Effects of Raloxifene on Circulating Prolactin and Estradiol Levels in Premenopausal Women at High Risk for Developing Breast Cancer

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Abstract

Background: Prolactin is a peptide hormone necessary for normal breast development that may contribute to breast tumorigenesis. Estrogen is a significant positive regulator of prolactin synthesis; therefore, raloxifene, a selective estrogen receptor modulator under study as a breast cancer prevention agent, may modulate both estradiol and prolactin levels by inhibiting estradiol from binding to its receptor. Methods: Premenopausal women at increased risk for invasive breast cancer participated in a pilot chemoprevention trial and were given 60 mg raloxifene daily for 24 months. Fasting serum samples collected at baseline and after 12 months on drug were used to measure circulating prolactin, estradiol, and sex hormone binding globulin (SHBG) levels.

Results: Of the 27 subjects who completed 12 months of raloxifene, 23 had paired prolactin samples, and 20 had paired estradiol and SHBG samples. Prolactin levels did not significantly change with raloxifene treatment, but SHBG levels increased (mean change = 7.3 nmol/L; \( P = 0.0001; \) 95% confidence interval, 3.9-10.7). Estradiol (mean change = 42 pg/mL; \( P = 0.048; \) 95% confidence interval, 1-84 pg/mL) levels were elevated when comparing 15 of the 20 women with paired estradiol measurements who also had both of these samples taken during the early follicular phase of the menstrual cycle.

Conclusions: This report is the first to examine the long-term effects of raloxifene on prolactin, estradiol, and SHBG levels in premenopausal women who are also at increased risk for developing invasive breast cancer. Raloxifene had no significant effect on prolactin levels but did increase estradiol and SHBG measurements. (Cancer Epidemiol Biomarkers Prev 2006;15(6):1153–8)

Introduction

Prolactin is a peptide hormone responsible for growth and development of the normal human breast. Prolactin also enhances proliferation, migration, and survival of human breast cancer cells \textit{in vitro} (1-7). \textit{In vivo}, prolactin functions in both an endocrine manner when secreted by the pituitary and in an autocrine/paracrine manner when produced and secreted locally by both normal and malignant human breast cells (8, 9). The modulation of prolactin synthesis and secretion is not fully understood; however, estrogen is a significant positive regulator of prolactin production in the pituitary (10, 11).

In a recent prospective study, high circulating serum prolactin levels in premenopausal women were reported to be associated with increased risk of developing breast cancer [relative risk, 1.5; 95% confidence interval (95% CI), 1.0-2.5; ref. 12]. Although the biological basis for the correlation between high prolactin levels and the development of breast cancer remains an active area of investigation, high prolactin levels in premenopausal women also have been associated with well-studied risk factors for breast cancer, including nulliparity, oral contraceptive use, and family history of breast cancer (1). Furthermore, parity, a protective factor for breast cancer, has been associated with a decrease in prolactin levels. Circulating prolactin levels have been shown to decrease by ~50% and remain suppressed following the first full-term pregnancy (13, 14).

High circulating levels of estradiol have also been associated with an increased risk of breast cancer in postmenopausal women (15, 16). In addition, other studies examining correlates for estrogen exposure, such as age at menarche, age at first birth, and age at menopause, show that cumulative lifetime exposure to estrogen is a significant risk factor for the development of breast cancer (17). In this report, we examine the effects of raloxifene on estradiol and sex hormone binding globulin (SHBG), which binds to estradiol and modulates the bioavailable levels of this steroid hormone. To date, there is no evidence to suggest that SHBG would directly affect prolactin levels.

Raloxifene is a selective estrogen receptor modulator. Postmenopausal women who were taking raloxifene in osteoporosis trials exhibited a decreased incidence of breast cancer (18, 19). Therefore, raloxifene is currently being compared with tamoxifen, also a selective estrogen receptor modulator and the only drug currently approved by the Food and Drug Administration for the prevention of breast cancer, in the Study of Tamoxifen and Raloxifene, a National Surgical Adjuvant Breast and Bowel Project–sponsored trial (20). The Study of Tamoxifen and Raloxifene trial will compare both the efficacy and potential side effects of raloxifene as a chemopreventive agent for breast cancer to that of tamoxifen. Although tamoxifen has been shown to reduce the incidence of estrogen receptor–positive breast tumors, there are negative side effects associated with this drug, including an increased risk of developing endometrial cancer (21). Raloxifene may have a more favorable side effect profile than tamoxifen, in...
that raloxifene does not promote endometrial cancer (18, 22). A limitation of the Study of Tamoxifen and Raloxifene trial, as well as other clinical trials of raloxifene, is that the study population consists of only postmenopausal women (23, 24), resulting in a scarcity of knowledge regarding the effects of raloxifene in a premenopausal population.

Recently, a phase II trial examining the safety of raloxifene and its effects on bone mineral density, the primary clinical end point, in premenopausal women at high risk for developing breast cancer was completed at the National Cancer Institute. In addition to the effects on bone mineral density, the effects of raloxifene on serum hormones, including circulating prolactin and estradiol levels, were assessed after 12 months on drug. We hypothesized that raloxifene treatment may increase estradiol levels, as has been shown in the only published study focused on raloxifene in premenopausal women (25) and in studies of tamoxifen in premenopausal women (26, 27). In addition, raloxifene treatment may also decrease circulating levels of prolactin by modulating the interaction of estrogen receptors with the estrogen response element in the prolactin promoter. Circulating levels of SHBG also were measured to further evaluate any changes in circulating estradiol.

In the one study that examined the relationship between raloxifene treatment and circulating prolactin and estradiol levels in premenopausal women, subjects between the ages of 21 and 45 years with regular menstrual cycles were given raloxifene for either 5 or 28 days; however, no information on breast cancer risk factors was collected (25). In this study, we are the first to examine the effects of raloxifene on circulating prolactin, estradiol, and SHBG levels in premenopausal women at high risk for breast cancer and the first to examine these effects of raloxifene over a period of >28 days.

Materials and Methods

Study Population and Design. The study population, design, treatment plan, and sample collection have been published previously (28) but are described briefly. The serum samples were provided by women enrolled in a phase II trial of raloxifene to evaluate the safety of this drug in a population of premenopausal women at high risk for developing invasive breast cancer (protocol 98-C-0123 approved by the National Cancer Institute Institutional Review Board). All subjects provided written informed consent for participation in the trial. Subjects eligible for this trial included women who were between the ages of 23 and 47 years and who were having regular menses. These women were also determined to be at high risk for developing breast cancer by at least one of the following criteria: Gail model estimate of ≥1.7% 5-year risk; previous diagnosis of atypical ductal hyperplasia, ductal carcinoma in situ, and/or lobular carcinoma in situ; or a family history concordant with a hereditary breast/ovarian syndrome. Raloxifene has not been approved for premenopausal women and has been shown to be teratogenic in animal studies. Therefore, all subjects agreed to use nonhormonal birth control methods throughout the trial and for 3 months after completing the trial. Women were excluded from the trial if they were postmenopausal or had irregular menses, were allergic to the drug, were using hormonal therapy (e.g., oral contraceptives and tamoxifen) within the 6 months before starting the trial, or had a history of gynecologic problems (e.g., infertility with a suspected ovarian etiology, recurrent ovarian cysts, and cervical dysplasia) or clotting/bleeding disorders. Information on concurrent medications was collected at each clinical visit.

The subjects were given 60 mg raloxifene daily for 24 months. The raloxifene was self-administered and supplied by Eli Lilly and Co., Indianapolis, Indiana. Calcium carbonate (1,200 mg/d) was also prescribed as per NIH Consensus Conference guidelines (29) and self-administered by the subjects.

Sample Collection. For these analyses, serum samples collected at baseline and after 12 months on raloxifene were evaluated. The prolactin, estradiol, and SHBG measurements were determined from fasting morning serum samples collected before physical exam. When possible, samples were collected during early follicular phase of the menstrual cycle (3-9 days after the start of menses), and the serum was immediately separated and stored at −70°C.

Prolactin, Estradiol, and SHBG Measurements. The prolactin measurements were determined by microparticle enzyme immunoassay. In the microparticle enzyme immunoassay, two distinct antibodies specific to prolactin bind to prolactin, forming an antibody-antigen-antibody complex. This complex is then bound irreversibly to a glass fiber matrix. The concentration of prolactin is calculated by the AxSYM instrument (Abbott Laboratories, Abbott Park, IL), which has been calibrated with known prolactin concentrations. Using commercially available controls of human prolactin, the interassay coefficient of variance was calculated to be 6.9% to 7.5%, and the intraassay coefficient of variance was 2.5% to 3.8%. Estradiol and SHBG levels were determined using the Immulite 2000 system (NIH Clinical Center Laboratory, Bethesda, MD). The interassay coefficients of variance for analyzing estradiol and SHBG were <10%. All measurements were conducted within the Clinical Chemistry Service, Department of Laboratory Medicine, NIH.

Statistical Analysis of Data. The effects of raloxifene on circulating prolactin, estradiol, and SHBG levels were examined using the Wilcoxon signed rank test to analyze the paired baseline and 12-month on-drug samples. For the prolactin values, the distribution of the baseline data was skewed to the right but became consistent with a normal distribution after base 10 log transformation of the data. Therefore, the log-transformed data were used for the analyses of prolactin, and the values presented in Table 2 are the data after transformation back to prolactin values. The geometric mean values from these analyses are reported along with the range of prolactin values from the untransformed data. The mean change in prolactin is reported as the percent change in the geometric mean, and its CI was calculated from the paired differences in the log-transformed baseline and 12-month values and then transformed back. In addition, both the effects of parity and antidepressant medication on prolactin levels were independently evaluated using Wilcoxon rank sum analysis. The Wilcoxon rank sum test was also used to determine if the estradiol measurements that were collected from five of the subjects after day 9 of the menstrual cycle (n = 2 for baseline measured at day 10 or 11 and n = 3 for 12 months measured at day 10 or 11) were significantly different from the measurements from days 3 to 9 (n = 15).

Results

Study Population. The National Cancer Institute Phase II trial of raloxifene originally enrolled 37 women; however, seven women dropped out of the trial during the run-in period. Two subjects dropped out before completing 12 months of raloxifene, and one subject’s samples were removed from analysis because she became postmenopausal, resulting...
Effect of Raloxifene on Circulating Prolactin Levels. The baseline log transformation of the prolactin values was useful for analyses of the baseline, 12 months, and change in prolactin levels. When the prolactin levels were examined by Wilcoxon rank sum analysis to evaluate parity, there were no significant differences in the baseline ($P = 0.12$), 12 months ($P = 0.25$), or the change ($P = 0.62$) in prolactin levels between the parous and nulliparous groups (Table 2). Also of importance to our analysis, 9 of the 23 subjects with paired prolactin measurements were taking antidepressant medication. Dopamine is a negative regulator of prolactin synthesis, and certain classes of antipsychotics and antidepressants block the dopamine receptor, thereby causing elevated prolactin levels (30). However, by Wilcoxon rank sum analysis, there was no significant difference in prolactin levels at baseline ($P = 0.68$), at 12 months on raloxifene ($P = 0.39$), or in the change in these two measurements ($P = 0.73$) when comparing subjects taking antidepressants to those who were not.

Because there were no statistical differences in prolactin levels at baseline, 12 months, or in the change in prolactin when the measurements were evaluated for either parity or antidepressant use, the data were combined, and the results were reported for the study population of $n = 23$. The baseline geometric mean prolactin measurement was 10.9 ng/mL (Table 2). The percent change in geometric mean for all subjects was 5% ($P = 0.98$; 95% CI, −15% to +30%; Table 2).

Within the study population of $n = 23$, 11 subjects had a decrease in prolactin levels (range of percent change = −9% to −42%), and 12 subjects exhibited an increase in prolactin levels (range of percent change = 2-70% with one outlier at 425%).

Effect of Raloxifene on Circulating Estradiol and SHBG Levels. Although 20 women had paired baseline and 12 months on raloxifene estradiol samples, only 15 had both measurements taken during the early follicular phase (days 3-9) of the menstrual cycle. The data regarding the change in estradiol (Table 3) are reported for the entire group ($n = 20$): those with both measurements taken during days 3 to 9 ($n = 15$) and two subgroups with either the baseline or 12-month measurement taken outside of the day 3 to 9 window ($n = 2$ and $n = 3$, respectively). For the entire group of women who had paired estradiol measurements, the mean change in estradiol was 48 pg/mL ($P = 0.03$; 95% CI, 6-90 pg/mL). However, there were striking differences between the baseline and 12-month measurements of estradiol taken during early follicular phase and those taken outside of the day 3 to 9 window. The latter have higher means, and these biases are reflected in the mean change in estradiol levels presented in Table 3.

In fact, the baseline estradiol measurements taken at days 10 to 11 ($n = 2$) were significantly different at the $P < 0.05$ level from the baselines of the women who had both measurements taken during the early follicular phase ($n = 15$, $P = 0.015$) and from all the women with baseline measurements taken during early follicular phase ($n = 18$, $P = 0.011$). This result, in addition to other differences near the $P = 0.1$ level among the groups in Table 3, led us to exclude the two groups with measurements outside the day 3 to 9 window to avoid any potential biases on the conclusion. When the estradiol analysis was restricted to the 15 women with both measurements taken during days 3 to 9 in the menstrual cycle, the mean baseline estradiol level for this group was 87 ± 50 pg/mL. When comparing baseline measurements to the measurements taken after 12 months on raloxifene, raloxifene treatment increased estradiol levels (mean change = 42 pg/mL; $P = 0.048$; 95% CI, 1-84 pg/mL).

SHBG levels were also measured in this same population. No statistically significant differences in the baseline, 12 months, or change in SHBG levels were detected among the three subgroups identified in the estradiol analyses, either pairwise or in combinations; therefore, the data were combined, and the mean SHBG levels for the entire study population ($n = 20$) was calculated. The mean baseline SHBG measurement was 57.9 ± 26.0 nmol/L (Table 4). SHBG levels increased significantly with raloxifene treatment (mean change = 7.3 nmol/L; $P = 0.0001$; 95% CI, 3.9-10.7 nmol/L).

Table 2 also contains the SHBG analysis for the subgroup of 15 women who had both measurements taken during the early follicular phase of the menstrual cycle for comparison with the more restricted estradiol analysis.

**Discussion**

High levels of both prolactin and estradiol have been associated independently with increased risk of the development of breast cancer in postmenopausal populations.
and were on raloxifene for greater duration (12 months compared with 28 days).

Baker et al. also examined estradiol levels in premenopausal women treated with raloxifene. These authors reported an increase in estradiol over the entire menstrual cycle when premenopausal women were given 400 mg raloxifene daily for 5 days during early follicular phase or 200 mg raloxifene daily for 28 days (57% and 45%, respectively; ref. 25). In the study presented here, estradiol levels increased 48% when the mean baseline level was compared with the mean after 12 months on raloxifene. In addition, a more complete hormonal profile assayed on 11 days during both a pretreatment and an on-raloxifene menstrual cycle was collected from 14 subjects enrolled in this trial, and similar results for estradiol were seen. Therefore, the estradiol data from our study are consistent with Baker’s results, although in our study, the increase in estradiol was measured by comparing baseline levels with levels after 12 months on drug. Our data also are consistent with previous studies showing that tamoxifen treatment increases estradiol levels in premenopausal women (26, 27).

Raloxifene blocks binding of estradiol to the estrogen receptor (24); therefore, when raloxifene is present and the available estrogen receptors are saturated with this drug, one could hypothesize that an increase in estradiol levels may not have a physiologic effect. Furthermore, excess estrogen could be bound to SHBG and, therefore, not bioavailable. Our data support this hypothesis. The prolactin gene contains an estrogen response element and estrogen is a significant positive regulator of prolactin (10, 36), yet no concomitant increase in prolactin was seen with the increase in estradiol levels. Although there are other factors that regulate prolactin expression, such as prolactin itself and progesterone (11), one could hypothesize that a physiologically significant increase in estradiol levels also would contribute to the synthesis and secretion of prolactin. In fact this can be seen in the rat where estradiol regulates the prolactin surge during proestrus (37) and in humans where serum prolactin levels parallel the levels of 17β-estradiol during the menstrual cycle (38).

In our study population, no effect of raloxifene treatment on circulating prolactin levels was observed, however, several limitations may have affected our ability to detect a small change. Hypothyroidism can be associated with increased

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**Table 3. Estradiol (E₂) levels at baseline and after 12 months on raloxifene**

<table>
<thead>
<tr>
<th>Serum E₂ levels (pg/mL)</th>
<th>Baseline, mean ± SD</th>
<th>12 mos on raloxifene, mean ± SD</th>
<th>Mean change from 0 to 12 mos ± SD</th>
<th>P*</th>
<th>95% CI for mean change</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects (n = 20)</td>
<td>102 ± 67</td>
<td>150 ± 102</td>
<td>48 ± 90</td>
<td>0.03</td>
<td>6-90</td>
</tr>
<tr>
<td>Subjects with both E₂ measurements at days 3-9 of menstrual cycle (n = 15)</td>
<td>87 ± 50</td>
<td>129 ± 101</td>
<td>42 ± 74</td>
<td>0.048</td>
<td>1-84</td>
</tr>
<tr>
<td>Subjects with baseline E₂ measurement at day 10 or 11 of menstrual cycle¹ (n = 2)</td>
<td>240 ± 71</td>
<td>182 ± 83</td>
<td>−59 ± 12</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Subjects with 12-mo E₂ measurement at day 10 or 11 of menstrual cycle² (n = 3)</td>
<td>85 ± 43</td>
<td>234 ± 99</td>
<td>149 ± 103</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

*Based on Wilcoxon signed rank analysis.

¹Twelve-month measurement at days 3 to 9 of menstrual cycle.

²Baseline measurement at days 3 to 9 of menstrual cycle.

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(12, 16, 31), but the data in premenopausal women are inconsistent (32). In addition, the literature regarding the use of raloxifene in premenopausal women is particularly scarce. This is the first study to examine the long-term effects of raloxifene on circulating prolactin, estradiol, and SHBG levels in a population of premenopausal women at high risk for developing breast cancer. In this population, there was an increase in estradiol and SHBG levels, whereas prolactin levels remained unchanged.

The prolactin levels were analyzed to determine the effects of parity and the use of antidepressant medication. Although there was no statistical difference in the prolactin levels between the parous and nulliparous women, the difference in the baseline means between these two groups is consistent with prior reports documenting a persistent decrease in prolactin levels subsequent to the first pregnancy (13, 33). For example, Musey et al. showed that prolactin levels in premenopausal parous women are, on average, only 54% of those measured in their nulliparous counterparts (13). In our study, the baseline geometric mean for the parous women was 61% of the baseline geometric mean for the nulliparous women.

Also of concern to the analysis of prolactin levels was the number of women in our study population, ~39%, who were taking antidepressants. For the age range of the participants in our trial (median age = 43 years), this may not be an unusually high proportion of women taking antidepressants. A recently published review on perimenopause and depression cited two cross-sectional studies of women ages 40 to 54 years and ages 45 to 65 years that found the frequency of depression in the specific age ranges to be 52% and 25% to 30%, respectively (34). Furthermore, when prolactin levels were compared between women who were taking antidepressant medication and those who were not, no significant differences were detected. This result is not unexpected because the women who were taking antidepressant medication were prescribed selective serotonin reuptake inhibitors most often. Antidepressants in the selective serotonin reuptake inhibitor class do not significantly alter circulating prolactin levels (35). In addition to selective serotonin reuptake inhibitors, bupropion hydrochloride was prescribed for some subjects; however, this drug also does not alter circulating prolactin levels (35).

After observing that there was no statistical difference between the subgroups, we analyzed the effects of raloxifene on prolactin levels for all women in the study. Given the relative mean change of 5% with \( P = 0.98 \) (Table 2) for the study population of \( n = 23 \) and the balanced changes within this population, we conclude that raloxifene did not significantly alter circulating prolactin levels in our study population. In the only other study to examine prolactin levels in premenopausal women treated with raloxifene, there was no difference detected in the prolactin levels when women were given 100 to 200 mg raloxifene daily for 28 days; however, the authors did observed a 21% decrease in prolactin during a period of 5 days when 400 mg raloxifene was taken each day (25). Our results are consistent with the results published by Baker et al. (25), although women in our study received a lower dose of raloxifene (60 mg daily versus 100-200 mg daily) and were on raloxifene for greater duration (12 months compared with 28 days).

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7 A. Premkumar et al., in preparation.
prolactin levels (39) and thyroid function of these subjects was not routinely checked. However, because no change was appreciated, this is unlikely to be a mitigating factor.

Raloxifene also may be able to modulate prolactin signaling in breast tissue through other mechanisms that may not be reflected in a global measurement of circulating prolactin levels. Raloxifene could affect the autocrine/paracrine prolactin system by altering prolactin secretion locally within the breast tissue. This local change may not be detectable in the measurement of circulating prolactin levels. In addition, tamoxifen can bind directly to the prolactin receptor and inhibit downstream signaling mediated by prolactin (40-42). Tamoxifen has also been shown to down-regulate prolactin receptor mRNA expression in the breast tissue of postmenopausal women given 20 mg tamoxifen daily for 7 days (43). Perhaps, raloxifene can also modify the actions of prolactin locally by either regulating prolactin receptor expression or by inhibiting prolactin receptor signaling in breast tissue.

In conclusion, raloxifene treatment results in an increase in estradiol and SHBG levels in premenopausal women at high risk for breast cancer, but it is unclear if this increase has physiologic consequences or how long the elevated levels of estradiol persist after cessation of raloxifene treatment. In addition, there was no significant change in the circulating levels of prolactin with raloxifene treatment, but the effects of raloxifene on both local prolactin concentrations and signaling of the prolactin receptor in breast tissue remain uncertain. The autocrine/paracrine prolactin system promotes cell proliferation and migration of breast tumor cells in culture (2, 6) and may have significant implications in vivo. Therefore, additional research regarding the regulation of the autocrine/paracrine functions of prolactin by potential breast cancer treatment and prevention agents is warranted.

Acknowledgments

We thank Dr. Heather Young (The George Washington University) for her guidance and insightful discussions; Dr. Alan Remaley (NIH Clinical Chemistry Service) for measuring the prolactin, estradiol, and SHBG levels; and Eli Lilly and Co. for supplying the raloxifene for this trial.

References


Table 4. SHBG levels at baseline and after 12 months on raloxifene

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<td>All subjects (n = 20)</td>
<td>57.9 ± 26.0</td>
<td>65.2 ± 29.4</td>
<td>7.3 ± 7.3</td>
<td>0.0001</td>
<td>3.9-10.7</td>
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<td>Subjects with both SHBG measurements at days 3-9 of menstrual cycle (n = 15)</td>
<td>59.6 ± 28.9</td>
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<td>6.0 ± 6.2</td>
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