Effects of Reserpine on Prolactin Levels and Incidence of Breast Cancer in Postmenopausal Women


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ABSTRACT

Epidemiological studies of reserpine use and breast cancer have generally found only small increases in breast cancer risk, even after long-term use. Prolactin levels in short-term reserpine users have been reported to be in the range of those of lactating women, levels which rodent experiments suggest should greatly increase breast cancer incidence. We measured prolactin levels in 15 women who had been taking reserpine-containing drugs for at least 5 years and compared them to levels in 15 women taking non-reserpine-containing antihypertensives and 15 women taking no antihypertensive medicines. Although reserpine users had significantly elevated levels of prolactin, their mean level was only approximately 50% greater than the mean level of the combined results from the two control groups. Based on a statistical model of breast cancer incidence, we calculate that such increases in prolactin in the postmenopausal period would be likely to cause only small increases in breast cancer risk, as have been observed in epidemiological studies.

INTRODUCTION

In recent years, there has been intensive interest in the role of prolactin in breast carcinogenesis, primarily because of the important role of prolactin in mammary tumor induction in rodents. Pituitary isografts, hypothalamic lesions, and drugs which enhance prolactin secretion all increase the incidence of mammary tumors in rats and mice (18). Both prolactin and ovarian hormones are needed to obtain optimal conditions for chemical transformation of breast epithelium and for growth of established or transplanted mammary tumors in rodents (17).

Various drugs, including reserpine, phenothiazines, methyl-dopa, and tricyclic antidepressants, are known to increase prolactin secretion in humans. Short-term use of reserpine markedly elevates serum prolactin levels into the range typical of lactation (16), and this effect persists for weeks after reserpine use is stopped. Such large elevations of prolactin in rodents would lead to greatly increased mammary cancer rates (12). At least 11 case-control studies of reserpine and breast cancer have clearly shown that such large increases in risk of breast cancer do not occur in women taking reserpine (1–7, 9–11, 13). Most of these studies found a positive association but with an average increased relative risk of less than 2.0 in long-term users, and it may be argued that even this modest apparent increased risk may be due to confounding by socioeconomic status or other breast cancer risk factors.

The reason for the failure to find a large increase in breast cancer risk in reserpine users may be because prolactin does not have a role in breast carcinogenesis in humans. Alternatively, we thought it possible that the elevation of prolactin during short-term reserpine use may not persist if use is continued. This question appears not to have been studied.

We report here a comparison of prolactin levels in women who had been taking reserpine-containing drugs for at least 5 years with those in 2 groups of age-matched controls, women taking other antihypertensive drugs and women with no history of hypertension.

MATERIALS AND METHODS

In 1981, we mailed a detailed health survey to the 17,860 permanent residents of a retirement community in Orange County, CA. Residents of this community, two-thirds of whom are women, have a mean age of about 75, and most are white and affluent. Questionnaires were returned by 11,524 persons. Residents were queried, among other things, about their use of antihypertensives and estrogens, their menstrual and reproductive history, smoking and alcohol habits, and height and weight. We selected for study the first 15 female respondents to this survey who reported continuous use of a reserpine-containing drug for more than 5 years. Their average age was 76. For each of these 15 cases, we randomly selected a respondent of the same age (±1 year) who reported current use of a non-reserpine-containing antihypertensive and one who reported no history of hypertension.

We contacted each reserpine user first by letter and then by telephone to be certain that she was still taking a reserpine-containing drug and to ask her to participate in the study. A convenient morning for blood drawing was arranged, and the woman was instructed to withhold use of any medications on that morning until the sample had been taken. The participant was further instructed to arise from bed at least one-half hr prior to her scheduled appointment. All samples were collected in the participants' homes between 8 and 10 a.m. All controls were given identical instructions, and an attempt was made to collect samples at identical times in the reserpine user and in her 2 matched controls. At the time of sampling, a detailed list of each medication currently being taken was compiled.

Samples were placed on ice and transported to our laboratory, where they were centrifuged and where the serum was drawn off and frozen at -20°. Coded samples of plasma were sent on dry ice to Dr. Darrel Mayes of Endocrine Sciences Laboratory, Tarzana, CA, where prolactin was measured by radioimmunoassay.

Differences in the prolactin levels and the associations between variables were tested using standard statistical techniques.

RESULTS

The mean serum prolactin value in reserpine users was 19.8 ng/ml, compared to 12.3 ng/ml in the women using other antihypertensives and 14.8 ng/ml in the nonhypertensive controls. Women using reserpine-containing antihypertensive medications had significantly higher mean serum prolactin levels than did...
women in either control group (1-sided p values of 0.001 and 0.02). There was a clear excess of high values among the reserpine users (Chart 1). The mean serum prolactin values in the 2 control series were not significantly different.

There was no significant correlation between prolactin levels and weight ($r = -0.05$), age at first pregnancy ($r = -0.03$), or age at last menstrual period ($r = 0.01$), nor was there any significant difference in prolactin values between women who did and did not regularly consume alcoholic beverages, between parous and nulliparous women, or between users and nonusers of estrogen or thyroid replacement therapy, 2 of the more commonly used drugs among these women. Differences in prolactin levels in reserpine users compared with controls remained after stratification on each of these variables.

We studied the relationship between dose of reserpine and prolactin by first calculating a "monthly reserpine dose" equal to the product of reserpine content of each pill times the number of pills taken monthly. The mean monthly reserpine dose was 6.1 mg. The 5 highest prolactin values were observed in the 5 women with the highest monthly reserpine doses. At lower monthly doses, there was no apparent correlation with prolactin levels.

The median duration of use among the 15 reserpine users was 9 years, and 5 women had been taking such medication for more than 15 years. We could detect no correlation between prolactin levels and duration of use of reserpine.

By combining our 2 control series, we calculated that long-term reserpine use was associated with about a 50% increase in serum prolactin.

**DISCUSSION**

Although short-term reserpine use leads to more than a 100-fold increase in serum prolactin (16), the present study demonstrates that this phenomenon does not persist in long-term users. Thus, experiments showing that large elevations in prolactin greatly increase mammary tumor incidence in rodents are not relevant to breast cancer in long-term users of reserpine.

Our data may help resolve the apparent discrepancy between the predictions from animal models and the results of epidemiological studies in humans. Our results are based on a single sample and cannot preclude transient markedly elevated levels of prolactin after drug ingestion. However, our results do preclude the possibility of permanent elevations of prolactin in the range of lactating women in the majority of long-term users of reserpine.

What effect on breast cancer incidence rates might a 50% increase in postmenopausal prolactin produce? Although we cannot answer this question directly, we can approach the question through our recently published statistical model of breast cancer incidence (15). The model has the form

$$l(t) = a[d(t)]^{4.5}$$

where $l(t)$ is the probability of being diagnosed with the cancer at age $t$ (the incidence rate at age $t$) and $d(t)$ is the "relevant age" of breast tissue. $d(t)$ incorporates the effects of age at menarche, age at first full-term pregnancy, and age at menopause: the model essentially assumes that "breast tissue aging" starts at menarche, moves regularly (at rate $f_0 = 1$) to first full-term pregnancy, and then slows to rate $f_1 (0.7)$ until menopause, when it slows further to rate $f_2 (0.1)$. The concept of "breast tissue aging" is associated closely with the cell kinetics of breast tissue "stem" cells; further details of, and the procedure adopted for estimating the parameters of, this model can be found in Ref. 15.

The table shows predicted relative risks from the model for various durations of reserpine use beginning at age 50, assuming various changes in the "breast tissue aging" rate ($f_2$) associated with such use. For example, for a 60-year-old woman who does not use reserpine, with menarche at age 13, first full-term pregnancy at age 23, and menopause at age 50, the relevant breast tissue age, $d(60)$, is calculated as

$$d(60) = f_0(23 - 13) + f_1(50 - 23) + f_2(60 - 50)$$

$$= 10 + 0.7(27) = 29.9$$

If reserpine use doubled the "breast tissue aging" rate in the postmenopausal period, so that $f_2$ changed from 0.1 to 0.2, the "relevant breast tissue age" for a 60-year-old woman with the same characteristics but who had taken reserpine for 10 years can be calculated to be $d(60) = 12 + 0.7(27) + 0.2(10) = 29.9$, and the relative risk for such use would be

$$a(30.9)^{4.5} / a(29.9)^{4.5} = 1.16$$

It is difficult to know what change in "breast tissue aging" to expect with a 50% increase in prolactin. Our statistical model of breast cancer incidence suggests that the decrease in breast
cancer risk associated with early first full-term pregnancy is due to a decrease in the "breast tissue aging" rate. Several groups of investigators have reported a decrease in prolactin levels after a full-term pregnancy (8, 14), suggesting a hormonal mechanism for the long-term beneficial effect of this event, and the proportional decrease in the "breast tissue aging" rate (i.e., \(f_0 / f_1 = 1 \) to 0.7) from the fitted model is almost identical to the proportional decrease (30%) in circulating prolactin levels in parous women to 0.7) from the fitted model is almost identical to the proportional decrease (30%) in circulating prolactin levels in parous women when compared to nulliparous women (19). Therefore, one might predict that a 50% increase in prolactin in the postmenopausal period would also lead to a 50% increase in the "breast tissue aging" rate. Long-term reserpine use in the epidemiological studies showing small increases in risk of breast cancer referred to an average use of reserpine of no more than 10 years. Based on the 50% increase in "breast tissue aging" rate and 10 years of reserpine use beginning at age 50, we would expect a user to have a relative risk of breast cancer of 1.08 compared to a non-reserpine user of the same age (Table 1). If a 50% increase in serum prolactin in the postmenopausal period had twice this effect on "breast tissue aging," the expected relative risk after 10 years of use would still be only 1.16. After 25 years of reserpine use, the risk of breast cancer would only be 41% higher. It would appear unlikely that reserpine could have a greater effect than to double the "breast tissue aging" rate, and these results therefore suggest that reserpine would not greatly increase the relative risk of breast cancer, consistent with the findings of most epidemiological studies of this question.

### Table 1

<table>
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<th>Duration of reserpine use (yr)</th>
<th>Predicted relative risks at the following &quot;breast tissue aging&quot; rates after menopause ((f_2))</th>
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### REFERENCES

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