Background: A high body mass index (BMI) has been related to a reduced risk of breast cancer in premenopausal women. The mechanisms underlying this association have not been elucidated.

Methods: We explored whether factors affecting ovulation may explain the inverse association between BMI (calculated as weight in kilograms divided by the square of height in meters) and breast cancer in 113,130 premenopausal participants in the Nurses’ Health Study II. During 1,225,520 person-years of prospective follow-up between 1989 and 2003, 1,398 incident cases of invasive breast cancer were diagnosed. Weight, height, ovulatory infertility, menstrual cycle patterns, and a multitude of covariates were assessed throughout follow-up. Cox proportional hazards regression was used to compute hazard ratios and 95% confidence intervals (CIs).

Results: We observed a significant linear inverse trend between current BMI and breast cancer incidence (P < .001) that was not explained by menstrual cycle characteristics or infertility due to an ovulatory disorder (covariate-adjusted hazard ratio for breast cancer in women with a BMI ≥30 vs 20.0-22.4, 0.81; 95% CI, 0.68-0.96). We found BMI at age 18 years to be the strongest predictor of breast cancer incidence (covariate-adjusted hazard ratio for breast cancer in women with a BMI at age 18 years ≥27.5 vs 20.0-22.4, 0.37; 95% CI, 0.41-0.81).

Conclusions: Body size during the early phases of adult life seems to be particularly important in the development of premenopausal breast cancer. Factors other than anovulation are likely to mediate the protection conferred by a high BMI.

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THE INVERSE ASSOCIATION BETWEEN body mass index (BMI) and the risk of breast cancer among premenopausal women has been observed in numerous studies, but the biological mechanisms underlying this perplexing link have remained largely unresolved. A high BMI can be associated with irregular or long menstrual cycles or with polycystic ovary syndrome (PCOS), and it has been suggested that anovulation, which is associated with such characteristics and with decreased estradiol and progesterone levels, may explain the lower risk of breast cancer in these women. However, few studies have explored whether these or other factors provide mechanistic insights into the unexpected protection that a high body mass confers on the premenopausal breast.

We investigated whether menstrual cycle characteristics, infertility due to an ovulatory disorder, or PCOS might explain the inverse association between BMI and premenopausal breast cancer incidence in participants in the Nurses’ Health Study II (NHS II).

METHODS

STUDY POPULATION: NHS II

In 1989, 116,609 female registered nurses aged 25 to 42 years living in 1 of 14 US states responded to a self-administered questionnaire about their medical history and lifestyle. Participants have since been followed up by means of biennial questionnaires updating information on demographic variables, lifestyle factors, and medical events.

For this analysis, women were excluded at baseline in 1989 if they were postmenopausal (n = 2813), reported cancer (n = 989), were missing the date of diagnosis of invasive breast cancer (n = 28), or were missing information on height or weight (n = 322) (not mutually exclusive). This study was approved by the institutional review boards of Brigham and Women’s Hospital and Harvard School of Public Health.

ASSESSMENT OF EXPOSURE AND COVARIATE INFORMATION

Information on height, weight at age 18 years, and current weight was obtained via the NHS II baseline questionnaire in 1989. The infor-
mation on current weight was updated every 2 years. The BMI was calculated (as weight in kilograms divided by the square of height in meters) for age 18 years and at all prospective follow-up questionnaire cycles.

On the baseline questionnaire, participants reported characteristics of their menstrual cycle. Information was requested on cycle length (<21 days, 21-25 days, 26-31 days, 32-39 days, >30 days, >50 days, or too irregular to estimate) and pattern (very regular [±3 days], regular, usually irregular, always irregular, or no periods) at ages 18 to 22 years, excluding those who were pregnant or using oral contraceptives. In 1993, the participants were asked to describe their current menstrual cycle length and pattern using the same categories offered in the baseline questionnaire.

Infertility status was assessed at baseline and on every subsequent questionnaire. Participants were asked whether they had tried to get pregnant for 1 year without success. If they answered “yes,” they were asked to indicate the cause(s) of their infertility: tubal blockage, ovulatory disorder, endometriosis, cervical mucous factors, factors related to their spouse, no investigation done, cause not found, or other. Polycystic ovary syndrome was defined as probable if a participant had at least 3 of the following 4 characteristics: hirsutism, a BMI of 27 or greater, irregular menstrual cycles, and infertility due to an ovulatory disorder.

Information on potential confounding variables was assessed at baseline and during follow-up. Participants were asked for their date of birth, age at menarche, and family history of breast cancer (in mother, sister, or grandmother) at baseline. History of benign breast disease, parity, age at first birth, alcohol consumption, oral contraceptive use, and physical activity were assessed via the baseline and subsequent questionnaires. Data from subsequent questionnaires were used to update information on confounding variables for each individual in each period.

ASCERTAINMENT OF BREAST CANCER CASES

New cases of breast cancer were identified through the biennial questionnaires mailed between 1989 and 2003. Deaths were reported by family members or by the US Postal Service in response to the follow-up questionnaires, and the National Death Index was searched to investigate the deaths of nonresponders. When a case of breast cancer was reported, we asked the participant (or next of kin for those who had died) for confirmation of the diagnosis and for permission to obtain relevant hospital records and pathology reports. Medical records were obtained for more than 90% of the cases. Pathology reports confirmed breast cancer in more than 99% of the women whose reports were reviewed. We restricted the study end point to invasive breast cancer. Cases of carcinoma in situ were censored at the time of diagnosis.

STATISTICAL ANALYSIS

Women were followed up prospectively from the time they first reported their weight and height in 1989 until the end of follow-up in 2003. Person-years of follow-up were calculated as the time from completion of the 1989 questionnaire to the date of return of the 2003 questionnaire, the date of diagnosis of invasive or in situ breast cancer, any other cancer (except nonmelanoma skin cancer), death, loss to follow-up, or reaching menopause, whichever occurred first. Women were also censored if they did not report their weight on 3 or more questionnaires. The total number of observations varied between analyses depending on the number of women missing the main exposure (ie, current BMI or BMI at age 18 years) or outcome of interest (ie, receptor-specific breast cancer).

A Cox proportional hazards regression model was used to calculate the hazard of developing invasive breast cancer associated with a particular level of BMI. For the analysis of current BMI, weight reported on the questionnaire preceding the report of an incident breast cancer diagnosis was used. We assessed the association between current BMI or BMI at age 18 years and breast cancer incidence, adjusting for age (in months), family history of breast cancer in a first-degree relative (dichotomous), history of benign breast disease (dichotomous), age at menarche (≤10, 11, 12, 13, 14, ≥15 years), parity (0, 1, 2, 3, or ≥4), age at first birth (≤24, 25-30, or ≥30 years), oral contraceptive use (never, past for >5 years, current for ≥5 years, current for 5-9 years, or current for ≥10 years), alcohol intake (none, <7.5 g/d, 7.5-14 g/d, ≥15-29 g/d, or ≥30 g/d), physical activity (≤3, 3-8, 9-17, 18-26, 27-41, or ≥42 metabolic equivalents per week), menstrual cycle characteristics (≤25 days and regular, 26-31 days and regular, ≥32 days and regular, ≤25 days and irregular, 26-31 days and irregular, or ≥32 days and irregular), infertility due to an ovulatory disorder (dichotomous), and probable PCOS (dichotomous). Covariate values were updated in the analysis whenever new information was obtained from the biennial questionnaire.

Analyses were stratified by menstrual cycle length (<32 vs ≥32 days), age (<40 vs ≥40 years), and use of oral contraceptives (current, past, or never). Effect modification was assessed by creating the cross-products between BMI and each potential effect modifier. We measured the significance of potential effect modification using the likelihood ratio test, comparing a model with the cross-products representing interaction terms and the nested model without these terms. Separate analyses were performed for estrogen receptor (ER)-positive and ER-negative breast cancer and for progesterone receptor (PR)-positive and PR-negative breast cancer. We used polytomous logistic regression with 3 outcome categories (ER-positive breast cancer, ER-negative breast cancer, and no breast cancer or PR-positive breast cancer, PR-negative breast cancer, and no breast cancer) to evaluate whether trends in BMI at age 18 years and in current BMI differed by the receptor status of the tumor. Likelihood ratio tests with 1 df were used to compare a model with different slopes for each outcome with a model with a common slope. We used χ² tests to obtain 2-sided P values for the likelihood ratio statistics. Trend tests were performed using the midpoint of the intervals. All the tests of statistical significance were 2-sided.

RESULTS

During 1 225 520 person-years of follow-up, 1398 incident cases of invasive breast cancer were diagnosed in this premenopausal population, which included 113 130 women. Women with a higher current BMI were older, had a higher BMI at age 18 years, had an earlier age at menarche, were less likely to have a history of benign breast disease, were more likely to report menstrual cycle irregularity in 1993 and a history of ovulatory infertility, and reported lower alcohol consumption than women with a lower BMI (Table 1). Women on both ends of the BMI distribution were more likely to be nulliparous than women in the middle categories (Table 1).

We observed a significant linear inverse trend between current BMI and breast cancer incidence (P < .001) (Table 2). Women with a BMI of 30.0 or higher had an age-adjusted hazard ratio for breast cancer of 0.79 (95% confidence interval [CI], 0.67-0.94) compared with...
women with a BMI between 20.0 and 22.4. Further adjustment for a family history of breast cancer, a history of benign breast disease, height, age at menarche, age at first birth, parity, alcohol consumption, physical activity, and current or past use of oral contraceptives did not alter this estimate appreciably (Table 2). Additionally, adjusting for menstrual cycle characteristics, infertility due to an ovulatory disorder, or probable PCOS similarly did not affect the estimates (Table 2). When the analysis of current BMI and breast cancer was adjusted for BMI at age 18 years, the association was considerably attenuated, eliminating the previously significant trend (Table 2). Restricting the analysis to women with no reported history of infertility due to an ovulatory disorder did not appreciably change the results (data not shown). Body mass index at age 18 years was significantly inversely associated with the incidence of premenopausal breast cancer (Table 3). Women with a BMI of 27.5 or higher at age 18 years had a covariate-adjusted hazard ratio of 0.57 (95% CI, 0.41-0.81) compared with women with a BMI between 20.0 and 22.4 at age 18 years. This association did not appreciably change when adjusting for current BMI (Table 3). Similarly, adjustment for waist-hip ratio did not alter the association (data not shown).

Separate analyses were also performed for ER-positive and ER-negative breast cancer cases and for PR-positive and PR-negative breast cancer cases.
### Table 3. BMI at Age 18 Years and the Incidence of Breast Cancer in Premenopausal Participants in the Nurses’ Health Study II, 1989-2003

<table>
<thead>
<tr>
<th>BMI at Age 18 y</th>
<th>Cases, No.</th>
<th>Follow-up, Person-Years</th>
<th>Age Adjusted Hazard Ratio (95% CI)</th>
<th>Multivariate* Hazard Ratio (95% CI)</th>
<th>Multivariate Controlling for Current BMI Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>136</td>
<td>111 348</td>
<td>1.08 (0.89-1.30)</td>
<td>1.04 (0.86-1.26)</td>
<td>1.01 (0.83-1.23)</td>
</tr>
<tr>
<td>18.5-19.9</td>
<td>462</td>
<td>367 883</td>
<td>1.12 (0.99-1.27)</td>
<td>1.09 (0.96-1.24)</td>
<td>1.07 (0.94-1.22)</td>
</tr>
<tr>
<td>20.0-22.4</td>
<td>496</td>
<td>439 847</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>22.5-24.9</td>
<td>191</td>
<td>172 230</td>
<td>0.99 (0.84-1.17)</td>
<td>0.99 (0.84-1.17)</td>
<td>1.01 (0.85-1.20)</td>
</tr>
<tr>
<td>25.0-27.4</td>
<td>59</td>
<td>69 316</td>
<td>0.76 (0.58-0.99)</td>
<td>0.73 (0.56-0.96)</td>
<td>0.76 (0.57-1.01)</td>
</tr>
<tr>
<td>≥27.5</td>
<td>35</td>
<td>54 058</td>
<td>0.60 (0.42-0.84)</td>
<td>0.57 (0.41-0.81)</td>
<td>0.61 (0.42-0.87)</td>
</tr>
<tr>
<td>Test for trend, P value</td>
<td>NA</td>
<td>&lt;.001</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Continuous BMI at age 18 y (per 5-U increase in BMI)</td>
<td>1379</td>
<td>1 214 682</td>
<td>0.80 (0.73-0.89)</td>
<td>0.81 (0.73-0.89)</td>
<td>0.83 (0.74-0.94)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; NA, not applicable.

*Adjusted for age, family history of breast cancer, history of benign breast disease, height, age at menarche, age at first birth, parity, alcohol consumption, physical activity, and current and past oral contraceptive use.

### Table 4. Current BMI and the Incidence of Receptor-Specific Breast Cancer in Premenopausal Participants in the Nurses’ Health Study II, 1989-2003

<table>
<thead>
<tr>
<th>Current BMI</th>
<th>Cases, No.</th>
<th>Follow-up, Person-Years</th>
<th>Age Adjusted Hazard Ratio (95% CI)</th>
<th>Multivariate* Hazard Ratio (95% CI)</th>
<th>Multivariate Controlling for Current BMI Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER-positive cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20.0</td>
<td>69</td>
<td>134 061</td>
<td>1.05 (0.80-1.39)</td>
<td>1.04 (0.79-1.38)</td>
<td></td>
</tr>
<tr>
<td>20.0-22.4</td>
<td>184</td>
<td>326 739</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>22.5-24.9</td>
<td>147</td>
<td>277 708</td>
<td>0.84 (0.68-1.05)</td>
<td>0.86 (0.69-1.07)</td>
<td></td>
</tr>
<tr>
<td>25.0-27.4</td>
<td>98</td>
<td>183 143</td>
<td>0.79 (0.62-1.01)</td>
<td>0.81 (0.63-1.04)</td>
<td></td>
</tr>
<tr>
<td>27.5-29.9</td>
<td>60</td>
<td>97 064</td>
<td>0.88 (0.66-1.18)</td>
<td>0.91 (0.68-1.23)</td>
<td></td>
</tr>
<tr>
<td>≥30.0</td>
<td>111</td>
<td>206 036</td>
<td>0.73 (0.58-0.93)</td>
<td>0.76 (0.59-0.97)</td>
<td></td>
</tr>
<tr>
<td>Test for trend, P value</td>
<td>NA</td>
<td>NA</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>.01</td>
</tr>
<tr>
<td>Continuous BMI†</td>
<td>669</td>
<td>1 224 750</td>
<td>0.89 (0.83-0.97)</td>
<td>0.91 (0.84-0.99)</td>
<td></td>
</tr>
<tr>
<td>ER-negative cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20.0</td>
<td>25</td>
<td>134 008</td>
<td>0.90 (0.57-1.42)</td>
<td>0.89 (0.56-1.40)</td>
<td></td>
</tr>
<tr>
<td>20.0-22.4</td>
<td>74</td>
<td>326 610</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>22.5-24.9</td>
<td>63</td>
<td>277 615</td>
<td>0.94 (0.67-1.32)</td>
<td>0.96 (0.68-1.35)</td>
<td></td>
</tr>
<tr>
<td>25.0-27.4</td>
<td>47</td>
<td>183 081</td>
<td>1.05 (0.73-1.52)</td>
<td>1.07 (0.74-1.55)</td>
<td></td>
</tr>
<tr>
<td>27.5-29.9</td>
<td>19</td>
<td>97 020</td>
<td>0.79 (0.48-1.32)</td>
<td>0.81 (0.48-1.35)</td>
<td></td>
</tr>
<tr>
<td>≥30.0</td>
<td>57</td>
<td>205 975</td>
<td>1.10 (0.77-1.55)</td>
<td>1.10 (0.76-1.58)</td>
<td></td>
</tr>
<tr>
<td>Test for trend, P value</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>.04</td>
<td>.02</td>
</tr>
<tr>
<td>Continuous BMI†</td>
<td>285</td>
<td>1 224 309</td>
<td>1.03 (0.91-1.14)</td>
<td>1.03 (0.91-1.15)</td>
<td></td>
</tr>
<tr>
<td>PR-positive cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20.0</td>
<td>62</td>
<td>134 052</td>
<td>1.03 (0.77-1.38)</td>
<td>1.01 (0.75-1.35)</td>
<td></td>
</tr>
<tr>
<td>20.0-22.4</td>
<td>170</td>
<td>326 724</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>22.5-24.9</td>
<td>140</td>
<td>277 695</td>
<td>0.87 (0.70-1.09)</td>
<td>0.89 (0.71-1.11)</td>
<td></td>
</tr>
<tr>
<td>25.0-27.4</td>
<td>93</td>
<td>183 141</td>
<td>0.81 (0.63-1.05)</td>
<td>0.83 (0.64-1.08)</td>
<td></td>
</tr>
<tr>
<td>27.5-29.9</td>
<td>60</td>
<td>97 063</td>
<td>0.96 (0.71-1.29)</td>
<td>0.99 (0.73-1.33)</td>
<td></td>
</tr>
<tr>
<td>≥30.0</td>
<td>111</td>
<td>206 035</td>
<td>0.79 (0.62-1.01)</td>
<td>0.81 (0.63-1.05)</td>
<td></td>
</tr>
<tr>
<td>Test for trend, P value</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>.05</td>
<td>.12</td>
</tr>
<tr>
<td>Continuous BMI†</td>
<td>636</td>
<td>1 224 710</td>
<td>0.93 (0.85-1.00)</td>
<td>0.94 (0.86-1.02)</td>
<td></td>
</tr>
<tr>
<td>PR-negative cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20.0</td>
<td>31</td>
<td>134 016</td>
<td>1.02 (0.68-1.55)</td>
<td>1.02 (0.67-1.54)</td>
<td></td>
</tr>
<tr>
<td>20.0-22.4</td>
<td>81</td>
<td>326 615</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>22.5-24.9</td>
<td>63</td>
<td>277 617</td>
<td>0.86 (0.62-1.19)</td>
<td>0.87 (0.63-1.22)</td>
<td></td>
</tr>
<tr>
<td>25.0-27.4</td>
<td>49</td>
<td>183 081</td>
<td>0.98 (0.69-1.40)</td>
<td>1.01 (0.70-1.44)</td>
<td></td>
</tr>
<tr>
<td>27.5-29.9</td>
<td>19</td>
<td>97 021</td>
<td>0.70 (0.43-1.16)</td>
<td>0.73 (0.44-1.21)</td>
<td></td>
</tr>
<tr>
<td>≥30.0</td>
<td>57</td>
<td>205 977</td>
<td>0.97 (0.69-1.37)</td>
<td>1.01 (0.71-1.45)</td>
<td></td>
</tr>
<tr>
<td>Test for trend, P value</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>.67</td>
<td>.87</td>
</tr>
<tr>
<td>Continuous BMI†</td>
<td>300</td>
<td>1 224 327</td>
<td>0.96 (0.86-1.08)</td>
<td>0.98 (0.86-1.10)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; ER, estrogen receptor; NA, not applicable; PR, progesterone receptor.

*Adjusted for age, family history of breast cancer, history of benign breast disease, height, age at menarche, age at first birth, parity, alcohol consumption, physical activity, and current and past oral contraceptive use.

†Per 5-U increase in BMI.
The association between current BMI and premenopausal breast cancer incidence was stronger for ER-positive than ER-negative cases \((P\text{ for heterogeneity}=0.19)\), whereas no apparent difference was observed between PR-positive and PR-negative cases \((P\text{ for heterogeneity}=0.94)\) (Table 4). The association with BMI at age 18 years was also strongest for ER-positive breast cancer \((P\text{ for heterogeneity}=0.68\text{ for ER and 0.78 for PR})\) (Table 5). When we stratified by menstrual cycle length at ages 18 to 22 years \((<32\text{ vs }\geq 32\text{ days})\), associations were somewhat stronger in women with longer cycle durations, but there was no significant heterogeneity \((P\text{ for heterogeneity}=0.72)\) (Table 6). No effect modification by age or use of oral contraceptives was apparent.

Women with probable PCOS had a covariate-adjusted hazard ratio for breast cancer of 0.89 (95% CI, 0.71-1.10) compared with women who were unlikely to have PCOS. When also adjusting for BMI at age 18 years and for current BMI, the hazard ratio for breast cancer associated with PCOS was 0.98 (95% CI, 0.78-1.23), indicating that any association between PCOS and breast cancer is likely to be mediated by BMI rather than other characteristics of PCOS.

**COMMENT**

Among the premenopausal participants in the NHS II, a high BMI was inversely associated with the incidence of breast cancer. This association was not explained by menstrual cycle characteristics, self-reported infertility due to an ovulatory disorder, or probable PCOS. The BMI at age 18 years, however, explained part of the association between current BMI and breast cancer incidence.

In several studies, an inverse association has been reported between body size and premenopausal breast cancer. Of studies in which the relation between BMI at ages 16 to 25 years and the risk of breast cancer was explored, a significant inverse association with premenopausal breast cancer risk was found in some\(^{11,18,20}\) but not all.\(^{14,21-26}\) High current BMI has been linked to a reduced risk of breast cancer in premenopausal women or...
in women younger than 50 to 55 years in numerous studies, but this link was not confirmed in other studies. In a pooled analysis of 7 prospective cohort studies including 337,819 women and 723 incident cases of invasive premenopausal breast cancer, a nonlinear association between BMI and premenopausal breast cancer was found; women with a BMI exceeding 31 had a relative risk of 0.54 (95% CI, 0.34-0.85) compared with women with a BMI of 21 or less. In 3 studies, a positive association between BMI and breast cancer diagnosed before menopause or before age 55 years was observed.

Key and Pike suggested that the mechanism underlying the inverse association between BMI and premenopausal breast cancer is anovulation in the heavier women, resulting in decreased estradiol and progesterone levels. We cannot exclude a possible role of anovulation because we cannot measure anovulation directly. However, because adjustment for menstrual cycle patterns, infertility due to ovulatory disorder, probable PCOS, and use of oral contraceptives did not even slightly attenuate the association with BMI, anovulation does not seem to be a primary explanation for the reduced risk in heavier women. Among women with no history of infertility due to an ovulatory disorder, the inverse association between BMI and premenopausal breast cancer incidence persisted, lending further support to the role of mechanisms other than anovulation. In the same population, women with infertility due to an ovulatory disorder had a lower incidence of premenopausal breast cancer, whereas menstrual cycle pattern was not associated with breast cancer incidence except in women younger than 40 years.

In this population of premenopausal women, BMI during earlier periods of adult life was more consistently associated with breast cancer incidence than BMI during adulthood. Body fatness during childhood has also been related to a lower incidence of breast cancer in the premenopausal women of the NHS II. A high BMI during adulthood is highly correlated with a high body mass during adolescence, which may be more important for the development of breast cancer before menopause. Although a high birth weight has been fairly consistently linked to an increase in the risk of premenopausal breast cancer, the BMI-breast cancer association seems to reverse at some point during the first years of life, only to revert back after menopause.

Because BMI was more clearly related to ER-positive than ER-negative breast cancer, a role of sex steroid hormones is likely. High plasma estradiol levels have been associated with an increased risk of premenopausal breast cancer in some studies but not in others. Most studies collected samples at any time in the menstrual cycle, making interpretation more difficult given the fluctuation of estradiol levels and other sex steroid hormone levels throughout the menstrual cycle. In the NHS II, 18,506 premenopausal women provided blood samples in the early follicular and midluteal phases; higher levels of follicular total and free estradiol levels were associated with an increased incidence of breast cancer, whereas no association was apparent for estradiol levels in the luteal phase.

Premenopausal overweight women have been found to have lower estradiol levels than lean women, but the evidence is inconsistent. In studies in which the collection of blood specimens was timed during the menstrual cycle, a significant inverse association between total estradiol concentration and BMI was found and a nonsignificant inverse association was found in another. In the NHS II, we also observed a significant inverse association between total estradiol levels during the follicular and luteal phases and BMI at blood sampling but not between free estradiol levels and BMI. Obese women have decreased levels of sex hormone–binding globulin. Because sex hormone–binding globulin is the main protein carrier of estradiol, free estradiol levels should increase with higher BMI, but the pituitary gland and hypothalamus regulate free estradiol in premenopausal women; hence ovarian production of estradiol may be kept low. Potischman et al suggested that more free estradiol may be cleared by the liver and other tissues in obese women. Alternatively, obese women may experience ovulatory insufficiency, resulting in compromised estradiol production capacity. Whether decreased estrogen blood levels in obese premenopausal women explain the inverse association with breast cancer remains to be determined. The observation that this inverse association is stronger for ER-positive breast cancer lends support to this mechanism.

Finally, detection bias has to be considered as a possible explanation for the observed associations. Obese women are less likely to seek breast cancer screening than normal-weight women. It is possible that obese women with preclinical breast cancer delay their diagnosis, moving the detection of their cancer from the premenopausal to the postmenopausal phase.

In conclusion, a large body size during early adulthood is inversely related to the incidence of breast can-
cer in premenopausal women. Factors related to ovulation, such as menstrual cycle characteristics, infertility due to an ovulatory disorder, and probable PCOS, do not seem to explain this association.

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