Plasma Prolactin Levels and Subsequent Risk of Breast Cancer in Postmenopausal Women

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Background: In animal studies, prolactin has been found to be important for mammary epithelial development and its administration has been shown consistently to increase the rate of mammary tumor formation. Previous epidemiologic studies of prolactin and breast cancer risk in postmenopausal women have been limited in size, and the results have been inconsistent. We conducted a nested case–control study within the prospective Nurses’ Health Study cohort to better determine the relationship between plasma prolactin levels and postmenopausal breast cancer risk. Methods: Blood samples were collected from cohort members during the period from 1989 through 1990. Prolactin levels were measured by use of a microparticle enzyme immunoassay. Included in this analysis were 306 postmenopausal women who were diagnosed with breast cancer after blood donation but before June 1, 1994. One or two postmenopausal control subjects were matched per case subject on the basis of age, postmenopausal hormone use, and time of day and month of blood collection; the study included a total of 448 control subjects. Results: In conditional logistic regression analyses, a significant positive association was observed between plasma level of prolactin and postmenopausal breast cancer risk (highest versus lowest quartile, multivariate relative risk = 2.03; 95% confidence interval = 1.24–3.31; two-sided P for trend = .01). The relationship was independent of plasma sex steroid hormone levels and was similar after excluding case subjects diagnosed in the first 2 years after blood collection. Conclusions: These prospective data suggest that higher plasma prolactin levels are associated with an increased risk of breast cancer in postmenopausal women. [J Natl Cancer Inst 1999;91:629–34]

Prolactin, a polypeptide hormone, is essential for mammary gland development and lactation (1,2). Whether it also influences the risk of breast cancer in women is unclear. In animals, prolactin is important in mammary epithelial development; administration of exogenous prolactin increases rates of mammary tumor formation and suppression of prolactin levels decreases tumor formation (3,4). Prolactin also increases the growth of both normal and malignant breast cells in vitro (5–7), although these findings have not been entirely consistent (8,9).

The epidemiologic data relating plasma prolactin levels to risk of breast cancer have been limited and the results inconsistent. In postmenopausal women, prolactin levels have been associated with an increased risk in several (10–11), but not all (12–14), case–control studies. Because prolactin secretion can be affected by either physical or psychological stress (15–17), levels in women with breast cancer may not reflect predisease levels. To date, only one prospective study of prolactin and breast cancer risk has been reported (18), with just 40 postmenopausal breast cancer cases, and a nonsignificant positive relationship was observed.

To evaluate the relationship between plasma prolactin levels and breast cancer risk in postmenopausal women, we conducted a nested case–control study within the large prospective Nurses’ Health Study (NHS) cohort.

Methods

Study Population

The NHS cohort was established in 1976 when 121,700 U.S. female registered nurses, 30–55 years of age, completed and returned a mailed questionnaire. The cohort continues to be followed every 2 years by questionnaire to update exposure status and to identify cases of newly diagnosed disease. Data have been collected on risk factors for breast cancer, including height, weight, ages at menarche and menopause, age at first birth, parity, postmenopausal hormone (PMH) use, diagnosis of benign breast disease, and family history of breast cancer. Weight, use of PMH, and diagnosis of benign breast disease have been updated every 2 years.

From 1989 through 1990, blood samples were collected from 32,826 cohort members who were 43–69 years of age at collection. Details regarding the blood collection methods have been published previously (19). Briefly, each woman arranged to have her blood drawn and shipped, via overnight courier and with an icepack, to our laboratory where it was processed and separated into plasma, red blood cell, and white blood cell components. Ninety-seven percent of the samples were received within 24 hours of being drawn. The stability of prolactin in whole blood for 24–48 hours has been previously documented (20). Samples have been archived in continuously monitored liquid nitrogen freezers since collection. At blood collection, women were asked if they were currently using antidepressant medications, many of which (e.g., phenothiazines) can increase prolactin levels. Subjects were not queried about other medications that can alter prolactin levels. As of 1994, the follow-up rate among women who provided a blood sample was 98%. The study was approved by the Committee on the Use of Human Subjects in Research at the Brigham and Women’s Hospital.

Both case patients and control subjects are women who were postmenopausal at the time of blood collection. Women were defined as postmenopausal if they reported having a natural menopause (no menstrual cycles in the previous 12 months) or a bilateral oophorectomy, or, for women who reported a hysterectomy and who had either one or both ovaries remaining, when they were 56 (if a nonsmoker) or 54 (if a current smoker) years of age—ages at which natural menopause had occurred in 90% of the cohort.

Case patients were women with no reported cancer diagnosis prior to blood collection and who were diagnosed with breast cancer after blood collection, but before June 1, 1994. In all, 337 cases of breast cancer were reported. All cases of breast cancer were confirmed by medical record review with one exception, for which the nurse confirmed the diagnosis but the medical record was unavailable; because of the high confirmation rate (99%) upon medical record review, this case was kept in the analysis. Time from blood collection to diagnosis...
ranged from less than 1 month to 57 months (mean, 27.8 months). For each case patient who reported PMH use within 3 months prior to blood collection (i.e., “recent use” of PMH) (n = 181), one control was matched per case by age (±2 years), recent PMH use, month of blood collection (±1 month), time of day of blood draw (±2 hours), and fasting status (at least 10 hours since a meal versus <10 hours or unknown). For each case patient who had not reported recent PMH use at blood collection (n = 156), two control subjects were selected using the same matching factors (this was done to increase our statistical power in analyses using only this patient subgroup). Exact control subject matches were obtained for 94% of the patients based on age, 96% based on time of day, and 98% based on month; the most relaxed match was ±5 years of age, ±7 hours, and ±3 months, respectively.

Reproducibility Study

Three hundred ninety NHS participants who gave a first blood sample from 1989 through 1990 were asked to collect two additional samples over the following 2–3 years. The women were postmenopausal, had no prior diagnosis of cancer (except nonmelanoma skin cancer), and had no history of recent PMH use; these criteria were applied at each sample collection. Of the 390 women, 186 (48%) sent two additional samples. A random sample of 80 of these women who had all three samples drawn between 6 AM and 12 noon was sent for prolactin analysis, at the same laboratory as the main study, and forms the basis of the reproducibility study. Details regarding this study have been published elsewhere (21).

Laboratory Analyses

Prolactin was assayed at C. Longcope’s laboratory at the University of Massachusetts Medical Center. Prolactin was measured using a microparticle enzyme immunoassay (IMx System; Abbott Laboratory, Abbott Park, Ill.). The assay detection limit was 0.6 ng/mL; none of our values was less than this limit.

All case-control pairs (or case-control–control triplets) were assayed together; the samples were ordered randomly within a pair (or triplet) and labeled such that the laboratory could not identify case-control status. Although all members of a pair (or triplet) were analyzed at the same time, the pairs (or triplets) were analyzed in two different batches (1993 and 1996). In each batch, we interspersed replicate plasma samples, labeled to preclude their identity for batch-specific distributions (e.g., the highest quartile contained 41% of batch 1 control subjects and 18% of batch 2). Because the mean levels of the quality control samples varied in the same manner between batches, this difference appeared to be due to laboratory variation over time. We therefore defined batch-specific cut points, based on the distribution of the control values in each batch. The quartile cut points were 6.4, 9.3, and 13.7 ng/mL for batch 1 and 5.9, 7.6, and 9.7 ng/mL for batch 2.

One matched set was removed from the analysis because the case patient’s estrogen values were in the premenopausal range. In addition, individual prolactin values met more than 2.5-fold higher than the normal range (1.8–18 ng/mL) were removed from the analysis (four case patients and one control subject); however, in a secondary analysis that included these participants, our findings were essentially unchanged. A number of women either did not have plasma available for laboratory analysis or had implausible values related to initial technical difficulties with the assay, resulting in a loss of 25 case patients and 33 control subjects. One case patient and nine control subjects were excluded because the other members of their matched set did not have prolactin values. Overall, 306 case patients (representing 277 invasive, 28 in situ, and one unknown breast cancer) and 448 control subjects were included.

To test for differences in means between case patients and control subjects, we used mixed-effect regression models for clustered data to adjust for possible confounding due to the matching factors and for any residual correlation between case patients and control subjects within the matched set (24). To compare proportions between case patients and control subjects, we employed the Mantel–Haenszel test (25). We used conditional logistic regression analyses to estimate relative risks (RRs) or odds ratios and 95% confidence intervals (95% CIs) (26). Tests for trend were conducted by modeling prolactin levels continuously and calculating a Wald statistic (27). All P values were based on two-sided tests and, if less than .05, considered statistically significant.

Table 1. Baseline characteristics of breast cancer case subjects and matched control subjects from the Nurses’ Health Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case subjects: mean (SD)</th>
<th>Control subjects: mean (SD)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.5 (5.0)</td>
<td>61.9 (4.8)</td>
<td>MF</td>
</tr>
<tr>
<td>Age at menarche, y</td>
<td>12.5 (1.4)</td>
<td>12.6 (1.5)</td>
<td>.30</td>
</tr>
<tr>
<td>Age at menopause, y</td>
<td>49.1 (4.1)</td>
<td>49.4 (4.4)</td>
<td>.39</td>
</tr>
<tr>
<td>BMI‡ at age 18 y, kg/m²</td>
<td>21.1 (2.7)</td>
<td>21.4 (2.9)</td>
<td>.18</td>
</tr>
<tr>
<td>BMI§ at blood collection, kg/m²</td>
<td>25.7 (5.0)</td>
<td>25.7 (4.6)</td>
<td>.92</td>
</tr>
<tr>
<td>Family history of breast cancer, %</td>
<td>16.6</td>
<td>12.7</td>
<td>.05</td>
</tr>
<tr>
<td>History of benign breast disease, %</td>
<td>49.8</td>
<td>37.5</td>
<td>.003</td>
</tr>
<tr>
<td>Median plasma prolactin, ng/mL (range)</td>
<td>9.0 (1.5–37.4)</td>
<td>7.9 (2.5–32.1)</td>
<td>.01</td>
</tr>
</tbody>
</table>

†Two-sided P values from mixed-effects regression model, controlling for the matching factors (MFs) age, postmenopausal hormone use, and time of day of blood collection, and fasting status; P values <.05 are statistically significant.
‡Among parous women only.
§Body mass index = weight in kg/height in m².

The regression calibration method was used to correct point and interval estimates of the RRs for laboratory measurement error and random within-person variation (28–31). The within-person variance was calculated from the reproducibility study and the between-person variance from the case-control study; thus, the intraclass correlation coefficient for prolactin was slightly different from the previously published value (21). Because the measurement error correction methods require that the relationship between exposure and disease be linear on the logistic scale, four knot-restricted cubic spline models (32) for breast cancer incidence in relation to log-transformed prolactin levels were fit to the data. With the use of these graphical techniques as well as significance testing criteria for nonlinearity, prolactin levels did not show evidence of departure from linearity (P = .99).

RESULTS

At blood collection, women ranged in age from 45 to 69 years (mean age, 62 years) and had been menopausal for at least 1 year (mean, 12 years) (Table 1). Mean age at menarche and parity were similar between case patients and control subjects. Mean body mass index (BMI), defined as weight in kilograms per height in meter squared, and age at menopause were essentially identical in case and control groups, but this partly reflects the matching of case patients and control subjects on PMH use at blood collection (a 1:2 case:control ratio for no recent PMH use and a 1:1 ratio for recent use).

Among hormone nonusers at blood collection, case patients had a later mean age at menopause and higher mean BMI at blood collection than control subjects, as expected, although these differences were not statistically significant. The median prolactin level in case patients was sig-
nificantly higher than that in control subjects (9.0 versus 7.9 ng/mL; P = .01).

We observed a linear increase in breast cancer risk with increasing category of plasma prolactin level (Table 2) (P for trend = .02). Women in the highest quartile of plasma prolactin levels had a statistically significant 87% higher risk of breast cancer compared with women with the lowest levels (RR = 1.87; 95% CI = 1.19–2.94). When we controlled for several established breast cancer risk factors, the relationship strengthened slightly in the highest quartile (RR = 2.03), primarily due to control for BMI at age 18 years and for parity. Controlling, in addition, for duration of use of oral contraceptives did not materially alter these estimates. Qualitatively similar positive associations were observed within each laboratory batch, although none of the RR estimates for batch 1 was statistically significant (RRs for increasing quartiles of prolactin levels: batch 1 [121 case patients and 176 control subjects]—1.0, 1.45, 1.81, and 1.83 [95% CI = 0.79–4.23]; batch 2 [185 case patients and 272 control subjects]—1.0, 0.87, 1.53, and 2.47 [95% CI = 1.28–4.76]).

Current use of postmenopausal hormones tends to increase circulating prolactin levels. After controlling for age, batch, fasting status, and time of day of blood collection, mean prolactin levels were 8.4 ng/mL (SD = 0.99) in nonusers and 9.5 ng/mL (SD = 1.03) in hormone users (P = .01). When we examined the relationship between prolactin and breast cancer separately according to PMH use at blood collection, the RRs were stronger among women not on hormones (top versus bottom quartile comparisons for women not on PMH: multivariate RR = 2.45; 95% CI = 1.25–4.79, versus women on PMH: multivariate RR = 1.86; 95% CI = 0.86–4.04). Among women who reported never using PMH (77 case patients and 181 control subjects), however, the comparable unconditional RR was similar (multivariate RR = 1.93; 95% CI = 0.78–4.79).

Controlling in addition for levels of plasma IGF-I, another hormone that may influence risk of breast cancer (22,33), did not alter the observed relationship. We also were able to control for plasma levels of several sex steroid hormones among the 145 case patients and 290 control subjects who were not using PMH at the time of blood collection. None of the steroids substantially altered the relationship between plasma prolactin and breast cancer risk. For example, when controlling for quartile of plasma estradiol levels, the RR for the top versus bottom quartile of plasma prolactin changed from 2.45 to 2.35 (95% CI = 1.20–4.61).

We also evaluated this relationship after excluding the 28 case patients with in situ breast cancer and observed that the RRs were slightly strengthened (Table 2). When we excluded case patients who were diagnosed with breast cancer within the first 2 years of providing their blood sample (and their matched control subjects), the RRs were very similar to those observed for all case patients and control subjects combined (top versus bottom quartile comparison RR = 2.39; 95% CI = 1.24–4.61). Ten case patients and 21 control subjects had reported antidepressant medication use at the time of blood collection; removing these women from the analysis also did not appreciably alter the RRs. Controlling for fasting status more tightly (in 2-hour increments) also did not alter our findings.

The RR associated with having prolactin levels at or above the 87.5 percentile (i.e., median of the top quartile) compared with levels at or below the 12.5 percentile (i.e., median of the bottom quartile) was 1.62 (95% CI = 1.12–2.37). The intraclass correlation coefficient for prolactin, measured over a 2- to 3-year period, was 0.45. Correcting for measurement error resulted in a substantially higher RR for the same contrast in levels (RR = 3.05; 95% CI = 1.27–7.36).

**DISCUSSION**

In this prospective analysis, we observed a positive relationship between plasma prolactin and subsequent risk of breast cancer. The observed trend in RR was also confirmed in the subset of women not on hormone therapy. Moreover, the magnitude of the RR was similar to that observed in the Nurses’ Health Study, where the highest quartile of plasma prolactin levels had an RR of 1.84 (95% CI = 1.28–2.64) in nonsmokers and 83% higher risk in smokers (RR = 1.84; 95% CI = 1.18–2.89) compared with nonsmokers. In the current analysis, the RR for the top versus bottom quartile was 2.45 (95% CI = 1.25–4.79). Among women not on hormones, the RR was even higher (2.53; 95% CI = 1.15–5.56). These findings suggest that plasma prolactin levels may be a risk factor for breast cancer.

**Table 2.** Relative risk (RR) of breast cancer by category of plasma prolactin level among postmenopausal women in the Nurses’ Health Study

<table>
<thead>
<tr>
<th>Quartile* of plasma prolactin level</th>
<th>1 (lowest)</th>
<th>2</th>
<th>3</th>
<th>4 (highest)</th>
<th>P for trend†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All women (n = 306 case patients/448 control subjects)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case patients/control subjects</td>
<td>64/121</td>
<td>63/112</td>
<td>79/112</td>
<td>100/103</td>
<td></td>
</tr>
<tr>
<td>Simple RR‡ (95% confidence interval)</td>
<td>1.0 (referent)</td>
<td>1.08 (0.68–1.71)</td>
<td>1.44 (0.93–2.23)</td>
<td>1.87 (1.19–2.94)</td>
<td>.02</td>
</tr>
<tr>
<td>Multivariate RR‡ (95% confidence interval)</td>
<td>1.0 (referent)</td>
<td>1.05 (0.65–1.71)</td>
<td>1.45 (0.91–2.31)</td>
<td>2.03 (1.24–3.31)</td>
<td>.01</td>
</tr>
<tr>
<td><strong>Invasive cancer only (n = 278 case patients/406 control subjects)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Simple RR (95% confidence interval)</td>
<td>1.0 (referent)</td>
<td>1.19 (0.73–1.93)</td>
<td>1.61 (1.01–2.57)</td>
<td>2.21 (1.35–3.62)</td>
<td>.02</td>
</tr>
<tr>
<td>Multivariate RR (95% confidence interval)</td>
<td>1.0 (referent)</td>
<td>1.26 (0.75–2.13)</td>
<td>1.61 (0.98–2.64)</td>
<td>2.64 (1.54–4.51)</td>
<td>.007</td>
</tr>
<tr>
<td><strong>Excluding first 2 years of follow-up (n = 183 case patients/272 control subjects)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple RR (95% confidence interval)</td>
<td>1.0 (referent)</td>
<td>0.73 (0.40–1.33)</td>
<td>1.31 (0.75–2.29)</td>
<td>1.99 (1.10–3.59)</td>
<td>.008</td>
</tr>
<tr>
<td>Multivariate RR (95% confidence interval)</td>
<td>1.0 (referent)</td>
<td>0.69 (0.37–1.32)</td>
<td>1.34 (0.72–2.51)</td>
<td>2.39 (1.24–4.61)</td>
<td>.004</td>
</tr>
</tbody>
</table>

*Quartile cut points for prolactin measurements in batch 1 were less than or equal to 6.4, 6.5–9.3, 9.4–13.7, and greater than 13.7 ng/mL, and for prolactin measurements in batch 2 were less than or equal to 5.9, 6.0–7.6, 7.7–9.7, and greater than 9.7 ng/mL. Because of substantial differences in prolactin values between the two batches, batch-specific cut points were used.

†All P values are two-sided and, if <.05, are considered statistically significant.

‡Conditional model, controlling for matching factors only.

§Conditional model controlling for matching factors and additionally controlling for body mass index (weight in kg/height in m², rounded to the nearest tenth) at age 18 years (<21, 22–22.9, 23–24.9, and ≥25), history of breast cancer (no family history or mother or sister had breast cancer), age at menarche (<12, 12, 13, and ≥14 years), age at first birth/parity (nulliparous, one to four children/age at first birth <25 years, one to four children/age at first birth 25–29 years, one to four children/age at first birth ≥30 years, five or more children/age at first birth <25 years, and five or more children/age at first birth ≥25 years), age at menopause (<45, 45–49, 50–55, ≥55 years, and missing), and duration of postmenopausal hormone use (continuous).

[Includes both invasive and in situ breast cancer.]

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breast cancer; women in the upper 25% of prolactin levels had approximately a two-fold higher risk of breast cancer compared with those in the lower 25% of the distribution. This relationship was similar after controlling for a number of established risk factors for breast cancer, plasma estrogen and androgen levels, and IGF-I levels. After excluding case patients diagnosed in the first 2 years after blood collection, similar RRs were observed.

Our study is larger than all of the previous epidemiologic studies of postmenopausal prolactin levels and risk of breast cancer combined and much larger than the only other published prospective study (n = 40 case patients). Because prolactin is known to be influenced by both physical and emotional stress, the prospective nature of our study is an important strength. The observation of similar RRs after excluding case patients diagnosed in the first 2 years after blood collection further assures that the relationship is not due to an influence of the breast cancer on hormone levels. Although 9% of our case samples were unavailable for analysis, this is unlikely to have been related to their prolactin levels and thus would not bias our RRs. Prolactin levels were measured with excellent precision by the laboratory. However, substantial drift in the prolactin values between the two laboratory batches limited our ability to evaluate the relationship between absolute levels of plasma prolactin and risk of breast cancer; nevertheless, positive findings were observed in each of the two batches. Circulating prolactin has a strong circadian variation (17), increases substantially with a noontime meal (34), and—postmenopausally—tends to fluctuate more over time (within a woman) than do most sex steroid hormones (21). To minimize misclassification related to these factors (which would have attenuated our RRs), we closely matched our case patients and control subjects on both time of day of blood draw and fasting status; furthermore, by using multiple hormone measures from a subset of study participants, we were able to correct our RR estimates for the random (and largely biologic) variation in hormone levels that cannot be captured by a single hormone measurement.

Postmenopausal prolactin levels have been evaluated in relation to risk of breast cancer in a few previous studies. In addition to the potential limitations of case–control studies of prolactin described above, these studies were all small, with the largest including just 66 cases (10). In these studies, either a positive association (10,11) or essentially no association (12–14) between prolactin and breast cancer has been observed. In the only previous prospective study (18), women in the top quintile of prolactin levels were at a non-significant 63% higher risk of breast cancer compared with those in the bottom quintile, results comparable to our findings. Epidemiologic data on premenopausal prolactin levels and breast cancer risk are similarly sparse (10,11,13, 18,35,36) and thus additional assessments are needed.

Long-term recent use of both oral contraceptives and postmenopausal hormones has been associated with an increased risk of breast cancer (37,38). The increase in prolactin levels observed with use of these hormones (17) could conceivably be playing a role in this effect. Other medications also are known to increase (e.g., reserpine, haldol, cimetidine, and phenothiazines) or decrease (e.g., levodopa) plasma prolactin levels (17). Of these, the relationship between reserpine use, an antihypertensive medication, and breast cancer risk has been evaluated most extensively. Reserpine initially causes an acute elevation of prolactin; however, long-term use (>5 years’ duration) results in a 50% elevation in plasma levels (39). Although a positive association between reserpine use and breast cancer was noted in several previous studies (40–42), this finding has not been consistently observed (43–48). Reasons for this lack of consistency may include the small size of many of the studies and the exposure definition used (e.g., most investigators reported the relationship with “ever use” of reserpine only). If prolactin is a promoter rather than an initiator of breast cancer (as would seem most likely), only longer durations of use might be expected to have a discernible influence on risk, as is observed with postmenopausal hormone use (37). Further assessment of this and other medications known to alter prolactin levels, including an evaluation of the effect of duration of medication use, is warranted.

Several indirect lines of evidence suggest prolactin could play a role in breast carcinogenesis. Although prolactin is secreted primarily by the anterior pituitary, expression in both normal (49) and malignant (49–51) breast tissue has been reported. In addition, prolactin receptors have been found on more than 50% of breast tumors (52,53). Prolactin also increases DNA synthesis of breast cancer cells in vitro (5–7) and the hormone’s removal inhibits the growth rate of epithelial cells from nonmalignant breast tissue (54). These findings have not been universal (8,9), however, and might relate to the amount or type of prolactin used or the prolactin receptor status of the cells (5). Prolactin administration also is well documented to increase rates of mammary tumors in mice (3).

Several forms of prolactin circulate in human plasma, including the native hormone (23 kd), a 16-kd fragment (55,56), and several glycosylated forms (57,58). These different forms appear to have varying bioactivities (59,60) and perhaps differing biologic actions (60,61). Which isoform(s) are most implicated in increasing the risk of breast cancer is unknown. The two laboratory methods used most commonly to assess prolactin levels are immunoassay (which we used) and bioassay. Immunoassay will identify most prolactin isoforms, but to differing degrees (62); this assay is unable to distinguish between these different forms. The correlation between the two assays has generally been reported to be high (63,64); however, this may vary by study population as a differential release of prolactin isoforms can occur (17,58,65).

Most research on endogenous hormones and breast cancer has focused on plasma estrogens (4,66). The positive relationship we observe between plasma prolactin levels and the risk of breast cancer is generally similar in magnitude to that observed for plasma estrogen levels and breast cancer. Because our study provides the first detailed evaluation of this relationship, additional prospective assessments are warranted.

**REFERENCES**


NOTES
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