Cyclic Ovarian Function and Breast Cancer

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Abstract

We postulated previously that systematic differences in menstrual cycle length and/or variability might be used as indicators of underlying hormonal abnormalities that could help explain the endocrine biology of some breast cancer risk factors. In the present study, we prospectively and retrospectively analyzed menstrual cycle patterns in breast cancer cases and controls in two populations. No significant differences were found. This and previous studies emphasize that contemporary women have a long reproductive experience characterized by uninterrupted, regular menses, which is a condition of maximum ovulation potential and which contributes to estrogen stimulation over time.

Introduction

Age at menarche, age at first pregnancy, nulliparity, and age at menopause are established risk factors for breast cancer (9, 11). Most of these factors show a modest relative risk of 1.5 to 3.5, and even when considered together, they may not be adequate for screening individuals (4). Yet, the biological relationship of these events to breast neoplasia is important to an understanding of the pathogenesis of the disease.

Certain features of these risk factors deserve emphasis: they include the major events of the female reproductive experience; the hormonal changes surrounding them are complex and enormously variable; they span reproductive life; and an interval of many years usually separates the diagnosis of breast cancer from these events. It is therefore not surprising that identification of specific hormonal alterations responsible for increased breast cancer risk has been a source of frustration.

We have approached the problem by examining the relationship of menstrual cycle patterns to breast cancer risk factors. This effort was based on the assumption that systematic differences in cycle length and/or variability might be used as a marker for hormonal abnormalities occurring during these cycles. More specifically, we postulated that several of the breast cancer risk factors might be associated with abnormal ovarian follicular maturation and irregular or deficient progesterone production by the corpus luteum (14). This would result in a hormonal environment of relative estrogen excess and progesterone deficiency, a situation theoretically conducive to the development and propagation of breast neoplasia. This report concerns menstrual cycle patterns in breast cancer patients.

Methods

Two separate populations were studied. In the first, a historical prospective analysis of cycle patterns in breast cancer patients was made possible by the existence of the MRH (2) initiated and maintained by Dr. A. E. Treloar. In 1934, Dr. Treloar began to enroll female students at the University of Minnesota to record reproductive events and menstrual cycle intervals through life (21). Participating women were given calendars on which they noted all days of vaginal bleeding and reported related contraceptive, reproductive, and medical events. Many returned information each year until menopause. In addition, many daughters of the original subjects were enrolled from the time of menarche. To date, nearly 5000 women have participated. In 1975, we mailed a questionnaire to 2400 current and previously active participants in the study for whom at least 5 years of uninterrupted records were available to obtain information concerning health-related events, including breast cancer. Surveillance methods included follow-up of last known address of subjects, review of death records from the state of Minnesota, and telephoning of persons in the Minneapolis metropolitan area. Ultimately, the vital and breast cancer status was determined for 80% of the subjects sought.

In the second population, retrospective information regarding menstrual cycle characteristics was derived from a case-control study conducted between 1974 and 1978 on 151 patients seen for primary breast cancer surgery at the University of Iowa Hospitals. Each breast cancer patient had a single control patient selected from the general medicine and surgery wards by an algorithm using the computerized daily census of the hospital. Control subjects were matched for age and hospital payment category and were free of a history of any cancer. All study subjects were white. A trained interviewer, blinded to the study hypotheses, administered a questionnaire to all subjects. The items included a menstrual and reproductive history, including an item in which subjects were asked to recall temporal patterns and the predictability of their menstrual cycle onset when not using exogenous hormones. The response categories were: regular (within ± 2 days); somewhat irregular (within 1 week); and totally irregular and unpredictable.

Results

We identified 51 women who developed breast cancer from among the participants in the MRH contacted in 1975. Forty-five of those women were part of the first cohort enrolled in the study. All diagnoses of breast cancer were made between the ages of 36 and 64 years. Individual women had recorded from 62 to 414 cycles (mean, 266). While in most cases records were available to obtain information concerning health-related events, including breast cancer. Surveillance methods included follow-up of last known address of subjects, review of death records from the state of Minnesota, and telephoning of persons in the Minneapolis metropolitan area. Ultimately, the vital and breast cancer status was determined for 80% of the subjects sought.

Table 2 shows that, in the case-control study, breast cancer patients and controls did not significantly differ in the recollection.
tion of menstrual cycle predictability at any stage of reproductive life. Both groups reported a slight increase in irregular cycles after menarche and a change to more irregular cycles before menopause.

Discussion

Many of the epidemiological risk factors pertaining to breast cancer incidence are related to major events in the female reproductive experience. Several years ago, in an attempt to synthesize these observations, we proposed a theory that focused on abnormal corpus luteum function as a major endocrine determinant of breast cancer risk (14). Testing that hypothesis by direct hormone measurement is difficult because of the need to prospectively obtain multiple, appropriately timed blood samples from many subjects during many separate cycles. Because we observed that deficient corpus luteum progesterone production is a common consequence of abnormal follicular maturation, often associated with unusually short or long menstrual intervals (15–17), and because menstrual irregularity is a frequent clinical symptom sometimes associated with infertility, we examined menstrual cycle intervals in the hope that they would be a marker for hormonal abnormalities related to breast cancer risk and provide a common explanation for such factors as age at menarche, age at menopause, nulliparity, and age at first birth.

Treloar et al. (21) described the pattern of menstrual cycles throughout reproductive life. He showed that the variable nature of postmenarcheal cycles was followed by regular cycle intervals throughout mature reproductive life until irregular cycles resumed before menopause. In our prior studies of the relationship between menstrual cycle patterns and breast cancer risk factors using MRH data (24), we found that women with early menarche more quickly established a regular pattern of menses than did those with later menarche and that increased postmenarcheal cycle length and variability were characteristic of women with menarche after the age of 15. Therefore, in women with early menarche, a predictor of increased breast cancer risk, the breast is exposed to a full complement of sex steroids and probably fewer anovulatory cycles than those with late menarche, which is opposite to what we had initially predicted.

At the other extreme of reproductive life, we found that women with later menopause, which is also associated with increased breast cancer risk, had longer mean cycle length and greater variability in the 4 years prior to menopause than did women with earlier menopause (24), consistent with our hypothesis. If irregular menses are an indicator of luteal phase insufficiency (16, 23), then women with later menopause not only have a longer total exposure to ovarian hormones but may also have a situation in which there is a sufficiency of estrogen in the absence of regular sustained increases in progesterone.

We postulated that, in some situations, late first pregnancy might be a manifestation of involuntary infertility and might be associated with unusually long or short menstrual cycles. When we contrasted the cumulative proportion of subjects becoming pregnant in the first 5 years of marriage according to cycle length and variability during the 2 years prior to marriage, we could find no relationship between cycle characteristics before marriage and the cumulative pregnancy rate, which was about 90% within 5 years of marriage (24). It is possible, however, that this question is not testable in a population where child-bearing is largely voluntary.

Because increased relative weight (or obesity) is a breast cancer risk factor (9) and in clinical practice is frequently associated with disorders of follicular maturation characterized by amenorrhea or oligomenorrhea, we looked for systematic differences in menstrual cycle length and variability in women in the upper and lower quartiles of the distribution of relative weight at all stages of reproductive life. We found no relationship of relative weight indices and menstrual cycle patterns between the ages of 24 and 43 or during the 7 years before menopause (18). This was also true when comparing the upper and lower tenth percentiles of the relative weight distribution. It was only during the third and fourth years after menarche that heavier women had longer menstrual cycles and greater

<table>
<thead>
<tr>
<th>Cases</th>
<th>Control</th>
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</table>

### Table 1

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>n</th>
<th>Case Mean ± S.D.</th>
<th>Control Mean ± S.D.</th>
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<tr>
<td>20–24</td>
<td>38</td>
<td>29.0 ± 3.6</td>
<td>29.6 ± 4.0</td>
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<tr>
<td>25–29</td>
<td>41</td>
<td>29.2 ± 3.5</td>
<td>29.5 ± 5.2</td>
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<td>30–34</td>
<td>37</td>
<td>28.2 ± 3.9</td>
<td>28.6 ± 3.6</td>
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<tr>
<td>35–39</td>
<td>34</td>
<td>26.7 ± 3.0</td>
<td>27.7 ± 3.1</td>
</tr>
<tr>
<td>40–44</td>
<td>29</td>
<td>27.2 ± 5.9</td>
<td>27.4 ± 5.5</td>
</tr>
<tr>
<td>45–49</td>
<td>22</td>
<td>30.2 ± 12.6</td>
<td>32.6 ± 20.8</td>
</tr>
</tbody>
</table>

* Mean ± S.D.

### Table 2

<table>
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<th>Age (yr)</th>
<th>Regular ± 1-2 days (%)</th>
<th>Somewhat irregular (%)</th>
<th>Totally irregular (%)</th>
<th>n</th>
<th>Regular ± 1-2 days (%)</th>
<th>Somewhat irregular (%)</th>
<th>Totally irregular (%)</th>
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<td>130</td>
<td>76.3</td>
<td>10.7</td>
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<tr>
<td>15–19</td>
<td>78.5</td>
<td>9.4</td>
<td>12.1</td>
<td>149</td>
<td>81.3</td>
<td>9.3</td>
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<td>80.0</td>
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<tr>
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<td>38.6</td>
<td>49</td>
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Within each 5-year interval, 0 to 4 subjects with missing information are excluded from the analysis. Cases and controls were compared separately for each 5-year study interval using the χ² statistic. No significant differences were found.
cycle variability than their leaner counterparts (18). These findings contrast with clinical experience and with results from studies of women in a weight reduction program (8), where there may be an association of increased relative weight with increased cycle length and variability. While menstrual irregularity may be a relatively common clinical complaint among heavier women, our data suggest that such abnormal cycle patterns may have little impact on breast cancer risk in the general population.

In the present study, we were unable to discern either prospectively using the MRH population or retrospectively using a case-control design any systematic difference in menstrual cycle patterns in patients with breast cancer. The prospectively recorded information represents over 12,000 menstrual cycles and gives no indication that women who later develop breast cancer have an antecedent menstrual experience different from that of unaffected women. While this is consistent with our case-control findings and similar previous studies (25), retrospective studies may be compromised by the doubtful accuracy of recall for menstrual cycle events (1). It is also possible that, while the MRH data are extensive, the number of breast cancer cases available was too limited or somehow biased so as not to reflect small differences in cycle length, variance, or other special patterns.

When we used the MRH population to examine the relationship between relative weight and menarcheal and menopausal age, we found, as have others, that adult height, weight, and a derived index of adiposity

\[
\text{Quetelet index, } \frac{\text{wt}}{\text{height}^2}
\]

were related to both an earlier age at menarche and later age at menopause (18, 19). This is consistent with the anthropological observations that a long reproductive life span, multiple regular ovulatory cycles, and short episodes of lactational amenorrhea are characteristic of advanced, well-nourished cultures (2, 3, 5, 10, 20) and may be one way in which nutritional factors, early menarche, and late menopause interact to increase risk. In addition, obesity may contribute to the overall estrogen burden by increasing extragonadal estrogen production and the concentration of free estrogen in blood (6, 7). If cycle irregularity is a marker for luteal phase inadequacy, then perhaps some heavier women may also be exposed to an increased ratio of estrogen to progesterone during adolescence and before menopause.

The hormonal characteristics of regular ovulatory menstrual cycles have been well described (13, 22), and other than corpus luteum dysfunction, there have been few systematic hormonal abnormalities identified in menstruating women. There is even evidence that luteal inadequacy can occur during menstrual cycles of normal length (12). While we acknowledge the limitations of the use of menstrual cycle patterns to reflect the hormonal milieu, our findings suggest that breast cancer patients have normal menstrual patterns and that the breast cancer risk factors are not associated with particularly distinct cycle patterns. We would therefore predict that most breast cancer patients have normal cyclic ovarian function.

References

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