

# Antibiotics and Risk of Breast Cancer: Up to 9 Years of Follow-up of 2.1 Million Women

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## Abstract

Antibiotic use has been associated with risk of breast cancer in previous reports. Using Cox proportional hazards analysis, we evaluated this association in 2,130,829 adult female subscribers of a health care program according to their receipt of prescriptions of antibiotics from outpatient pharmacies. Hormone use was taken into account. Altogether, 18,521 women developed breast cancer in up to 9.4 years of follow-up. Use of any antibiotic was associated with slightly increased risk [hazard ratio (HR), 1.14; 95% confidence interval (95% CI), 1.10-1.18] but there was little, if any, evidence of dose response, with HR of 1.17 (95% CI, 0.97-1.42) for >1,000 days of use compared with no use. The only two weakly associated antibiotic groups (HR >1.10 for >100 days of use) were tetracyclines and macrolides with

HRs (95% CI) of 1.23 (1.11-1.36) and 1.16 (0.98-1.36), respectively. An association of lincosamides with breast cancer in an earlier, smaller database was not confirmed, but follow-up was too short in the present data for adequate evaluation. Medical record review suggested that acne and/or rosacea could be the underlying factor, associated with long-term antibiotic therapy and found by others to be associated with risk of breast cancer. Although causality cannot be ruled out, the observed associations of antibiotics overall, tetracyclines, and macrolides with breast cancer were weak and could be explained by uncontrolled confounding by the diseases being treated or by other factors. (Cancer Epidemiol Biomarkers Prev 2006;15(11):2102-6)

## Introduction

Two recent reports by Velicer et al. (1, 2) have raised concern that exposure to antibiotic therapy might increase a woman's risk of developing breast cancer. In the first, biological mechanisms whereby antibiotics could either increase or decrease risk of breast cancer were described. The second was a large case-control study in which use of several classes of antibiotics was associated with risk of developing breast cancer with evidence of dose-response relationships. A previous study (3) found an association of antibiotic treatment of urinary tract infections and subsequent breast cancer in women under 50 years of age. Other studies have not, or at most weakly, confirmed increased risk of breast cancer following antibiotic use (4-7). Velicer et al. (8) also found a trend toward less favorable tumor features associated with antibiotic use, which was not statistically significant.

We have been screening pharmaceuticals for possible carcinogenic effects since the 1970s (9-12). Reported here are our findings about antibiotics and breast cancer.

## Materials and Methods

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 >3 million members (about half women), who compose ~30% of the residents of the areas served surround-

ing San Francisco Bay. The membership is fairly representative of the local population except for some underrepresentation of both extremes of the economic spectrum (13).

Ascertainment of antibiotic use was based on the Pharmacy Information Management System (PIMS) of the program, which records all prescriptions dispensed to outpatients. Based on surveys of diabetic patients between 2000 and 2003, ~97% of subscribers have at least partial payment for prescriptions covered by KPMCP and ~93% of subscribers fill all of their prescriptions at KPMCP pharmacies.<sup>4</sup> Women ages ≥20 years with KPMCP drug coverage were identified and followed up starting in August 1994, when implementation of PIMS in all KPMCP pharmacies was completed. Follow-up began at the time of both joining the program and having drug coverage, if later than August 1994. All women were considered to be nonusers of antibiotics until one was dispensed to them after the start of follow-up. PIMS records of days of supply were used to estimate duration of use of each drug, and if a later prescription for the same drug was issued before days of supply was supposed to have been used up, the later days of supply was started after the previous days of supply was to have ended. Ascertainment of dispensing of antibiotics ended on December 31, 2003.

Cancer occurrence was ascertained through KPMCP Cancer Registry, which covers all subscribers and contributes to the local Surveillance, Epidemiology, and End Results program (14). Only invasive breast cancer was considered during follow-up, and patients diagnosed before an antibiotic dispensing was first recorded were excluded from follow-up of that antibiotic. Follow-up ended when breast cancer was diagnosed, when the subject left KPMCP for any reason including death, or at the end of 2003, whichever came first.

Relative risk of breast cancer [estimated as the hazard ratio (HR)] was determined by Cox proportional hazard modeling

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<sup>4</sup> Dr. Andrew Karter, personal communication.

using the SAS system (15), in which ages of women were used as the time scale and antibiotic use was a time-dependent variable. Once a subject received an antibiotic, she was never later reclassified as a nonuser.

Drug usage statistics and subscriber surveys also indicated that antibiotic use was associated with use of estrogens, progestins, and other female hormone preparations for birth control, menopausal hormone therapy, and other indications. For example, among 18,983 women, the age- and ethnicity-adjusted antibiotic user/nonuser odds ratio (OR) for a survey response of "yes" to use of estrogens during the previous 12 months was 1.61 [95% confidence interval (95% CI), 1.47-1.76]. Therefore, use of these hormones, plus tamoxifen and raloxifene, all of which may affect risk of breast cancer, was included in our analytic models as time-dependent variables. Use was defined as receiving at least two prescriptions for the particular category of hormones. When a woman received the second prescription, her status was changed from nonuser to user and she remained a user for the remainder of follow-up.

To test for trend of risk with increasing duration of use, nonusers were excluded and successive duration categories were assigned the numbers 1, 2, 3, and 4. For each subject, the category number was entered into the same Cox models instead of use versus nonuse.

For the two antibiotic groups with the highest risk associated with >100 days of use, tetracyclines and macrolides, we reviewed the medical records of a random sample of 25 cases each with this high use, looking primarily for likely confounding by indication or other evidence for or against a causal relation. One of these tetracycline recipients had a prior breast cancer and was excluded from the review. We also reanalyzed tetracyclines and macrolides independently of each other by excluding women who had used the other drug group before the one of interest and ending follow-up when a drug in the other group was received. Hormone use was included in these models.

In previous analyses involving a smaller cohort who received prescriptions from KPMCP pharmacy in San Francisco in 1969 to 1973, the incidence of breast cancer in users of a drug or drug group was compared with that of the entire pharmacy cohort by means of the standard morbidity ratio (SMR; refs. 9-12). The SMR is the ratio of the number of cases observed in the users of the drug group to the number expected, when the age/sex-specific incidence rates of the entire cohort were applied to the users. The findings for antibiotics were all similar to those to be presented in this larger analysis, except for lincosamides, which showed an association with breast cancer risk in the earlier data. Therefore, we also reviewed the medical records of the 16

women who developed breast cancer among these earlier lincosamide users.

The study was approved by the Institutional Review Board of the Kaiser Foundation Research Institute.

## Results

The study group included a total of 2,130,829 women at least 20 years of age, of whom 1,469,680 received at least one antibiotic and 18,521 developed breast cancer. The risk of breast cancer was slightly elevated among all users of any antibiotics with no clear dose-response relationship, using the breakpoints reported by Velicer et al. (2). Hormones were also related to risk and adjustment for them lowered the risk associated with use of antibiotics (Table 1). For all antibiotic recipients, the HR (95% CI) following first use with no adjustment for hormone use was 1.24 (1.20-1.28). Adjustment for hormone use reduced the HR to 1.14 (1.10-1.18). Excluding breast cancer cases during the first 2 years of follow-up (2-year lag analysis) made virtually no difference. With 2-year lag, the hormone-adjusted HR for all antibiotics was 1.13 (1.09-1.17).

Findings for individual drug groups are presented for >100 days of use, the highest breakpoint used by Velicer et al. (ref. 2; Table 2). Findings for shorter durations of use not presented here are available from the authors by request.

**Tetracyclines.** These consisted largely of tetracycline, doxycycline, and minocycline. There was evidence of dose response based on the trend of increasing risk with increasing duration among all users (Table 3). Two-year lag changed the HR minimally for all tetracycline users, from 1.07 (1.03-1.12) to 1.08 (1.04-1.13).

The medical records of a random sample of 24 of the  $\geq 101$ -day users who developed breast cancer did not reveal anything unusual about the histologic type of cancer and breast cancer risk factors. Although some patients had received the drug for other indications as well, 21 of 24 had received it for treatment of acne or rosacea.

The earlier San Francisco pharmacy follow-up data for 11,882 recipients of at least one dispensing of tetracyclines showed a SMR of 1.20 (95% CI, 1.10-1.31; 501 observed and 416.0 expected cases). For the 1,809 women who received three or more prescriptions, the SMR was 1.78 (95% CI, 1.43-2.20; 88 observed and 49.3 expected cases). Tetracyclines and lincosamides were the only antibiotic groups with statistically significant associations of three or more dispensings with breast cancer in these data.

**Macrolides.** These consisted largely of erythromycin, azithromycin, and clarithromycin. Although the risk for the

**Table 1. Relative risk of breast cancer among women who received any antibiotic by total days of use and receipt of various hormone therapies**

Antibiotics, days of use	Thousands of person-years	No. cases (total: 18,521)	Model 1	Model 2
			HR (95% CI)	HR (95% CI)
None	1,830.2	4,425	1.00 (reference)	1.00 (reference)
$\leq 50$	5,180.5	8,558	1.19 (1.15-1.23)	1.13 (1.09-1.18)
51-100	1,172.6	2,746	1.25 (1.20-1.32)	1.16 (1.11-1.22)
101-500	1,469.5	2,511	1.28 (1.22-1.34)	1.16 (1.11-1.22)
501-1,000	96.4	170	1.18 (1.02-1.38)	1.07 (0.91-1.24)
>1,000	55.1	111	1.31 (1.08-1.58)	1.17 (0.97-1.42)
Hormone preparations*				
Menopausal*	1,547.5	5,674		1.24 (1.20-1.28)
Oral contraceptives*	2,045.7	888		1.17 (1.09-1.25)
Other*	592.6	1,736		1.16 (1.10-1.22)
Tamoxifen or raloxifene*	35.2	120		0.90 (0.75-1.08)

NOTE: Model 2 included hormone use; model 1 did not.

\*Use defined as receiving at least two prescriptions.

**Table 2. Relative risk of breast cancer associated with >100 days of use of various antibiotics and antibiotic groups compared with no use**

Antibiotic(s)	Thousands of person-years	No. cases	HR (95% CI)
Penicillins	252.5	468	1.03 (0.94-1.13)
Tetracyclines	344.8	393	1.23 (1.11-1.36)
Macrolides	116.8	145	1.16 (0.98-1.36)
Quinolones	18.0	34	0.76 (0.54-1.07)
Cephalosporins	67.7	131	0.92 (0.77-1.09)
Lincosamides	4.4	8	0.79 (0.40-1.59)
Aminoglycosides*	13.6*	30*	1.03 (0.72-1.47)*
Sulfonamides	115.7	223	1.03 (0.90-1.17)
Trimethoprim	95.9	168	0.94 (0.81-1.10)
Trimethoprim/ sulfamethoxazole	88.6	155	0.97 (0.82-1.13)
Metronidazole	4.7	8	0.97 (0.48-1.93)
Isoniazid	62.4	34	0.72 (0.51-1.00)
Rifampin	5.1	7	0.83 (0.39-1.73)
Nitrofurantoin	60.9	121	0.92 (0.77-1.11)

NOTE: Controlled for hormone use.

\*Findings for  $\geq 11$  days of use. There was only one case with  $\geq 101$  days of use. Most aminoglycoside administration is parenteral and not recorded in the PIMS records.

$\geq 101$ -day users was consistent with the findings for all antibiotics combined, the HR in the  $\geq 101$ -day users, 1.16, was somewhat higher than in users for shorter durations. However, the HRs for  $\leq 10$ , 11 to 30, and 31 to 100 days of use were well within the 95% CI of  $\geq 101$  days, and the test for trend among all users proved not statistically significant (Table 3). As with all antibiotics and tetracyclines, 2-year lag changed the HR minimally for all macrolide recipients, from 1.05 (1.02-1.09) to 1.04 (1.01-1.08).

The medical records of a random sample of 25  $\geq 101$ -day users did not reveal anything unusual about the histologic type of cancer and breast cancer risk factors. The most common indications were respiratory infections. Acne or rosacea was mentioned at least once about eight patients and was the most frequent indication in five of them.

**Use of Tetracyclines or Macrolides but not Both.** Excluding the other drug group had little effect on the findings (Table 3). The reduction in the HR with tetracycline for the  $\geq 101$ -day use group and the increase in the lower categories apparently indicate that some tetracycline users destined to get breast cancer received a macrolide before progressing to the highest-duration group. This was not evident for macrolides when tetracycline use was excluded. The trend of increased risk with increasing duration of use of tetracyclines became somewhat smaller and lost statistical significance when macrolide use was excluded. For macrolides, excluding use of tetracyclines did not change the lack of evidence for trend of risk with increasing duration of use.

**Lincosamides.** In the current data set, the only lincosamide prescribed was clindamycin. There was no elevated risk in the users for  $\geq 101$  days although 95% confidence limits were fairly wide and compatible with some risk elevation. There was no

indication of dose response, the HRs for  $\leq 10$  days, 11 to 20, 21 to 100, and  $\geq 101$  days of use being 1.07, 0.95, 1.15, and 0.79, respectively. The lower 95% confidence limits for  $\leq 10$  days and 21 to 100 days were 0.97 and 0.96, so neither of the elevations in these subgroups reached conventional statistical significance.

The earlier San Francisco pharmacy follow-up data for 212 recipients of at least one lincosamide prescription showed a SMR of 2.52 (95% CI, 1.44-4.09; 16 observed and 6.4 expected cases). The SMR for 33 women who received three or more prescriptions was 8.50 (95% CI, 1.75-24.8; 3 observed and 0.4 expected cases). Fourteen of these 16 cases had received clindamycin, and two, lincomycin. Their medical records showed that 10 had received only one prescription for a lincosamide, two had received two, and one each received 3, 5, 10, and 16 (one more woman than the three or more based on only computer-stored data). All but one woman who was diagnosed with breast cancer at age 82 years had taken female hormones for various reasons. There was nothing unusual about the histologic types of cancer and breast cancer risk factors. Indications were quite varied, including acne in three women.

The intervals from first known prescription to diagnosis of breast cancer ranged from 2 to 29 years. Only three of these intervals were less than the maximum 9.4 years of follow-up in the more recent pharmacy (PIMS) cohort. Eight were from 12 to 18 years and five were from 21 to 29 years. The mean age at first recorded lincosamide prescription was 46.7 years with a range of 22 to 69 years, and the mean age at breast cancer diagnosis was 62.9 years with a range of 36 to 83 years. So the relatively long drug-to-diagnosis intervals were not due to receipt of these drugs by children and adolescents.

**Other Antibiotics.** There was no statistically significant increase in risk of breast cancer associated with >100 days of use of penicillins, quinolones, cephalosporins, sulfonamides, trimethoprim, metronidazole, isoniazid, rifampin, or nitrofurantoin; HRs >1.0 were no greater than 1.03 (Table 2). There was only one case with >100 days of use of aminoglycosides and the HR for >10 days of use was 1.03 (Table 2). The small number of cases among  $\geq 101$ -day users of metronidazole and rifampin raises interest in the next highest duration of use studied. For 15 to 100 days of use of metronidazole, the HR (95% CI) was 1.02 (0.94-1.12). For 31 to 100 days of use of rifampin, it was 1.07 (0.56-2.05). The largest HR observed for any duration category for all antibiotic groups other than tetracyclines, macrolides, and lincosamides was 1.13 (95% CI, 1.08-1.19) for 11 to 30 days of use of cephalosporins.

Combinations of different antibiotics were included in the analysis of each drug in the combination. The combination of trimethoprim and sulfamethoxazole accounted for most cases and person-years of both the trimethoprim and sulfonamide groups and was therefore included as an additional category in Table 2.

## Discussion

We observed a slightly increased risk of breast cancer with antibiotic use overall with minimal, if any, evidence for a dose-response relationship. Only two antibiotic groups, tetracyclines

**Table 3. Relative risk [HR (95% CI)] of breast cancer according to days of use of tetracyclines and macrolides, excluding or not excluding the other drug group**

Antibiotic	1-10 d	11-30 d	31-100 d	101+ d	Trend*
Tetracyclines	1.04 (0.98-1.10)	1.04 (0.97-1.11)	1.13 (1.04-1.22)	1.23 (1.11-1.36)	1.06 (1.02-1.09)
Tetracyclines excluding macrolides	1.06 (0.98-1.15)	1.08 (0.99-1.18)	1.16 (1.04-1.30)	1.14 (0.99-1.31)	1.04 (0.99-1.09)
Macrolides	1.05 (1.01-1.10)	1.06 (1.01-1.11)	1.03 (0.95-1.11)	1.16 (0.98-1.36)	1.01 (0.97-1.04)
Macrolides excluding tetracyclines	1.07 (1.03-1.12)	1.03 (0.96-1.09)	1.01 (0.91-1.12)	1.18 (0.93-1.49)	0.98 (0.94-1.03)

NOTE: Reference group was not used; controlled for hormone use.

\*Relative risk per increase in one duration category; nonusers were excluded.

and macrolides, showed HRs of >1.1 for >100 days of use, and the 95% CI for macrolides overlapped 1.0. Tetracyclines showed some evidence of dose response. Lincosamide use documented in an earlier, smaller database was associated with breast cancer risk in longer-term follow-up than is yet available for the more recent pharmacy (PIMS) cohort. This association could not be adequately reevaluated and could have been due to chance.

Chance sampling variation is an unlikely explanation for the small increase in risk seen for use of any antibiotic of up to 500 days, given the narrow confidence intervals (Table 1). A more likely explanation for small increases in risk is uncontrolled confounding. The use of antibiotics for symptoms of breast cancer before it was diagnosed was ruled out by the similarity of findings from analyses with and without a 2-year lag. Other possible explanations are that exposure to certain antibiotics may increase risk or that infections may increase risk or be associated with increased risk. Our data are not sufficient to determine which, if any, of these explanations holds. The biological mechanisms linking antibiotic use with breast cancer proposed by Velicer et al. (1) and Knekt et al. (3) included effects of antibiotics on the metabolism by intestinal microflora of phytochemicals related to estrogen metabolism and their effects on immune and inflammatory factors.

The case-control study of Velicer et al. (2) involved 2,266 cases and 7,953 controls in a medical care program similar to ours. It is the only large study to date, from which the authors reported substantially increased risk of breast cancer associated with antibiotic use—a 2-fold increased odds with >1,000 days of use. Increased risk was noted for all antibiotic groups studied: macrolides, tetracyclines, penicillins, cephalosporins, sulfonamides, and nitrofurantoin. Knekt et al.'s (3) finding in a Finnish cohort of an OR of 1.74 was limited to 86 cases among 5,536 women under age 50 years treated for urinary tract infection, with no increase in the OR (0.97) among older women. Sorensen et al. (4) found no increased risk in a large (2,728 cases and 27,280 controls) case-control study in Denmark; the OR was 1.0 for more than 10 prescriptions. Garcia Rodriguez and Gonzalez-Perez (5) also found a slight non-statistically significant OR elevation (1.2; 95% CI, 0.9-1.6) with >500 days of use among 3,708 cases and 20,000 controls in the General Practice Research Database in the United Kingdom. Kaye and Jick (6) reported another case-control study (1,268 cases and 6,291 controls) from the same database and found the same statistically nonsignificant elevated risk for >500 days of use of all antibiotics (OR, 1.2; 95% CI, 0.6-2.4); however, higher risks were found for penicillins (OR, 2.1; 95% CI, 0.4-10.8, for >500 days of use) and macrolides (OR, 6.3; 95% CI, 2.5-15.9, for 101 to 500 days of use). Although nominally statistically significant, the authors did not believe that the latter single finding, based on only 10 cases and 8 controls, contradicted their overall conclusion that an antibiotic-breast cancer link was not confirmed. Didham et al. (7), in a case-control study (695 female breast cancer cases and 695 controls) in New Zealand, found a slight, statistically significant elevation of the OR for penicillins (1.07; 95% CI, 1.02-1.13) but believed that a causal relationship was unlikely.

Although our study covered a very large number of subjects including 18,521 cases, it had several limitations. We could not control for important breast cancer risk factors other than age and hormone use after start of follow-up. However, Velicer et al. (2) did not find that controlling for them materially affected their findings. We could not account for antibiotic use before start of follow-up. It is likely that some women classified as nonusers had received antibiotics, thus attenuating differences between them and users. In fact, we found that approximately one third of all subscribers received at least one antibiotic each year. This is why, in contrast to our previous studies (9-12), we did not compare cancer incidence among all antibiotic recipients with incidence in the membership cohort studied.

Our duration of follow-up was limited to 9.4 years in the main study. However, the previous smaller study with follow-up of up to 31 years yielded similar findings except for lincosamides. As for all studies in which drug use is ascertained by drug prescription or dispensing, we cannot be certain how much, if any, of a drug was ingested. Our estimate of total days of prescribed use is only an approximation of the total dose to be ingested. A small number of breast cancers would have been missed if diagnosed before subjects joined KPMCP or before coverage by our cancer registry became complete within the program in 1988. Finally, if this were purely an exploratory study, our multiple comparisons might suggest that the nominally statistically significant findings for all antibiotics and for tetracyclines are due to chance. However, this study was designed as a test of previous findings on antibiotics and breast cancer.

Although no formal analysis was carried out, the information from our medical record review, particularly for long-term tetracycline use, suggests that acne or/and rosacea may be markers for increased risk of breast cancer. The only positive association (not statistically significant with full adjustment for available confounders) noted by Garcia Rodriguez and Gonzalez-Perez (5) was for skin infections; it was not stated how much acne was in this disease category. Baron et al. (16) found increased risk of breast cancer with diseases connected with androgen stimulation, including acne. Similarly, Moseson et al. (17) found increased risk among women with persistent adult acne, but only if associated with hirsutism. Breast cancer and benign breast disease have been associated with increased sebum production (18-20). In comparison with treatment for respiratory infections, Garcia Rodriguez and Gonzalez-Perez (5) found treatment for skin disorders, and Velicer et al. (2) did not find treatment for acne, to entail any greater risk.

We conclude that use of most antibiotics is associated with little, if any, increase in risk of breast cancer in up to 9 years of follow-up. Use of tetracyclines and, to a lesser extent, of macrolides, especially long-term use, showed evidence of a weak association, of uncertain causal significance. The underlying explanation may be an association of acne and/or rosacea with both use of these drugs and risk of breast cancer. Longer follow-up in the current data is needed to evaluate the association of lincosamides with breast cancer risk found in an earlier cohort.

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