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Pharmaceuticals That Cause Mammary Gland Tumors in Animals: Findings in Women

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Abstract

Risk of breast cancer in women was assessed for eight pharmaceuticals that produce mammary tumors in experimental animals, using nested case-control analyses in two cohorts with prescription records in a comprehensive medical care program. The two cohorts were: 1) earlier cohort: 78,118 female members who received prescriptions in 1969-1973, of whom 2,467 developed breast cancer, and 2) later cohort: 3,289,408 female members who received prescriptions in 1994-2006 of whom 24,528 developed breast cancer. Longest follow-up was until June 30, 2006. Ten randomly selected concurrent control women were age-matched to almost every case. Relative risks were estimated by conditional logistic regression. Case ascertainment was lagged by two years, or unlagged and subdivided by number of prescriptions received. Some analyses were controlled for hormone use and sensitivity analyses were conducted to estimate the effects of uncontrolled confounding. In the later cohort furosemide, and metronidazole showed statistically significant but very small increases in relative risk (ranging from 1.07 to 1.13). Of these, only furosemide showed increased risk in the earlier cohort: 2-year lag relative risk 1.66 (95% confidence interval 1.23-2.24) or as low as 0.97, assuming uncontrolled positive confounding. Griseofulvin showed significant increases in the later cohort: relative risk for three or more prescriptions 1.48 (1.08-2.03) or as low as 1.23 assuming uncontrolled positive confounding and non-significant increases were noted in the earlier cohort. Our findings are limited by their inconsistency across the two cohorts and our inability to directly control for most established breast cancer risk factors. Although inconclusive, our findings suggest a need for more research on furosemide and griseofulvin.

Keywords

breast neoplasms; pharmacoepidemiology; cyclophosphamide; furosemide; griseofulvin; indomethacin; isoniazid; metronidazole; nitrofurantoin; reserpine

Animal studies are currently a primary method of evaluating the potential carcinogenicity of chemical exposures in humans. While not all chemicals found to cause tumors in animals also cause tumors in humans, all known human carcinogens that have undergone animal testing have been found to increase the risk of tumors in animals at one of more organ sites (1). Nonetheless, only a small fraction of the 80,000 chemicals registered by the US Environmental Protection Agency (EPA) have been tested in animals for their potential carcinogenicity.

Recently, Rudel et al. provided a comprehensive review of chemicals found to cause mammary tumors in animals (1). The review identified 216 chemicals associated with an increase in mammary tumors in at least one study. Of these, 47 were pharmaceuticals.

As part of a project to screen pharmaceutical drugs for possible carcinogenicity (2,3) we have examined data in a large group of women to determine whether use of some pharmaceuticals among these substances is associated with an increased risk of developing breast cancer. We here report findings for cyclophosphamide, furosemide, griseofulvin, indomethacin, isoniazid, metronidazole, nitrofurantoin and reserpine. These were the only drugs listed in the review (1) on which we had sufficient data, and on which study in our setting was appropriate as explained below.

Cyclophosphamide is used for treatment of some cancers and auto-immune disorders and to prevent rejection of transplanted organs. Furosemide is a diuretic used for treatment of hypertension and fluid retention due to congestive heart failure or liver or kidney disease. Griseofulvin is used to treat fungal infections of the skin, hair and nails. Indomethacin is an anti-inflammatory drug used to treat rheumatoid disorders. Isoniazid, metronidazole and nitrofurantoin are anti-infective drugs used to treat, respectively, tuberculosis, certain bacterial and protozoal infections, and urinary tract infections. Reserpine, now rarely used, is an antihypertensive drug.

Methods

Setting, subjects and ascertainment of drug use

The study setting is the Kaiser Permanente Medical Care Program in northern California (KPMCP). The KPMCP is an integrated prepaid health care delivery system that provides comprehensive inpatient and outpatient care, including pharmacy services, to over 3 million current members (about half female), who comprise about 30 percent of the residents of the areas served surrounding San Francisco Bay and in the Central Valley. The membership is fairly representative of the local population except for some under-representation of both extremes of the economic spectrum (4). Two cohorts of members were the sources of data for this study.

Later cohort

In the larger, more recent cohort, ascertainment of pharmaceutical use was based on the program's Pharmacy Information Management System (PIMS), which records all prescriptions dispensed to outpatients. Surveys of subscribers with drug coverage indicate that they fill nearly 100% of their prescriptions at KPMCP pharmacies (5). A total of 3,289,408 females with KPMCP drug coverage were identified and followed up starting in August 1994,

when implementation of PIMS in all KPMCP pharmacies was completed. Cohort entry began at the time of both joining the program and having drug coverage, if later than August, 1994.

Earlier, smaller cohort

Before PIMS was established, our drug surveillance for possible carcinogenicity was based on another cohort of 143,574 subscribers (78,118 or 54.4% females) with computer-stored records of prescription dispensing in 1969-1973 at the Kaiser Permanente outpatient pharmacy in San Francisco (2,10-12). Although this database is much smaller and less detailed, it afforded an opportunity to look at much longer intervals between use of some of the drugs and cancer diagnosis.

Drugs selected for study

The animal mammary carcinogens (1) screened for breast cancer risk in women include cyclophosphamide, furosemide, griseofulvin, indomethacin, isoniazid, metronidazole, nitrofurantoin, and reserpine. Our findings for each of these eight drugs have been reported previously (2,7,10-12,14,15) and are updated for this report. Regarding other animal mammary carcinogens (1), phenacetin was included in analgesic combinations recorded only in the earlier cohort as it has been removed from the market. We did not study it because of large unknown over-the-counter use, and because urinary tract cancers have been clearly associated only with high-cumulative-dose abuse (16), which we believe is rare in this population. Because female hormones have been studied intensively as possible breast cancer risk factors with control for several possible confounders (17) we did not include Norlestrin (norethindrone and ethinyl estradiol) (1) in this study. Since we required at least 10 exposed cases in the later cohort for sufficient reliability for inclusion in this report, only cyclophosphamide, among all of the anti-cancer drugs (1), was included.

Ascertainment of breast cancer

Occurrence of invasive breast cancer was ascertained through KPMCP's Cancer Registry, which covers all subscribers and contributes to the local Surveillance, Epidemiology, and End Results (SEER) program (6). Additional ascertainment through hospital records was used for the earlier cohort (10) before 1988 when the Registry was expanded to cover the entire program. Women first diagnosed with breast cancer before a study period were excluded from the respective cohorts. In both cohorts follow up ended when breast cancer was diagnosed, when the subject left KPMCP for any reason including death, or at the end of June 2006, whichever came first. There were 24,258 women with breast cancer in the later and 2,467 in the earlier cohort.

The annual age-adjusted incidence of breast cancer in females in the KPMCP in 2000-2004, 136.8/100,000 was seven percent higher than that observed in all SEER registries combined, 127.8/100,000 (6).

Analytic methods

Analyses used a nested case-control approach with person-time or concurrent controls (8). For each breast cancer case, ten controls were randomly selected from all of the program's female subscribers with the same year of birth and same year of starting drug coverage. They had to be free of breast cancer by the date in the same year that would give the control equal follow-back time as that of the case. Controls were not excluded if they developed breast cancer later, or if they had been selected for one or more other cases. A few very elderly patients (five and three in the earlier and later cohorts, respectively) ages 94 to 104 years at breast cancer diagnosis, could be matched with fewer than ten controls.

Conditional logistic regression was used to calculate odds ratios as estimates of the relative risk of breast cancer associated with medications of interest using the SAS system (9). The three comparisons made were: any use vs. no use before diagnosis, any use vs. no use at least two years before diagnosis to rule out pre-diagnostic prescribing for symptoms possibly related to breast cancer ("2-year lag"), and one, two, and at least three prescriptions dispensed vs. no use to ascertain possibly greater risk for longer use. All women were considered non-users of a drug until our records showed that it was dispensed to them. Statistical significance is claimed for relative risk estimates if their 95% confidence intervals do not overlap 1.0. Based on animal experiments each of these drugs was hypothesized to be associated with breast cancer in women. Therefore no adjustment was made for multiple comparisons.

For tests of trend, number of prescriptions was entered as 0, 1, 2, or 3 (for 3+). For odds ratios and trend test for interval from second prescription to diagnosis, the interval group variable was entered as 0, 1, 2, or 3. Heterogeneity in associations across subgroups (e.g., age, calendar year) was estimated by incorporating interaction terms into the model.

Drug usage statistics and subscriber surveys also indicated that use of some drugs was associated with use of estrogens, progestins and other female hormone preparations for birth control, menopausal hormone therapy and other indications. Therefore, use of hormones, which may increase the risk of breast cancer and of tamoxifen or raloxifene, which may reduce the risk, was controlled in analytic models in the later cohort by adding four indicator variables: oral contraceptives, hormone replacement therapy, raloxifene/tamoxifen, and other hormones. Based on more limited hormone use in 1969-1973 there were two indicator variables, estrogens and oral contraceptives. Use was defined as receiving at least two prescriptions for the particular category of hormones.

Sensitivity analyses

Due to our inability to control for most breast cancer risk factors we conducted sensitivity analyses on the findings, using the method of external adjustment of Schneeweiss (13), to estimate changes in our risk estimates that might be due to unknown and uncontrolled confounding. Since this method allows adjustment for only a single variable, we assumed a dichotomy of breast cancer risk in our subjects, ranging in risk ratios of 3.0, 2.0 and 1.5 for increased risk and the inverse of these, 0.33, 0.50 and 0.67 for decreased risk. The prevalence of the increased/decreased breast cancer risk subgroup was set at 10%, 25% and 50%, and the odds ratio for the association of use of the drug with the subgroup was set at 1.5 and 2.0. The prevalence of use of the drug in the population was varied to approximate that of the drugs studied as follows: 10% for metronidazole, 5% for furosemide, indomethacin and nitrofurantoin, and 1% and 0.1% for the other drugs. All of these differences in drug use prevalence had virtually no effect on the results, and 1% will be shown for the other drugs. The spreadsheet program generates the percent bias under these various assumptions, which is applied to the observed relative risk. For example, if the percent bias is +10% and the observed relative risk is 1.50, the adjusted relative risk is $1.5/1.10 = 1.36$. The results presented are for the extreme confounder relative risk of 3.0 and 0.33, the larger drug/confounder association of 2.0, and the 25% or 50% prevalence of the risk group, which gave the highest values for positive and negative confounding, respectively. In every case the percent bias was approximately 20% for positive confounding and 16.8% for negative confounding. An additional analysis of positive confounding was conducted for furosemide since conditions it is used to treat, hypertension, congestive heart failure, renal disease (due to hypertension or diabetes mellitus) are associated with obesity, a risk factor for post-menopausal breast cancer (96.8% of furosemide-associated case patients were age 50 years or more). Another condition with fluid retention treated with furosemide, liver disease, is associated with alcohol use, also a breast cancer risk factor. For this analysis, the odds ratio for furosemide users belonging to

the subgroup with a threefold increase in breast cancer risk was set at 10, resulting in a percent bias of 71.6%, used to generate the lower sensitivity limit.

Ethics

The study was approved by the Institutional Review Board of the Kaiser Foundation Research Institute. Informed consent was not required or obtained for these analyses of stored data on thousands of patients.

Results

Characteristics of the subjects

Patients with breast cancer tended to be older in the earlier cohort with a difference in median age at diagnosis of two years. This is probably due at least in part to the longer follow up of the earlier cohort; most of its cases were diagnosed after the maximum 12 years of follow-up available in the later cohort. Because the later cohort was so much larger, many more users of each drug were available for study, except for reserpine, now little used to treat hypertension. (Table 1). Because controls could be used for more than one case and could become cases later, the 27,108 total cases and controls in the earlier cohort consisted of 19, 119 unique women. The corresponding numbers for the later cohort were 266, 821 and 229,505.

Relative risks

In the later cohort (Table 2) the result of controlling for hormone use, if any, was usually to decrease or leave unchanged the apparent relative risk. Negligible increases were noted only for cyclophosphamide (2-year lag), isoniazid and reserpine including combinations (3+ prescriptions). The few changes in the earlier cohort were also negligible (Table 3).

In the later cohort (Table 2) the only relative risk elevations that were statistically significant in both the 2-year lag and the 3+ prescriptions analyses were for furosemide and metronidazole. However these relative risks were all very small, ranging from 1.07-1.14 when hormone use was included in the analysis. Griseofulvin showed a more substantial statistically significant increase but only with 3+ prescriptions.

There was statistically significant supporting evidence from the earlier cohort (Table 3) only for furosemide, in the 2-year lag analysis. In that cohort, controlling for hormone use, compared to that for three or more prescriptions, the relative risk (95% confidence interval) following one prescription was slightly higher—1.61 (1.00-2.58) based on 20 exposed cases, and considerably higher following two prescriptions—3.53 (2.03-6.15) based on 17 exposed cases (not in Table).

Sensitivity analyses

The sensitivity analysis limits based on external adjustment represent assumptions that there may be marked uncontrolled confounding. In both cohorts (Tables 4, 5), except for 3+ prescriptions of griseofulvin in the later cohort, the lower limits of relative risk were all near or below unity (1.00).

Additional analyses of griseofulvin and furosemide

The higher and statistically significant risk elevation for 3+ prescriptions of griseofulvin led to additional analyses of this drug in the later cohort (Table 6). There was evidence of dose-response although the relative risk for only one prescription was below unity. The elevation in risk associated with 3+ prescriptions (vs. 0 prescriptions) was highest among women over age 70 (OR=1.95 vs. 1.27 for women less than age 50), although the test for interaction was not

significant. This was not attributable to their having received more griseofulvin prescriptions. The mean, median and range of number of prescriptions were, respectively: age < 50 years: 6.0, 5, 3-13; age 50-69 years: 5.5, 5, 3-9; and age 70+: 4.9, 4, 3-11. Risk after the second prescription appeared elevated in all follow-up intervals. The 3-<5 year interval showed the highest risk but all follow-up-duration-specific confidence intervals overlapped considerably. There was no statistically significant confirmation of a griseofulvin-breast cancer association from the earlier cohort but the wide confidence intervals did not rule out an increase in risk (Table 3).

The strong confirmation regarding furosemide in the earlier cohort, i.e., higher and statistically significant relative risk, led to further analyses. Women in the later cohort who received only one prescription for furosemide (Table 7) also showed a relative risk slightly below unity. The 2- and 3+-prescription recipients experienced somewhat higher risks, and although the trend was statistically significant, the increase did not appear monotonic as it had with griseofulvin and the differences were small. Age at diagnosis had little if any relationship with risk (not shown). Small risk increases were apparent in each follow-up interval after the second prescription. Risk was slightly higher after five years than before, with greatly overlapping confidence intervals. In the earlier cohort, risk appeared only slightly greater with longer follow-up, i.e., beyond 1989 (not shown). Thus the longer follow-up available for this group did not appear to explain the stronger association of furosemide with risk of breast cancer in this cohort.

Cyclophosphamide

Although the small risk elevation for cyclophosphamide was larger than for any of the other drugs in the 2-year lag analyses (Table 2), there were few exposed cases and the confidence intervals for both this and the 3+ prescription finding were wide, extending well into an inverse association. There was only one exposed case in the earlier cohort (Table 3).

Discussion

When carcinogenicity is found in animal experiments it is essential to determine whether this is also true for humans. Although our data have a number of limitations, it is somewhat reassuring that we could not confirm this association for indomethacin, isoniazid, nitrofurantoin and reserpine. The data concerning cyclophosphamide were too scanty, with wide confidence limits, for any conclusions to be drawn about its apparent small risk elevation. Indomethacin is in the class of nonsteroidal anti-inflammatory drugs (NSAIDs), have usually been associated with reduced risk of breast cancer in other epidemiological studies (16).

Due to the large number of women in this study, the narrow confidence intervals for the small positive associations of griseofulvin, furosemide and metronidazole in the larger later cohort essentially ruled out chance as an explanation. However, we were unable to account for any breast cancer risk factors other than age and, crudely, for hormone use. Uncontrolled confounding is always of concern in observational studies, especially with regard to weak associations (18). Although negative confounding and a resulting underestimation of risk are certainly possible, we believe it is more likely that women at higher risk are more likely to receive some of these drugs. Thus, we have focused more on the lower sensitivity limits based on assumptions of strong uncontrolled positive confounding. It also seems more appropriate to be conservative about accepting evidence for carcinogenicity in humans given the usefulness of these drugs and their importance for many patients. Nevertheless, uncontrolled confounding may have been minimal in our analyses and probably less than the rather strong sensitivity limits that we computed (Tables 4 and 5). That our risk estimates for these pharmaceuticals were little influenced by unknown and uncontrolled confounding received empirical support from the study of antibiotics and breast cancer by Velicer et al, who were able to control for

several breast cancer risk factors and found that this had no material effect on the observed drug/cancer associations (19).

We are unable to either confirm or rule out a small increase in risk to humans associated with use of any of the drugs studied as all had upper 95% confidence limits above a relative risk of 1.0. Our estimates of relative risk related to number of prescriptions dispensed are also limited by the duration of ascertainment. We could not account for prescriptions before August 1994 in the later cohort or prescriptions either before or after the four-year window, 1969-1973 in the smaller earlier cohort. One frequent limitation in drug surveillance studies, i.e., accounting for over-the-counter receipt, does not apply here as all of the drugs were obtainable only by prescription.

Our previous studies found no risk elevations for breast cancer for the antibiotics, isoniazid, metronidazole, or nitrofurantoin or for the antihypertensive drug, reserpine (rauwolfia), which is now rarely prescribed (2,7,10-12,14,15). Studies of antibiotics and breast cancer risk from other settings (summarized in 7, 19) did not report on isoniazid or metronidazole, but Velicer et al (20) reported an increased risk with nitrofurantoin, whereas Didham et al. (21) reported no increased risk. Of studies that evaluated cancer risk among users of metronidazole, none reported a statistically significant increase in breast cancer (16).

In contrast to our previous findings for use of all antibiotics combined (7), hormone use did not appreciably confound the relationship to breast cancer of any of the drugs studied here.

Although no conclusions or therapeutic recommendations can yet be drawn, griseofulvin and furosemide are the strongest candidates for further epidemiologic study. Although our evidence has some inconsistencies, of greatest concern for griseofulvin is the 1 ½-fold increase in risk among recipients of three or more prescriptions in the later cohort, and most concerning for furosemide is the 1.7-fold increase with 2-year lag in the earlier cohort, both statistically significant. The only evidence that we found of griseofulvin's mammary carcinogenicity in animals was one experiment (22) in which griseofulvin induced breast neoplasms in female mice and lung granulomas in mice of both sexes. Findings for other sites have been reviewed by the International Agency for Research on Cancer (IARC) (23,24); it produced liver tumors in mice and thyroid tumors in rats but not in hamsters. Griseofulvin has produced toxic effects in experimental animals but the only genetic effect that we found was increased tetraploidy in tissue culture (23). In another IARC review of experimental evidence, (25), furosemide induced a small increase in the incidence of mammary carcinomas in mice but there was no increase in tumors in rats. Furosemide has been reported to induce mutations and chromosomal damage in some cell lines in tissue culture (25). Findings in experimental animals for the other drugs studied were summarized in the report that stimulated these analyses (1).

All of these drugs are presumably prescribed for good reasons. So even if small increases in breast cancer risk are established, these must be balanced against the expected therapeutic benefit of taking these drugs, also considering alternative medications for the same indications.

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Table 1
Characteristics of the cases and controls and counts of drug users in each cohort.

	Earlier cohort				Later cohort			
	Cases		Controls		Cases		Controls	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Age at diagnosis*								
< 45 yr.	206	8.4	2060	8.4	2527	10.4	25270	10.4
45-54 yr.	448	18.2	4480	18.2	5534	22.8	55340	22.8
55-64 yr.	665	27.0	6650	27.0	6473	26.7	64730	26.7
≥ 65 yr.	1148	46.5	11451	46.5	9724	40.1	97223	40.1
Calendar years at diagnosis**								
Early	566	22.9	5660	23.0	6688	27.6	66872	27.6
Middle	694	28.1	6933	28.1	8520	35.1	85200	35.1
Late	1207	48.9	12048	48.9	9050	37.3	90491	37.3
Total number of female users								
cyclophosphamide			10				173	
furosemide			302				15106	
griseofulvin			113				1133	
indomethacin			973				12794	
isoniazid			103				948	
metronidazole			535				31035	
nitrofurantoin			276				14156	
reserpine			834				324	

* Same date for matched controls

** Early, middle, late were: earlier cohort: <1980, 1980-1989, 1990-; Later cohort: August 1994-June 1998, July 1998-June 2002, July 2002-June 2006.

Table 2
Odds ratios of breast cancer risk associated with use of several pharmaceuticals in the later cohort.

Drug	2-year lag			3 or more prescriptions filled		
	No. of cases who were users	Odds ratio (95%CI) *		No. of cases who were users	Odds ratio (95%CI) *	
		Univariate	Controlled for hormone use		Univariate	Controlled for hormone use
Cyclophosphamide	14	1.26 (0.72-2.20)	1.27 (0.73-2.22)	17	1.26 (0.76-2.09)	1.25 (0.76-2.07)
Furosemide	1132	1.13 (1.06-1.21)	1.13 (1.05-1.20)	1174	1.13 (1.06-1.21)	1.13 (1.06-1.20)
Griseofulvin	106	1.16 (0.95-1.42)	1.13 (0.92-1.38)	45	1.53 (1.12-2.09)	1.48 (1.08-2.03)
Indomethacin	996	1.04 (0.97-1.12)	1.02 (0.96-1.09)	361	1.08 (0.97-1.20)	1.06 (0.95-1.18)
Isoniazid	56	0.79 (0.60-1.04)	0.79 (0.60-1.04)	17	0.71 (0.44-1.17)	0.72 (0.44-1.17)
Metronidazole	2481	1.11 (1.06-1.16)	1.07 (1.02-1.12)	770	1.14 (1.06-1.23)	1.09 (1.01-1.18)
Nitrofurantoin	1034	1.00 (0.94-1.07)	0.97 (0.91-1.04)	304	1.00 (0.89-1.13)	0.96 (0.86-1.09)
Reserpine alone	25	0.86 (0.57-1.29)	0.86 (0.57-1.30)	23	0.94 (0.61-1.43)	0.94 (0.62-1.45)
Reserpine all **	34	1.01 (0.71-1.43)	1.01 (0.71-1.44)	31	1.06 (0.73-1.54)	1.07 (0.74-1.55)

* CI: confidence interval

** Includes preparations containing reserpine and thiazide diuretics.

Table 3
Odds ratios of breast cancer risk associated with use of several pharmaceuticals in the earlier cohort.

Drug	2-year lag			3 or more prescriptions filled		
	No. of cases who were users	Odds ratio (95%CI) *		No. of cases who were users	Odds ratio (95%CI) *	
		Univariate	Controlled for hormone use		Univariate	Controlled for hormone use
Cyclophosphamide	1	0.83 (0.11-6.41)	0.83 (0.11-6.40)	0	--	--
Furosemide	52	1.65 (1.23-2.23)	1.66 (1.23-2.24)	23	1.39 (0.90-2.16)	1.40 (0.90-2.18)
Griseofulvin	14	0.93 (0.54-1.61)	0.93 (0.54-1.61)	6	1.25 (0.54-2.93)	1.26 (0.54-2.94)
Indomethacin	125	1.02 (0.84-1.23)	1.02 (0.84-1.24)	35	1.18 (0.83-1.69)	1.18 (0.83-1.69)
Isoniazid	9	0.73 (0.37-1.44)	0.73 (0.37-1.43)	4	0.72 (0.26-2.00)	0.72 (0.26-2.00)
Metronidazole	57	0.86 (0.65-1.13)	0.85 (0.65-1.12)	0	--	--
Nitrofurantoin	29	0.85 (0.58-1.25)	0.85 (0.58-1.25)	2	0.91 (0.21-3.86)	0.91 (0.21-3.87)
Reserpine **	111	1.08 (0.88-1.33)	1.08 (0.88-1.33)	76	1.23 (0.96-1.57)	1.23 (0.96-1.57)

* CI: confidence interval

** Labeled as rauwolfia in previous reports (2,10-12,14) and included combinations with other antihypertensive drugs, mostly thiazide diuretics.

Table 4

Sensitivity analysis limits* of observed odds ratios, controlled for hormone use, in the later cohort.

Drug	2-year lag	3+ prescriptions
Cyclophosphamide	1.27 (1.06-1.48)	1.25 (1.04-1.46)
Furosemide	1.13 (0.66-1.32)*	1.13 (0.66-1.32)*
Griseofulvin	1.13 (0.94-1.32)	1.48 (1.23-1.73)
Indomethacin	1.02 (0.85-1.19)	1.06 (0.88-1.24)
Isoniazid	0.79 (0.66-0.92)	0.72 (0.60-0.84)
Metronidazole	1.07 (0.89-1.25)	1.09 (0.91-1.27)
Nitrofurantoin	0.97 (0.81-1.13)	0.96 (0.80-1.12)
Reserpine alone	0.86 (0.72-1.00)	0.94 (0.78-1.10)
Reserpine all**	1.01 (0.84-1.18)	1.07 (0.89-1.25)

* Upper limit based on high risk group's relative risk of breast cancer = 3.0, proportion of population in high risk group = 25%, and odds ratio of drug use by high risk group = 10 for furosemide, 2 for all other drugs. Lower limit based on low risk group's relative risk of breast cancer = 0.33, proportion of population in low risk group = 50%, and odds ratio of drug use by low risk group = 2. Prevalence of drug use ranging from 0.1% to 10% made virtually no difference in limits.

** Includes preparations containing reserpine and thiazide diuretics.

Table 5

Sensitivity analysis limits* of observed odds ratios, controlled for hormone use in the earlier cohort

Drug	2-year lag	3+ prescriptions
Cyclophosphamide	0.83 (0.69-0.97)	--
Furosemide	1.66 (0.97-1.94)*	1.40 (0.82-1.64)*
Griseofulvin	0.93 (0.77-1.09)	1.26 (1.05-1.47)
Indomethacin	1.02 (0.85-1.19)	1.18 (0.98-1.38)
Isoniazid	0.73 (0.61-0.85)	0.72 (0.60-0.84)
Metronidazole	0.85 (0.71-0.99)	--
Nitrofurantoin	0.85 (0.71-0.99)	0.91 (0.76-1.06)
Reserpine**	1.08 (0.90-1.26)	1.23 (1.02-1.44)

* Upper limit based on high risk group's relative risk of breast cancer = 3.0, proportion of population in high risk group = 25%, and odds ratio of drug use by high risk group = 10 for furosemide, 2 for all other drugs. Lower limit based on low risk group's relative risk of breast cancer = 0.33, proportion of population in low risk group = 50%, and odds ratio of drug use by low risk group = 2. Prevalence of drug use ranging from 0.1% to 10% made virtually no difference in limits.

** Labeled as rauwolfia in previous reports (2,10-12,14) and included combinations with other antihypertensive drugs, mostly thiazide diuretics.

Table 6

Odds ratio estimates of breast cancer risk associated with use of griseofulvin among women in the later cohort.*

Exposure	Category	Number of cases	Odds ratio (95% CI) **	p (trend)
No. of prescriptions	1	67	0.94 (0.73-1.21)	0.03
	2	26	1.23 (0.82-1.85)	
	3+	45	1.48 (1.08-2.03)	
Interval, 2 nd Rx **** to diagnosis *** (years)	< 3	25	1.31 (0.86-1.99)	0.03
	3-<5	20	1.77 (1.10-2.86)	
	5+	26	1.22 (0.81-1.84)	

* Reference group is non-users. Adjusted for hormone use.

** CI: confidence interval

*** Corresponding date for each case's matched controls

**** Rx: prescription. Recipients of one prescription were included in the model.

Table 7

Odds ratio estimates of breast cancer risk associated with use of furosemide among subgroups of women in the later cohort. *

Exposure	Category	Number of cases	Odds ratio (95% CI) **	p (trend)
No. of prescriptions	1	392	0.96 (0.87-1.07)	<0.01
	2	223	1.16 (1.01-1.34)	
	3+	1174	1.13 (1.06-1.20)	
Interval, 2 nd Rx **** to diagnosis *** (years)	<2	506	1.10 (1.00-1.21)	<0.01
	2-<5	484	1.10 (1.00-1.21)	
	5+	407	1.23 (1.11-1.37)	

* Reference group is non-users. Adjusted for hormone use.

** CI: confidence interval

*** Corresponding date for each case's matched controls

**** Rx: prescription. Recipients of one prescription were included in the model.