Menstrual Cycle Characteristics and History of Ovulatory Infertility in Relation to Breast Cancer Risk in a Large Cohort of US Women

Menstrual cycle characteristics and ovulatory infertility were evaluated in relation to breast cancer risk among 116,678 women in the Nurses' Health Study II, a prospective cohort study of female registered nurses who were aged 25–42 years and living in 14 US states at enrollment in 1989. During 396,299 person-years of follow-up between return of the baseline questionnaire and June 1993, 251 cases of breast cancer were identified in this cohort. The multivariate relative risk (RR) associated with age at menarche >13 years compared with age <12 years was 0.66 (95% confidence interval (CI) 0.44–0.99). Short and long menstrual cycle lengths at ages 18–22 years were associated with reduced risk. Compared with menstrual cycle length 26–31 days, the multivariate relative risks (95% CIs) for more extreme cycle lengths were: <26 days, 0.50 (0.25–0.98); 32–39 days, 0.81 (0.51–1.28); and >39 days or too irregular for estimation of a usual cycle length, 0.41 (0.18–0.94). The multivariate relative risk associated with a history of ovulatory infertility, compared with no such history, was 0.41 (95% CI 0.18–0.93). These results are consistent with the hypothesis that reduced exposure to ovulatory menstrual cycles provides a protective effect against breast cancer.

A role for endogenous hormones in breast cancer risk is supported by the increased risk with early age at menarche and late age at menopause, as well as the observation that the age-related rate of increase in risk slows considerably after menopause (1). Studies of endogenous hormones in relation to breast cancer risk in premenopausal women have been hindered by several methodological difficulties, including the influence of disease itself on hormone levels in case-control studies, differences in the day of the cycle when the sample is collected, and other sources of biologic and laboratory variation (2). Thus, studies of menstrual cycle characteristics and indicators of ovarian function such as history of ovulatory infertility may provide insight into hormonal factors that influence breast cancer risk.

Increased exposure to the luteal phase of ovulatory menstrual cycles has been proposed to increase the risk of breast cancer, a hypothesis that is biologically plausible because the mitotic activity of breast tissue has been observed to be greatest in the luteal phase of the cycle when estrogen and progesterone levels are both high (3). Early age at menarche is a well-established risk factor for both premenopausal and postmenopausal breast cancer (4). This may be attributable in part to longer exposure to ovulatory menstrual cycles among women with an early age at menarche, which may be further accentuated because early menarche is associated with more rapid establishment of ovulatory cycles (3, 5, 6). Independent of age at menarche, a shorter time interval between menarche and the establishment of regular ovulatory cycles would be expected to increase risk (3). The time interval between menarche and the establishment of regular cycles was inversely related to risk in one case-control study (3) but not in two other case-control studies (7, 8). Because the luteal phase of the cycle is not as variable in length as the follicular phase, women with longer ovulatory cycles may spend less of their
reproductive life in the luteal phase than women with shorter cycles and thus may be at decreased risk of breast cancer (3). Results of case-control studies of menstrual cycle length and breast cancer risk (8, 9–14) have been inconsistent. Women with a history of ovulatory infertility would also be expected to have had less exposure to ovulatory cycles (and specifically to the luteal phase of the cycle) (4). However, the epidemiologic data are inconsistent in regard to the relation between hormonal infertility (or chronic anovulation) and breast cancer risk (15–21).

It is plausible that menstrual cycle characteristics in early life are particularly relevant etiologically, because breast tissue may be more susceptible to carcinogenic insults during these years (22). We report here on the relations of menstrual cycle characteristics during adolescence and early adult life and ovulatory infertility with breast cancer risk in a large cohort of young US women.

MATERIALS AND METHODS

The Nurses’ Health Study II is a prospective cohort study of 116,678 female registered nurses who were aged 25–42 years and living in one of 14 US states when they responded to the baseline questionnaire in 1989. Women who reported cancer at enrollment (not including nonmelanoma skin cancer, hydatidiform mole, or cervical cancer) were excluded. Questionnaires are mailed to participants every 2 years to update information on exposure status and to obtain information about the occurrence of breast cancer and other major illnesses. The response rate among living participants was 93 percent to the 1991 questionnaire and 92 percent to the 1993 questionnaire.

The baseline questionnaire contained items about menstrual cycle patterns and history of ovulatory infertility. Participants were asked the age at which their menstrual periods had begun, with response categories for each year of age from \( \leq 9 \) years to \( \geq 17 \) years. Women were asked to specify the interval between menarche and the establishment of regular menstrual cycles; the response categories were: <1 year, 1–2 years, 3–4 years, \( \geq 5 \) years, and never. Participants were asked about their usual cycle length between the ages of 18 and 22 years with six possible responses: <21 days, 21–25 days, 26–31 days, 32–39 days, 40–50 days, and \( \geq 50 \) days or too irregular to estimate.

Participants were asked if they had ever tried to get pregnant for one 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. This set of questions on infertility was also included on the 1991 questionnaire. This method of assessing ovulatory infertility was evaluated in 100 randomly selected women who reported primary ovulatory infertility (23). Of 90 women who responded to a supplementary questionnaire on infertility diagnosis and treatment, 93.3 percent reported either a confirmatory diagnostic test result (abnormal basal body temperature chart, progesterone assay, endometrial biopsy, or other confirmatory test) or treatment (clomiphene, Pergonal®, human chorionic gonadotropin (hCG), or other confirmatory treatment). Of 40 medical records obtained for these women, 95 percent confirmed the diagnosis of ovulatory infertility by either a diagnostic test or treatment.

The baseline questionnaire also contained items on alcohol intake, history of benign breast disease, family history of breast cancer, height, weight, weight at age 18 years, pregnancy history, menopausal status, oral contraceptive use, and physical activity. Information on history of benign breast disease, weight, pregnancy history, menopausal status, oral contraceptive use, and physical activity was updated on the 1991 questionnaire. Women were considered postmenopausal if they reported that their periods had ceased for natural reasons or due to radiation or chemotherapy or if both ovaries had been removed. Activity scores for current leisure-time physical activity obtained from this questionnaire have been shown to correlate well with activity scores obtained from detailed activity diaries and past-week activity recalls (24).

We asked on the 1991 and 1993 follow-up questionnaires whether participants had been diagnosed with breast cancer in the previous 2 years. Deaths in the cohort are reported by family members and the postal service and are detected by a search of the National Death Index for participants whose vital status is unknown. The National Death Index has been shown to have a sensitivity of at least 96.5 percent in a similar cohort of nurses (25). When a case of breast cancer was identified, we asked the participant (or next of kin for those who had died) for confirmation of the diagnosis and for permission to seek relevant hospital records and pathology reports. Generally, after three unsuccessful attempts to contact the nurse by mail, an attempt was made to contact her by telephone. Pathology reports were obtained for 90 percent of the cases, and, of these, 98 percent confirmed the self-reported diagnosis of breast cancer. After exclusion of the four cases whose diagnosis was rejected based on the pathology reports and 35 cases of carcinoma in-situ, there were 251 cases of invasive breast cancer available for analysis. We included 28 cases whose diagnosis was based on the self-report only, because the accuracy of self-report was so high. Of these 28 cases,
10 had confirmed the diagnosis of breast cancer but refused to give permission to have their medical records released, 10 had confirmed the diagnosis of breast cancer but their medical records were not obtained, and eight confirmed the diagnosis of breast cancer by telephone but did not give permission to have their medical records released.

For each participant, follow-up time, equal to the number of months between return of the 1989 and 1991 questionnaires, was allocated to the strata formed by the unique combinations of all covariates in 1989. Follow-up time was similarly allocated for the subsequent 2-year interval according to the updated covariates in 1991. Participants missing follow-up questionnaires who were not diagnosed with breast cancer between return of the 1989 questionnaire and June 1, 1993 were considered lost to follow-up at their date of last questionnaire return. Participants contributed person-time in each 2-year interval until the earliest of the following: a diagnosis of breast cancer, death, loss to follow-up, or June 1, 1993. A total of 396,299 person-years was accrued between 1989 and 1993.

In the analysis of the time interval between menarche and the establishment of regular cycles, women who reported oral contraceptive use prior to the time when their cycles became regular were excluded to avoid misclassification due to oral contraceptive use. After exclusion of these participants, a subset of 247 cases and 385,513 person-years was included in this analysis. In the analyses of menstrual cycle length between ages 18 and 22 years, we excluded women with more than one year of oral contraceptive use between these ages because the question on menstrual cycle length did not specify that time spent on oral contraceptives should be excluded. More than one year of oral contraceptive use at these ages was reported by 49,634 women. After excluding these women, a subset of 149 cases and 226,167 person-years remained.

Incidence rates were calculated for each exposure category by dividing the number of cases in that category of exposure by the amount of person-time accrued in that exposure category. Relative risks were calculated by dividing the incidence rate in the exposed category by the incidence rate in the unexposed category. Relative risks were adjusted for age in 5-year categories. To adjust for age and other potential confounders simultaneously, proportional hazard models were used (26, 27). We calculated 95 percent confidence intervals for all relative risks.

RESULTS

A total of 251 cases of invasive breast cancer were diagnosed during 396,299 person-years of follow-up between 1989 and 1993. At baseline, the mean age (standard deviation (SD)) of the entire cohort was 34.4 years (4.7 years), while the mean age (SD) of the cases was 37.0 years (4.1 years). Compared with women with age at menarche <12 years, women with an older age at menarche were at reduced risk (table 1). The multivariate relative risk (RR) for age at menarche >13 years was slightly stronger than the age-adjusted relative risk and statistically significant (multivariate RR = 0.66, 95 percent confidence interval (CI) 0.44–0.99). The test for trend was statistically significant (p for multivariate test for trend = 0.03). When age at menarche was treated as a continuous variable, the multivariate relative risk for a one-year increase in age at menarche was 0.90 (95 percent CI 0.83–0.99).

The analysis of time from menarche to establishment of regular cycles was conducted among a subset (247 cases and 385,513 person-years) of participants who did not report any oral contraceptive use before the establishment of regular cycles (see Materials and Methods). Compared with women who reported establishing regular cycles <1 year after menarche, women who reported longer time intervals between menarche and the establishment of regular cycles were at slightly

<table>
<thead>
<tr>
<th>Age (years) at menarche</th>
<th>No. of cases</th>
<th>Person-years of follow-up</th>
<th>Age-adjusted RR†</th>
<th>95% CI†</th>
<th>Multivariate RR‡</th>
<th>95% CI‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12</td>
<td>75</td>
<td>97,149</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>73</td>
<td>118,933</td>
<td>0.82</td>
<td>0.59–1.13</td>
<td>0.79</td>
<td>0.57–1.10</td>
</tr>
<tr>
<td>13</td>
<td>64</td>
<td>106,359</td>
<td>0.77</td>
<td>0.55–1.08</td>
<td>0.74</td>
<td>0.53–1.03</td>
</tr>
<tr>
<td>&gt;13</td>
<td>37</td>
<td>70,560</td>
<td>0.72</td>
<td>0.48–1.06</td>
<td>0.66</td>
<td>0.44–0.99</td>
</tr>
</tbody>
</table>

p for trend 0.07 0.03

* Data on age at menarche was missing for two cases and 1,298 person-years.
† RR, relative risk; CI, confidence interval.
‡ Adjusted for age, alcohol intake, history of benign breast disease, family history of breast cancer, quintiles of current body mass index, parity, age at first full-term pregnancy, menopausal status, and duration of oral contraceptive use.

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and nonsignificantly reduced risk ($p$ for age-adjusted test for trend = 0.41) (table 2). The multivariate results were similar to the age-adjusted results. Time from menarche to the establishment of regular cycles was weakly positively correlated with age at menarche ($r = 0.09$).

In the analyses of menstrual cycle length and breast cancer risk, 49,634 women who reported more than one year of oral contraceptive use between ages 18 and 22 years were excluded (see Materials and Methods); after this exclusion, a subset of 149 cases and 226,167 person-years remained (table 3). Compared with women with cycle lengths of 26–31 days, women who reported longer or shorter cycle lengths appeared to be at reduced risk, i.e., multivariate relative risks (95 percent CIs) were 0.50 (0.25–0.98) for cycle lengths <26 days, 0.81 (0.51–1.28) for cycle lengths 32–39 days, and 0.41 (0.18–0.94) for cycle lengths >39 days or which were too irregular for estimation of a usual cycle length.

We evaluated time from menarche to establishment of regular cycles and menstrual cycle length simultaneously in relation to breast cancer risk; in these analyses, women with more than one year of oral contraceptive use between ages 18 and 22 years and women who reported oral contraceptive use before the establishment of regular cycles were excluded. The association of menstrual cycle length with breast cancer risk was not appreciably altered on adjustment for time from menarche to establishment of regular cycles; however, time from menarche to the establishment of regular cycles was even less strongly associated with breast cancer risk after adjustment for menstrual cycle length (data not shown).

Women who reported a history of ovulatory infertility had a significantly reduced risk of breast cancer compared with women with no history of ovulatory infertility (age-adjusted RR = 0.42, 95 percent CI 0.19–0.94), although this result was based on only six exposed cases (table 4). Confounding by pregnancy history is of concern in analyses of ovulatory infertility in relation to breast cancer risk. Of the women without a history of ovulatory infertility, the age-adjusted percents of women with different pregnancy histories were as follows: 30 percent were nulliparous, 37 percent had an age at first full-term pregnancy ≤25 years, and 33 percent had an age at first full-term pregnancy >25 years. For women with ovulatory infertility, the corresponding age-adjusted percents were 26, 28, and 46 percent, respectively. Results from multivariate models (including terms for pregnancy history) were similar to the age-adjusted results. On the baseline questionnaire, 43 percent of the women who reported a history of ovulatory infertility also reported another type of infertility. To address the concern that a report of ovulatory infertility may be less reliable among those who also report another type of infertility and to address the possibility of confounding by other types of infertility, we conducted analyses excluding participants who reported a history of any type of infertility other than ovulatory infertility. In this restricted analysis of 204 cases and 331,291 person-years of follow-up, the multivariate relative risk was similar to that observed in the primary analysis, although the confidence intervals were wider (RR = 0.52, 95 percent CI 0.19–1.40). In an analysis of all other types of infertility in relation to breast cancer risk, in which women with a history of ovulatory infertility were excluded from the analysis, the relative risk associated with a history of all other types of infertility was 1.06 (95 percent CI 0.76–1.48) with 45 exposed cases.

<table>
<thead>
<tr>
<th>Time (years) from menarche to establishment of regular menstrual cycles</th>
<th>No. of cases</th>
<th>Person-years of follow-up</th>
<th>Age-adjusted RR*</th>
<th>95% CI*</th>
<th>Multivariate RR†</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>124</td>
<td>180,661</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1–2</td>
<td>60</td>
<td>96,636</td>
<td>0.94</td>
<td>0.69–1.28</td>
<td>0.94</td>
<td>0.69–1.28</td>
</tr>
<tr>
<td>3–4</td>
<td>14</td>
<td>25,152</td>
<td>0.89</td>
<td>0.51–1.55</td>
<td>0.87</td>
<td>0.50–1.52</td>
</tr>
<tr>
<td>≥5</td>
<td>28</td>
<td>40,644</td>
<td>0.98</td>
<td>0.65–1.47</td>
<td>0.87</td>
<td>0.64–1.46</td>
</tr>
<tr>
<td>Never</td>
<td>21</td>
<td>42,420</td>
<td>0.81</td>
<td>0.51–1.29</td>
<td>0.81</td>
<td>0.51–1.29</td>
</tr>
<tr>
<td>$p$ for trend</td>
<td></td>
<td></td>
<td>0.41</td>
<td></td>
<td>0.43</td>
<td></td>
</tr>
</tbody>
</table>

* RR, relative risk; CI, confidence interval.
† Adjusted for age, alcohol intake, history of benign breast disease, family history of breast cancer, age at menarche, quintiles of current body mass index, parity, age at first full-term pregnancy, menopausal status, and duration of oral contraceptive use.

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**TABLE 2.** Time from menarche to establishment of regular menstrual cycles and risk of breast cancer, Nurses' Health Study II, 1989–1993
TABLE 3. Menstrual cycle length at ages 18–22 years and risk of breast cancer, Nurses' Health Study II, 1988–1993

<table>
<thead>
<tr>
<th>Menstrual cycle length (days)</th>
<th>No. of cases</th>
<th>Person-years of follow-up</th>
<th>Age-adjusted RR*</th>
<th>95% CI*</th>
<th>Multivariate RR†</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;26</td>
<td>9</td>
<td>21,983</td>
<td>0.52</td>
<td>0.27–1.03</td>
<td>0.50</td>
<td>0.25–0.98</td>
</tr>
<tr>
<td>26–31</td>
<td>112</td>
<td>145,741</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32–39</td>
<td>22</td>
<td>38,250</td>
<td>0.78</td>
<td>0.49–1.23</td>
<td>0.81</td>
<td>0.51–1.28</td>
</tr>
<tr>
<td>&gt;39 or too irregular to estimate</td>
<td>6</td>
<td>20,193</td>
<td>0.39</td>
<td>0.17–0.90</td>
<td>0.41</td>
<td>0.18–0.94</td>
</tr>
</tbody>
</table>

* RR, relative risk; CI, confidence interval.
† Adjusted for age, alcohol intake, history of benign breast disease, family history of breast cancer, age at menarche, quintiles of current body mass index, parity, age at first full-term pregnancy, menopausal status, and duration of oral contraceptive use.

When menstrual cycle length and ovulatory infertility were considered simultaneously, there was no appreciable change in estimate for either menstrual cycle length or ovulatory infertility (data not shown).

Because body mass index may be a predictor of menstrual cycle function (23, 28), we explored further the relation between this variable and menstrual cycle function at baseline. Body mass index, either at age 18 years or current, was moderately associated with age at menarche and not strongly associated with either menstrual cycle length or history of ovulatory infertility. The percents of women who reported an age at menarche <12 years, by increasing quintiles of body mass index at age 18 years, were 16, 20, 25, 29, and 34 percent. The percents of women who reported that they had a menstrual cycle of 26–31 days in length at ages 18–22 years, by increasing quintiles of body mass index at age 18 years, were 64, 67, 67, 67, and 65 percent. The percents of women who reported a history of ovulatory infertility, by increasing quintiles of body mass index at age 18 years, were 5, 5, 5, 5, and 6 percent. Results were similar for current body mass index. Thus, although body mass index was inversely related to risk of breast cancer (age-adjusted RR for highest vs. lowest quintile of body mass index at age 18 years = 0.69, 95 percent CI 0.48–1.02), analyses presented in tables 1–4 were similar in multivariate models (data not shown).

The results of analyses presented in tables 1–4 were similar at a time to multivariate models: physical activity during high school, physical activity during ages 18–22 years, and current physical activity (data not shown).

On exclusion of 28 cases whose diagnosis was based on self-report only, the association between age at menarche and breast cancer was slightly attenuated (multivariate RR associated with age at menarche >13 years = 0.77, 95 percent CI 0.51–1.17; p for multivariate test for trend = 0.17). Results of other analyses were similar on exclusion of 28 cases whose diagnosis was based on self-report only (data not shown). At baseline, 96.7 percent of the cohort was premenopausal. Ninety-three percent of the breast cancer cases were among premenopausal women. Results of analyses were similar when limited to premenopausal women (data not shown).

DISCUSSION

In this study, women with older ages at menarche were at reduced risk of breast cancer compared with women with a younger age at menarche. We observed slightly reduced risks associated with longer time between menarche and the establishment of regular menstrual cycles, but the results were compatible with chance. Reduced risks were observed for both short and long menstrual cycle lengths at ages 18–22 years compared with intermediate lengths. Women who had a history of ovulatory infertility were at significantly reduced risk of breast cancer.


<table>
<thead>
<tr>
<th>Ovulatory infertility</th>
<th>No. of cases</th>
<th>Person-years of follow-up</th>
<th>Age-adjusted RR*</th>
<th>95% CI*</th>
<th>Multivariate RR†</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>245</td>
<td>374,986</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>21,313</td>
<td>0.42</td>
<td>0.19–0.94</td>
<td>0.41</td>
<td>0.18–0.93</td>
</tr>
</tbody>
</table>

* RR, relative risk; CI, confidence interval.
† Adjusted for age, alcohol intake, history of benign breast disease, family history of breast cancer, age at menarche, quintiles of current body mass index, parity, age at first full-term pregnancy, menopausal status, and duration of oral contraceptive use.
Because of the prospective nature of this study, it is unlikely that our results are affected by recall bias. Additionally, we controlled for established breast cancer risk factors in our analyses, and thus our results are unlikely to be confounded by these risk factors to any large extent. We observed a moderate inverse association between body mass index and age at menarche, a finding that is consistent with previous studies (29). The heaviest women were only slightly more likely to experience extreme menstrual cycle lengths or ovulatory infertility; this is consistent with results from a previous study conducted among this cohort (23). In the earlier study, a significantly elevated risk of ovulatory infertility was found only among women whose body mass index at age 18 years was in the upper 12 percent of the distribution; the relative risk of ovulatory infertility exceeded 2.0 only for those women in the upper 3 percent of the distribution of body mass index at age 18 years. Similarly, the prevalence of menstrual abnormalities indicative of anovulation has been shown to be increased only in a small minority of obese women (30). Thus, we observed little evidence of confounding by body mass index.

The age range of the study population was 25–42 years at baseline, and therefore the extent to which our results are generalizable to older women is unclear. Consistent with many previous studies in both premenopausal and postmenopausal women (4), women with older ages at menarche were at reduced risk of breast cancer risk compared with women with younger ages at menarche. The attenuation of this association observed on exclusion of cases based on self-report only could be due to chance, because the exclusion of misclassified cases would normally be expected to strengthen, not to weaken, associations. The protective effect of a late age at menarche may be due in part to a shorter length of exposure to ovulatory menstrual cycles, an effect which may be further enhanced because late age at menarche is associated with a less rapid establishment of ovulatory cycles (3, 5, 6).

We observed only a very weak and nonsignificant inverse association between time from menarche to the establishment of regular menstrual cycles. The time interval between menarche and the establishment of regular cycles was inversely related to breast cancer risk in one case-control study (3) but not in two other case-control studies (7, 8). It is likely that this time interval is difficult to recall for many women, and thus it is possible that this exposure variable may be misclassified, leading to bias toward the null.

We found reduced risks of breast cancer among women who reported either short or long menstrual cycle lengths. Although it is probable that recorded menstrual cycle lengths are subject to misclassification, such misclassification is likely to be nondifferential with respect to development of breast cancer, and thus would attenuate associations. Results of previous studies on the relation between menstrual cycle length and breast cancer have been inconsistent. Studies have variously indicated no association with cycle length (9, 10), an increased risk due to shorter cycles (11, 12), a decreased risk associated with short cycles (13) or with both short and long cycles (8), and an increased risk with both long and short (compared with average) cycles (14). All of these studies except for two (10, 14) were case-control studies.

It has been postulated that because women with shorter ovulatory cycles spend more of their reproductive life in the luteal phase than women with longer cycles (due to the larger variability in length of the follicular phase compared with the luteal phase), they would be at increased risk of breast cancer (3). However, both shorter and longer cycle lengths have been found to be associated with a higher probability of anovulation (28). This may be particularly relevant in young adult life when the probability of anovulation is greater than at older ages (28), and thus our findings that shorter and longer cycle lengths at ages 18–22 years are associated with a decreased risk may be attributable to the lower probability of ovulation associated with these extreme cycle lengths in this age group. In most of the previous studies, cycle lengths were assessed at older ages, and the interpretation of cycle lengths at older ages may be different, with cycle length largely reflecting characteristics of ovulatory cycles. Further studies are needed to examine the age-specific characteristics of cycles of different lengths, including the number of ovulatory cycles per unit time and other hormonal parameters associated with short and long cycle lengths.

We observed a significantly reduced risk of breast cancer among women with a history of ovulatory infertility. Our method of assessing ovulatory infertility has been shown to be reasonably valid (23). We did not find any association between other types of infertility and breast cancer risk, which suggests that the observed inverse association is specific to ovulatory infertility. The possibility of confounding by pregnancy history is a concern. In this cohort, 84 percent of women with ovulatory infertility at baseline achieved a pregnancy by the time of their 1993 questionnaire return (31), which indicates that reported ovulatory infertility caused a delay in conception, not an absolute inability to conceive. Consistent with this, we found that a similar percent of women with and without a history of ovulatory infertility were parous at baseline, and women with a history of ovulatory infertility were more likely to have had a late age at first...
full-term pregnancy. However, results were similar when pregnancy history was included in multivariate models. Our results should be interpreted with caution, however, because they are based on a small number of exposed cases. Results of previous epidemiologic studies on the relation between hormonal infertility and breast cancer risk have been inconsistent. Although previous investigators have reported a decreased risk of breast cancer associated with polycystic ovary syndrome (15), a frequent cause of ovulatory infertility, others have reported a nonsignificantly increased risk associated with hormonal infertility or chronic anovulation (16–18) and null results (19–21).

Our finding of a reduced risk among women with a history of ovulatory infertility is consistent with the hypothesis that reduced exposure to ovulatory menstrual cycles results in a decreased risk of breast cancer. Interestingly, in polycystic ovary syndrome, the most frequent cause of ovulatory infertility (32), estrogen levels are in the normal range for the follicular phase of the menstrual cycle, but there is a progesterone deficiency due to the chronic anovulation. Thus, if ovulatory infertility (and polycystic ovary syndrome specifically) is related to a reduced risk of breast cancer, this would be consistent with a specific adverse effect of progesterone on breast cancer risk. Alternatively, ovulation-inducing drugs may influence breast cancer risk. Clomiphene citrate, an ovulation-inducing drug commonly prescribed to women with ovulatory infertility, is an estrogen antagonist that is structurally similar to tamoxifen (21) and thus may influence breast cancer risk. In one small prospective study (21), use of clomiphene citrate, and not ovulatory infertility itself, was associated with a reduced risk of breast cancer. However, other investigators (17) reported no association between the use of clomiphene citrate and breast cancer risk, although no details were given. On our initial questionnaires, we did not collect information on use of clomiphene citrate and other ovulation-inducing drugs. Thus, one limitation of the current study is the lack of data necessary to evaluate ovulatory infertility and its treatment separately in relation to breast cancer risk.

Because a large percent of women with ovulatory infertility will be prescribed such drugs, large studies are needed to separately study the effects of ovulatory infertility and of its treatment in regard to breast cancer risk.

Overall, our results are consistent with the hypothesis that anovulation is protective against breast cancer. However, more studies are needed to investigate the age-specific relations between menstrual cycle characteristics and the underlying hormonal environment and to investigate the separate effects of ovulatory infertility and its treatment on breast cancer risk.

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Menstrual Cycle and Breast Cancer Risk