significantly increased risk of postmenopausal breast cancer. There was also the suggestion that women who switched at menopause from being below the control median body size to above the control median were also at increased risk, although cell sizes for this pattern were small. There have been suggestions that such fluctuation in body size may be indicative of a preference for foods high in dietary fat or may adversely affect health via its effects on metabolic rate, body composition, and fat distribution (44, 45). While numbers for pattern analyses were small, there was no indication in our study that subjects with lifetime weight fluctuations had significantly greater dietary fat intakes than those whose weight remained more consistent (data not shown). To date, only one study has examined the effect of weight loss followed by weight gain on risk of postmenopausal breast cancer (26); no relation was reported between this definition of weight cycling and breast cancer.

Effects of recall bias may have been minimized in our study, since hypotheses relating breast cancer to body size gain were probably not well-known at the time the LIBCSP interviews were conducted. Additionally, height and weight questions would appear normal within the setting of a health study interview. Lower body weight has been promulgated as being socially desirable and indicative of a healthier lifestyle, making it possible that both cases and controls underestimated their body sizes and gains. If such nondifferential misclassification of exposure did occur in this study, the true effect of any gains in body size may have been attenuated toward the null value (46) or been inflated, since the exposure variable was not simply dichotomous (47).

Recall of body size information from the distant past is of potential concern. An investigation examining the long-term recall of high school height and weight among elderly subjects compared recalled values with measurements obtained during adolescence (48). Recalled and measured high school weight showed good correlation with one another, although there was slightly more underestimation with greater variability of high school weight among females who were obese as adolescents compared with those who were lean. No differences in high school weight recall were observed by adult body size. Another measurement-related concern in this

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Cases No.</th>
<th>Cases %</th>
<th>Controls No.</th>
<th>Controls %</th>
<th>Odds ratio 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistently low weight</td>
<td>216</td>
<td>28</td>
<td>229</td>
<td>30</td>
<td>1.00</td>
</tr>
<tr>
<td>Consistently high weight</td>
<td>240</td>
<td>31</td>
<td>227</td>
<td>30</td>
<td>1.22</td>
</tr>
<tr>
<td>Weight high in early adulthood and early mid-adulthood, low in peri- and postmenopausal years</td>
<td>63</td>
<td>8</td>
<td>73</td>
<td>9</td>
<td>0.96</td>
</tr>
<tr>
<td>Weight high in early adulthood, low in subsequent adulthood</td>
<td>58</td>
<td>8</td>
<td>53</td>
<td>7</td>
<td>1.18</td>
</tr>
<tr>
<td>Weight low in early adulthood, high in subsequent adulthood</td>
<td>48</td>
<td>6</td>
<td>58</td>
<td>8</td>
<td>0.82</td>
</tr>
<tr>
<td>Weight low in early adulthood and up to menopause, high in postmenopausal years</td>
<td>46</td>
<td>6</td>
<td>42</td>
<td>6</td>
<td>1.23</td>
</tr>
<tr>
<td>Weight high in early adulthood and up to menopause, low in postmenopausal years</td>
<td>48</td>
<td>6</td>
<td>32</td>
<td>4</td>
<td>1.52</td>
</tr>
<tr>
<td>Weight high in early adulthood and up to subsequent adulthood</td>
<td>30</td>
<td>4</td>
<td>34</td>
<td>4</td>
<td>0.97</td>
</tr>
<tr>
<td>Fluctuating weight</td>
<td>22</td>
<td>3</td>
<td>12</td>
<td>2</td>
<td>2.11</td>
</tr>
</tbody>
</table>

* Adjusted for age at reference date, number of pregnancies, lactation status, nulliparity, history of breast cancer in a mother, sister, or daughter, and history of benign breast disease.
† See Materials and Methods for explanation of patterns. “High” = greater than or equal to the control median; “low” = less than the control median.


that body size increases may preferentially lead to ER
by avoiding weight gain during this period. The possibility
women can still modify their breast cancer risk later in life
on the perimenopausal weight trajectory, suggesting that
significant public health issues. The current study adds to
(52), underscore the fact that weight gain and obesity are
51) and observations from prospective studies documenting
of increasing overweight and obesity in the United States (50,
population. These results, taken together with current trends
a decreased risk of postmenopausal breast cancer in our study
pear to be obscured by postmenopausal hormone use. Greater
body size change interval. The effects of body size gain ap-
ularly during the peri- and postmenopausal years, indepen-
breast cancer and weight gain throughout adulthood, partic-
this study had numerous strengths, including a large sam-
ple size, which increased the study’s power to detect small
associations and allowed for subgroup analyses. The study’s
population-based design and its reasonable overall response
rates (12) reduced the likelihood of biased sample selection
and increased the findings’ generalizability to all Long Island
women. Use of a comprehensive interviewer-administered
questionnaire provided detailed and well-measured informa-
tion on study variables, reducing misclassification and
enhancing study precision.

We report a positive association between postmenopausal
breast cancer and weight gain throughout adulthood, partic-
ularly during the peri- and postmenopausal years, independ-
ent of body size at age 20 years and at the beginning of the
body size change interval. The effects of body size gain ap-
pear to be obscured by postmenopausal hormone use. Greater
body size gains may increase the risk of ER+/PR+ breast
cancer. Weight loss over the lifetime was associated with a
decreased risk of postmenopausal breast cancer in our study
population. These results, taken together with current trends
of increasing overweight and obesity in the United States (50,
51) and observations from prospective studies documenting
greater mortality from cancer with increased body weight
(52), underscore the fact that weight gain and obesity are
significant public health issues. The current study adds to
the anthropometry and breast cancer literature by focusing
on the perimenopausal weight trajectory, suggesting that
women can still modify their breast cancer risk later in life
by avoiding weight gain during this period. The possibility
that body size increases may preferentially lead to ER+/PR+
breast cancers postmenopausally deserves further study.

ACKNOWLEDGMENTS

This work was supported in part by grants from the Na-
tional Cancer Institute and the National Institute of Environ-
mental Health Sciences (grants T32CA09529, U01CA66572,
K05CA89155, and P30ES10126), the Breast Cancer Re-
search Foundation, and the Babylon Breast Cancer Coalition.

For their valuable contributions to the Long Island Breast
Cancer Study Project, the authors thank the members of the
Long Island Breast Cancer Network; the 31 participating
institutions on Long Island and in New York City; their
National Institutes of Health collaborators, Dr. Gwen Colman
of the National Institute of Environmental Health Sciences
and Dr. G. Iris Obromas, formerly of the National Cancer
Institute; and members of the External Advisory Committee
to the population-based case-control study: Dr. Leslie Bernstein
(chair), Gerald Akland, Barbara Balaban, Dr. Blake Cady,
Dr. Dale Sandler, Dr. Roy Shore, and Dr. Gerald Wogan.
Conflict of interest: none declared.

REFERENCES

menarche, age at menopause, height and obesity as risk factors
for breast cancer: associations and interactions in an interna-
3. Layde PM, Webster LA, Baughman AL, et al. The independent
associations of parity, age at first full term pregnancy, and
duration of breastfeeding with the risk of breast cancer. Cancer
42:963–73.
4. Ewertz M, Duffy SW, Adami HO, et al. Age at first birth,
parity and risk of breast cancer: a meta-analysis of 8 studies
5. Cleary MP, Maible NJ. The role of body mass index in the
relative risk of developing premenopausal versus postmen-
28–43.
of change in body mass with breast cancer. Cancer Res 1990;
50:2152–5.
7. Siiteri PK. Adipose tissue as a source of hormones. Am J Clin
Nutr 1987;45:277–82.
8. Evans DJ, Hoffmann RG, Kalkhoff RK, et al. Relationship of
androgenic activity to body fat topography, fat cell morphol-
ogy, and metabolic aberrations in premenopausal women.
9. Mountjoy KG, Finlay GJ, Holdaway IM. Abnormal insulin-
receptor down regulation and dissociation of down regulation
from insulin biological action in cultured human tumor cells.
10. Stoll BA. Breast cancer: the obesity connection. Br J Cancer
11. Sepp-Lorenzino L, Rosen N, Lebwohl DE. Insulin and insulin-
like growth factor signaling are defective in the MDA MB-468
5:1077–83.
Breast Cancer Study Project: description of a multi-institutional

Body Size Changes and Postmenopausal Breast Cancer

45. Jeffery RW. Does weight cycling provide a health risk? Am J Clin Nutr 1996;63(suppl):452S–5S.