

# Rauwolfia Use and Breast Cancer: A Case-Control Study<sup>1,2</sup>

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**ABSTRACT**—Breast cancer risk among 1,362 cases and 1,250 controls participating in a large multicenter screening program was examined in relation to hypertension and the use of rauwolfia derivatives. A previous diagnosis of hypertension, reported by 22% of the cases and 23% of the controls, was not associated with an increased risk of breast cancer [odds ratio (OR)=0.9]; nor was there any excess risk for long-term hypertensives. In addition, there was no significant increase in risk associated with use of either rauwolfia derivatives (OR=1.2), thiazide preparations (OR=1.2), or methyl dopa (OR=1.1). However, there were significant excess risks among long-term users and those with extended intervals since first use of rauwolfia. Rauwolfia users of 10 or more years' duration or those whose initial use occurred greater than or equal to 10 years before diagnosis had risk ratios of 4.5 (95% CI, 1.2-19.8) and 3.8 (95% CI, 2.3-11.6), respectively. These results suggest that women exposed to long-term rauwolfia use have an elevated risk of developing breast cancer, although the results fail to support previous observations of a generalized adverse effect.—*JNCI* 1986; 76:817-822.

The relationship between exposure to rauwolfia derivatives and breast cancer was first examined over a decade ago. Interest was stimulated by knowledge that reserpine increases prolactin secretion, a hormone with recognized effects on breast tissue differentiation. Because of reserpine's effect on serum prolactin levels and prolactin's role in the induction and maintenance of mammary tumors in rodents, the question of whether reserpine altered a woman's predisposition to breast cancer became an important issue. Three studies reporting a significant association between use of reserpine (the major rauwolfia preparation) and breast cancer appeared in 1974 (1-3). Relative risk estimates ranged from 2.0 to 3.5. Following these initial reports, 12 case-control investigations (4-15) found no significant increase in risk of breast cancer following use of rauwolfia preparations; the risk associated with ever using rauwolfia ranged from 0.6 to 1.6. Four prospective studies (16-19) provided consistent findings of no overall excess risk, allaying fears evoked by earlier reports. Methodologic problems and variations among case-control studies of rauwolfia and breast cancer have been reviewed in detail (20, 21).

Although there does not appear to be an overall elevation of breast cancer risk associated with ever using rauwolfia medications, some analyses have suggested that risk may be increased among long-term users of rauwolfia derivatives (4, 12, 13) and among those with extended intervals since first exposure (4, 8), as well as among those with a short time since last exposure (8, 18). Positive associations identified in certain subgroups, however, were generally based on small numbers and have not been consistently confirmed. In addition, cer-

tain factors such as age and weight have been found to modify risk in some studies. Kodlin and McCarthy (12) found a higher risk in nonobese women, but Williams et al. (13) reported that heavier women on rauwolfia were at higher risk, although this was restricted to women 50 years of age or older at diagnosis. The effect of menstrual status on risk estimates has not been thoroughly examined, possibly reflecting the fact that few premenopausal women are likely to be exposed to rauwolfia.

In an effort to clarify the relationship between rauwolfia use and breast cancer, we analyzed information regarding history of hypertension and use of anti-hypertensive medications, specifically rauwolfia preparations, among women enrolled in a multicenter breast cancer screening project. Extensive data on medications used by this large group of women permitted evaluation of risk associated with rauwolfia by: subgroups, age at first exposure, recency, latency, and total years of use. Because thiazide diuretics are frequently prescribed for the treatment of hypertension or edema, analyses of breast cancer risk relative to thiazide use provide an additional treatment group for comparison.

## SUBJECTS AND METHODS

The study group consisted of participants in the BCDDP, a multicenter breast cancer screening program described in detail elsewhere (22). The present case-control investigation included cases whose breast cancers

**ABBREVIATIONS USED:** BCDDP = Breast Cancer Detection Demonstration Project; CI = confidence interval; OR = odds ratio(s); QI = Quetelet's index.

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were detected during the period of July 1973 through May 1977. Normal controls consisted of women who had not received either a recommendation for biopsy or a biopsy during participation in the BCDDP program. Control subjects were matched to cases on the screening center, by race, by age, for time of entry, and for length of participation in the screening program.

Home interviews conducted by trained nurse interviewers were completed for 86% of the eligible cases and 74% of the controls. The lower response rate for controls was explained primarily by the fact that more controls had moved out of the study area (12.9% controls vs. 5.0% cases) and that they more frequently refused to be interviewed (10.5% controls vs. 4.6% cases). A positive history at interview of high blood pressure and/or edema was based on a physician's diagnosis of the condition. Because cases were interviewed at different intervals after diagnosis, exposure information for antihypertensive and edema medications was truncated at the time of diagnosis for cases or at an equivalent time for controls. A woman was classified as a user if she had received antihypertensive or edema medications for a period of at least 6 months. The analysis was restricted to white women (91% of the total study population), and the final group for analysis consisted of 1,362 cases and 1,250 controls.

The measure of association used for case-control comparisons was the OR (23). Confounding variables were evaluated by stratified techniques, deriving adjusted maximum likelihood OR estimates and 95% confidence intervals (24). For exposure patterns, significance was assessed by using Mantel's linear trend test (25); two-tailed significance levels were used for trend test. Logistic regression was also performed (26) to simultaneously control for several potentially confounding factors. Since these results were consistent with stratified analyses, only the stratified are presented.

## RESULTS

Table 1 presents data regarding breast cancer risks associated with a previous diagnosis of hypertension or edema. Overall, 22% of the cases and 23% of the controls reported a history of hypertension, resulting in an OR of 0.9 (95% CI, 0.8-1.1). Risk estimates were similar whether a woman was ever treated or untreated for hypertension and did not vary significantly by the duration of hypertension. In addition, ever having edema diagnosed or treated was not found to increase a woman's risk of developing breast cancer.

Women were asked about specific preparations prescribed for the treatment of hypertension and/or edema (table 2). For these analyses, all comparisons were made relative to women without a previous diagnosis of hypertension or edema. The odds ratio of breast cancer associated with rauwolfia was 1.2 (95% CI, 0.9-1.8). Adjustment for age at diagnosis of breast cancer, for menopausal status, for weight, for QI (weight/height<sup>2</sup>), for age at first live birth, for family history of breast cancer, for history of breast feeding, for household income, for years of education, for ever use of thiazide diuretics, and for ever use of menopausal estrogens did not appreciably change the risk estimate. Rauwolfia exposure stratified by age at diagnosis of hypertension yielded no consistent patterns of risk. In addition, the risk estimate associated with rauwolfia use was similar to that presented in table 2 (OR=1.5) when the referent group was limited to women diagnosed and treated for hypertension. Other medications for the treatment of hypertension or edema, including thiazides and methyl-dopa, were associated with risks of 1.2 and 1.1, respectively. Low risks were associated with the use of other antihypertensive agents (OR=0.6; 95% CI, 0.3-1.2) and other nonthiazide diuretics (OR=0.7; 95% CI, 0.5-1.0).

Further analyses considered the relative odds of breast

TABLE 1.—OR of breast cancer by previous diagnosis and treatment for hypertension and edema<sup>a</sup>

Category	Cases, n=1,362	Controls, n=1,250	OR (95% CI)
Ever diagnosed with hypertension			
No	1,059	957	1.00
Yes	303	293	0.93 (0.8-1.1)
Ever treated	250	244	0.93 (0.8-1.1)
Untreated	52	49	0.96 (0.6-1.4)
Duration of hypertension			
Never diagnosed	897	814	1.00
<5 yr	98	100	0.89 (0.7-1.2)
5-9 yr	73	62	1.07 (0.7-1.6)
≥10 yr	87	88	0.90 (0.7-1.3)
Ever diagnosed with edema			
No	1,129	1,020	1.00
Yes	232	230	0.91 (0.7-1.1)
Ever treated	167	168	0.90 (0.7-1.1)
Untreated	62	62	0.90 (0.6-1.3)
Ever diagnosed with hypertension and edema			
No	897	814	1.00
Yes	70	87	0.73 (0.5-1.0)

<sup>a</sup> Adjusted for age at diagnosis of breast cancer of study subjects. Analysis excludes unknowns.

TABLE 2.—OR of breast cancer by treatment for hypertension and edema<sup>a</sup>

Ever use of:	Cases	Controls	OR (95% CI)
Rauwolfia	83	61	1.24 (0.9-1.8)
Thiazide	167	124	1.22 (0.9-1.6)
Methyldopa	55	48	1.10 (0.7-1.6)
Other antihypertensives	13	22	0.55 (0.3-1.2)
Other diuretics	62	85	0.67 (0.5-1.0)

<sup>a</sup> All risks relative to subjects without a history of hypertension or edema: 897 cases, 814 controls. OR adjusted for age at diagnosis of breast cancer of study subjects. Analysis excludes 89 cases and 75 controls with a previous diagnosis of hypertension or edema who were never treated.

cancer by specific parameters of rauwolfia and thiazide use, including total years of use, years since first use, years since last use, and age at first use. Significant linear trends in risk were observed with both years of use and years since initial use of rauwolfia (table 3). However, this mainly reflected the influence of excessive risks for the highest exposure categories rather than a consistent increase in the OR with increased exposure. Notably, those who used rauwolfia for 10 or more years and those whose first use began 10 or more years before the diagnosis of breast cancer were at significantly elevated risk (OR=4.5 and 3.8, respectively). Duration effects persisted when the analysis was limited to hypertensive women and were present among both prevalent and incident case groups (prevalent cases were those detected on the first screen, whereas incident cases were diagnosed during later screens). Analysis of years since last use showed that rauwolfia use that ended 4 or more years before diagnosis was associated with a significantly elevated risk (OR=3.9; 95% CI, 1.1-13.9), whereas current rauwolfia use was not associated with any significant elevation in risk (OR=1.1). No age-at-first-exposure effects were found.

TABLE 3.—OR of breast cancer by selected exposure variables for use of rauwolfia or thiazide<sup>a</sup>

Measure of use	OR	
	Rauwolfia	Thiazide
Yr of use		
<5	1.34 (37)	1.28 (82)
5-9	0.91 (16)	1.50 (33)
≥10	4.54 <sup>b</sup> (15)	1.33 (25)
χ <sub>1</sub> for trend	2.05 [P=.04]	1.93 [P=.06]
Yr since first use		
<5	0.91 (23)	1.27 (66)
5-9	1.36 (24)	1.70 (43)
≥10	3.81 <sup>b</sup> (21)	1.06 (35)
χ <sub>1</sub> for trend	2.55 [P=.01]	1.55 [P=.12]

<sup>a</sup> Numbers of cases are shown in parentheses. Unknowns excluded from linear trends. All risks are relative to subjects without a history of hypertension or edema: 897 cases, 814 controls. Analysis excludes subjects with unknown information regarding whether rauwolfia and/or thiazide was ever prescribed. Medication categories are not mutually exclusive.

<sup>b</sup> 95% CI excludes 1.0.

TABLE 4.—OR of breast cancer associated with years of rauwolfia use by selected risk factors

Category	OR; yr of rauwolfia use <sup>a</sup>		
	<5	5-9	≥10
Age at diagnosis, yr			
<55	1.03 (14)	0.77 (7)	3.54 (4)
≥55	1.33 (27)	0.74 (11)	4.07 (13)
Menstrual status			
Premenopausal	0.79 (8)	0.39 (3)	1.57 (2)
Postmenopausal	1.35 (31)	0.94 (15)	5.01 (15)
Natural	1.97 (23)	1.47 (10)	3.59 (7)
Surgical	0.71 (8)	0.54 (5)	7.76 (8)
Wt, lb			
<135	2.03 (12)	0.68 (4)	4.57 (9)
≥135	0.95 (29)	0.71 (14)	3.27 (8)
QI			
<23	1.78 (15)	0.59 (5)	2.53 (8)
≥23	0.97 (26)	0.80 (13)	7.76 (9)

<sup>a</sup> Numbers of cases are shown in parentheses. All risks relative to subjects without a history of hypertension or edema within each stratum: 897 cases, 814 controls. Analysis excludes subjects with unknown information regarding whether rauwolfia was ever prescribed.

In comparison to rauwolfia, the risks associated with thiazide preparations did not vary consistently according to length of use or recency. Neither of these exposure measures resulted in significant trends in risk, and none of the strata-specific risk estimates achieved statistical significance.

Estimates of risk associated with rauwolfia and thiazide (adjusted one for the other) provided results consistent with those presented in table 3. In addition, other breast cancer risk factors did not appear to confound or modify the observed OR. There was no evidence, for example, that women who used rauwolfia for 10 or more years were also older (≥30 yr) at first live birth.

Further exploration of the high risks among those with extended years of use and with years since first use of rauwolfia involved a cross tabulation of these two factors. Although numbers became sparse, it appeared that duration effects predominated. Within these high-risk, long-term users, there was a relationship of risk to recency of use, with current users being at highest risk (OR=5.4; 95% CI, 1.4-20.7).

A final examination of breast cancer risk associated with rauwolfia focused on years of use with a specific search for evidence of effect modification. Table 4 illustrates that, contrary to previous reports, the excess risk associated with long-term rauwolfia use risk was not restricted to older, heavier women. Effects did vary somewhat, however, by menstrual status and QI, with those who were postmenopausal or who had a QI of greater than or equal to 23 demonstrating the strongest effects associated with long-term rauwolfia use.

## DISCUSSION

In the present study, we evaluated the relative odds of breast cancer associated with a prior diagnosis of hypertension or edema, as well as according to use of a

number of different medications prescribed as treatment. We did not find hypertension to be a risk factor for breast cancer, a finding consistent with most other reports (10, 15, 27-29) but different from that of De-Waard et al. (30) who suggested that high blood pressure might be related to the risk of breast cancer among postmenopausal women. In our study, there was no substantial variation in risk according to the duration of hypertension; and both treated and untreated women with a prior diagnosis of hypertension showed no elevated risk. Furthermore, women ever diagnosed with edema were not at altered breast cancer risk.

In addition, we found no substantive or significant overall increase for ever use of any specific antihypertensive. The relationship of antihypertensives to breast cancer risk has been a controversial issue since Jick et al. (1) first reported over a threefold excess risk of breast cancer among women exposed to rauwolfia. This risk estimate was based on interview data obtained on newly diagnosed cases and hospitalized controls. Two other positive studies (2, 3), based on medical record review, also used hospitalized case-control study groups. Since these initial reports, numerous negative studies utilizing different populations and methodologies have been conducted (4-19).

Thus this study provides some further grounds for reassurance, particularly since we were able to examine the issue in a large group of women interviewed during participation in a breast cancer screening project. However, we did find significantly elevated risks among users of 10 or more years (OR=4.5) and among those who began use more than 10 years prior to diagnosis (OR=3.8). Although numbers became sparse in the analysis, it appeared that extended use was more important than latency and that long-term current users were at highest risk. This finding is of interest, given that Jick et al. (1) in a study of current reserpine users also found elevated risks, although in that study no increased risk was found for long-term users. They speculated that this result might reflect the fact that current users of rauwolfia tended to be short-term users, although we found that current users were more often long-term users. These studies fail to agree on which subgroup might be at highest risk, supporting the need for further evaluation of both duration and recency of use effects.

Our finding of an excess risk for long-term users of rauwolfia must be interpreted with caution due to the small number of exposed women and multiple comparisons in the analysis. However, our findings are consistent with results of some earlier studies. Aromaa et al. (9), limiting their analysis to rauwolfia use for 10 or more years, found a relative risk of 1.7 for prior rauwolfia use. Other studies (12, 13) that have defined rauwolfia exposure as 5 or more years of usage reported relative risks ranging from 1.6 to 2.0. Among hypertensive women exposed to rauwolfia for at least 5 years, Mack et al. (4) reported a risk ratio of 2.6. However, Friedman (19) in a recent large prospective study found no excess risk of breast cancer for rauwolfia users of 5 or more years; and other reports have also failed to establish

any link between breast cancer risk and either long duration of rauwolfia use (10, 15, 16) or extended intervals since first use (4, 8, 13).

On a biologic basis, the relationship between rauwolfia and breast cancer has been of concern because of the drug's ability to increase secretion by the adenohypophysis of prolactin (31, 32), a protein hormone that affects the development of mammary tissue and the secretion of milk by glandular cells. In vitro, prolactin has been shown to promote proliferation of breast tissue and mammary tumor cells (33-35), possibly by altering the hormone-responsiveness of target cells (36, 37). One prospective study, where serum prolactin levels were determined prior to the diagnosis of breast cancer, suggested that the hormone may act as a late-stage promoter (38). Another study (39) showed that daughters of breast cancer cases had measurably elevated prolactin levels compared to daughters of control women during the luteal phase of the menstrual cycle. Human studies have also suggested that other breast cancer risk factors, such as nulliparity and late age at first birth, may be mediated through a prolactin effect (40-42). Although animal studies have demonstrated limited evidence for a carcinogenic effect of rauwolfia (33, 43), elevated prolactin levels have been associated with the initiation and promotion of mammary tumor growth (32, 33, 44).

Clinical investigations have shown markedly elevated serum prolactin levels in hypertensive patients treated with rauwolfia (32, 45, 46). The levels appear to decrease shortly after drug discontinuation (45), at least in short-term users. Of special interest is the effect of long-term rauwolfia use on prolactin values. Ross et al. (47) found that women taking rauwolfia preparations for 5 or more years had significantly higher mean serum prolactin values than unexposed subjects. Long duration of rauwolfia use was estimated to increase serum prolactin levels by about 50%, which the authors suggest would only slightly increase the risk of postmenopausal breast cancer. Since, on an epidemiologic and laboratory basis, an excess risk associated with rauwolfia use may be limited to long duration exposures, the discrepancies of previous work may be due at least partly to short-term vs. long-term effects. However, the role of prolactin may be overstated since phenothiazines, methyldopa, and diazepam also increase plasma levels of prolactin, but have not been clearly shown to modify the risk of breast cancer (31, 32, 48). In addition, despite the maintenance of supranormal prolactin levels during lactation, extensive periods of breast feeding have not generally been associated with any alteration in breast cancer risk (49).

Several sources of potential bias also need to be considered in interpreting results from the current study. In particular, we were concerned that the risks seen in our study merely reflect the fact that long-term users had the most severe hypertension. Because we had no clinical information on the severity of disease (other than the age at first diagnosis) we were unable to assess whether severity of disease influenced the risk of breast cancer. However, this form of bias seems an unlikely explanation for our finding since duration of hypertension was

not found to be a risk factor, and results were unaltered when we examined rauwolfia use only among hypertensive women. In addition, excess risks were seen for long-term users of rauwolfia alone as well as for those who used it with other antihypertensives; in fact, the risk was higher (OR=7.3) among exclusive users compared with users of multiple medications (OR=2.7). We were also concerned that long-term users of rauwolfia might represent a group who are more likely to be consumers of medical care and medications in general. However, adjustment for income, for education, for age at diagnosis of hypertension, and for age at first exposure to rauwolfia did not modify risk estimates. In addition, we found that rauwolfia users were not unusual with respect to their use of nonhypertension medications, including oral contraceptives, estrogens, tranquilizers, or thyroid medications. Finally, the rauwolfia associations were examined separately for breast cancer cases diagnosed on the initial screen as opposed to those detected on later screens. The fact that results were similar for both case groups would seemingly argue against our findings being due to the selective inclusion of rauwolfia users who were actually symptomatic at the time of enrollment (50). Thus, while it seems unlikely that bias could totally explain the excess risks that we observed among long-term users of rauwolfia, further studies are needed to determine whether our results can be generalized to other populations.

Because previous analyses (12, 13) have suggested certain associations between rauwolfia and breast cancer in variously defined subgroups of the population, a final analysis examined duration effects of rauwolfia stratified by age at diagnosis, by weight, by QI, and by menopausal status. Williams et al. (13) found an association only in women over 50 years of age who were also heavier than average weight. As a follow-up, Friedman (19) reported that, even after limiting the analysis to women diagnosed at age 50 or more years, the use of rauwolfia was not linked to breast cancer. Shapiro et al. (15) also failed to find any elevation in risk among older women ( $\geq 50$  yr). We did not find that age or weight modified risk in our analyses. However, an examination of breast cancer risk by QI and of menstrual status showed the highest elevations in risk associated with long-term rauwolfia use among women with a QI greater than or equal to 23, as well as among those who had experienced natural or surgical menopause. However, the difference in risk for premenopausal vs. menopausal women may have merely reflected the fact that few premenopausal women reported extended periods of rauwolfia use.

Evidence for a generalized relationship between rauwolfia use and breast cancer has not been substantiated in our study. We, as well as others (4-19), have failed to confirm a significant excess risk of developing breast cancer among women exposed to rauwolfia. However, the increased risks among long-term users and those with extended intervals since first use are of concern and warrant further investigation.

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