



Use of Antibiotics and Risk of Breast Cancer

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A recent nested case-control study found that increasing use of antibiotics was associated with a significantly elevated risk of breast cancer. The authors attempted to replicate this finding with a similar study design using the General Practice Research Database in the United Kingdom. Women aged 30–79 years who were registered in the database between January 1995 and December 2001 comprised the study cohort. A total of 3,708 women with incident cases of breast cancer and 20,000 frequency-matched controls were entered into a nested case-control analysis. Use of antibiotics was not associated with an increased risk of breast cancer. For categories of increasing cumulative days of use (1–50, 51–100, 101–500, and ≥ 501 days), the corresponding odds ratios were 1.0 (95% confidence interval (CI): 0.9, 1.1), 1.0 (95% CI: 0.8, 1.1), 0.9 (95% CI: 0.7, 1.0), and 1.2 (95% CI: 0.9, 1.6) ($p = 0.31$ for trend). On the basis of these results, antibiotic use does not appear to be a major determinant of breast cancer risk.

anti-bacterial agents; breast neoplasms

Abbreviation: CI, confidence interval.

Antibiotic medications have effects on immune function and inflammation and reduce the ability of intestinal microflora to metabolize phytochemicals. Some authors have hypothesized that antibiotic use could increase the risk of cancer through these mechanisms (1). In a recent study, Velicer et al. (2), using data from the Group Health Cooperative of Puget Sound (Washington State), found that cumulative exposure to antibiotics of more than 500 days was associated with a relative risk of breast cancer greater than twofold (2). We attempted to replicate their findings using a similar study design (a nested case-control study) with data from the General Practice Research Database in the United Kingdom.

MATERIALS AND METHODS

The General Practice Research Database contains computerized medical information entered by general practitioners in the United Kingdom (3). Data on over 2 million patients are systematically recorded and sent anonymously to the Medicines and Health Products Regulatory Agency, which collects and organizes this information for use in

research projects. The computerized information includes data on demographic factors, details on visits to general practitioners, diagnoses from specialists' referrals and hospital admissions, results of laboratory tests, and a free text section. Prescriptions issued by general practitioners are directly generated from the computer. Several studies using the General Practice Research Database have documented its validity and completeness (4). An additional requirement for participating practices is the recording of indications for new courses of therapy.

We identified all females aged 30–79 years between January 1995 and December 2001. Women became members of the study population on the first day of the study period when they met the criteria of at least 1 year of enrollment with the general practitioner and 1 year since the first computerized prescription. That date was designated their starting date. Study members who had received a code for cancer before the starting date were excluded. We also excluded women aged 70 or more years at the starting date who had a follow-up period of more than 1 year and no data recorded during their total follow-up time, since this probably reflected a subgroup of women with gaps in data

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collection. Our final study cohort comprised 734,899 women.

All study participants were followed from the starting date to the occurrence of one of the following endpoints: a recorded diagnosis of breast cancer, diagnosis of any cancer other than breast cancer, age 80 years, death, or the end of the study period (December 2001).

We identified 4,005 patients with a recorded code for breast cancer and manually reviewed the computerized patient profile for all of them. Information obtained included demographic and clinical data, with information on personal identifiers removed. We did not distinguish between invasive breast cancer and in-situ breast cancer. We considered patients with confirmed cases to be those who, following the first diagnosis, had additional breast cancer diagnoses recorded on subsequent visits, regularly visited an oncology clinic, had a confirmatory biopsy, underwent surgical intervention (mastectomy, wide local excision), or started breast cancer drug therapy. We excluded 297 women, mainly for lacking confirmation of the breast cancer diagnosis (60 percent) or having a prevalent case (31 percent). Finally, we sent questionnaires to the general practitioners for validation of a random sample of 114 cases. A total of 108 questionnaires (95 percent) were received, and all of them confirmed the diagnosis of incident breast cancer. In the end, 3,708 patients were considered to have incident cases of breast cancer.

For cases, the date of initial diagnosis of breast cancer was designated the index date. A date during the study period was generated at random for every member of the study cohort. If the random date of a study member was included in her eligible person-time, we used her random date as the index date and marked that woman as an eligible control. Then we randomly sampled from the pool of eligible controls 20,000 cancer-free women, who were frequency-matched on age and calendar year to the cases. Under this sampling scheme, the probability of being selected as a control is directly proportional to the person-time at risk. The 3,708 cases and the 20,000 controls were used in the nested case-control analysis.

For all study subjects, we calculated the cumulative number of days of antibiotic exposure recorded in the database (including exposure recorded before 1995) and ascertained the indication for treatment. Most prescriptions (>95 percent) included information on duration of use. When this information was missing, a discretionary duration of 15 days was assigned to that particular prescription. We divided exposure into five categories according to increasing days of antibiotic use (never use and 1–50, 51–100, 101–500, and ≥ 501 days).

We collected information on subjects' use of health services (visits to the general practitioner, specialist referrals, and hospital admissions) in the 2 years prior to the index date. We also determined which patients had previously had benign breast disease (a breast lump and/or breast biopsy recorded at least 1 year before the index date). The presence of other risk factors, such as alcohol intake, body mass index, use of nonsteroidal antiinflammatory drugs, and hormone replacement therapy, was also determined. Further information on risk factors can be found in a previous report (5).

We used unconditional logistic regression to compute odds ratios (as estimates of the relative risk) and 95 percent confidence intervals associated with the use of antibiotics as compared with nonuse. We calculated odds ratios adjusted for age and calendar year, as well as fully adjusted estimates (adjusted for age, calendar year, body mass index, alcohol intake, hormone replacement therapy, use of nonsteroidal antiinflammatory drugs, prior benign breast disease, utilization of health-care services, and time under observation).

RESULTS

The incidence rate of breast cancer was 156 per 100,000 person-years, which is well in line with other reports from the United Kingdom (6). The prevalence of ever use of antibiotics among controls in our study was similar to the prevalence observed by Velicer et al. (2) (84 percent in our study vs. 81 percent in their study).

Use of antibiotics was not associated with increased risk of breast cancer. For categories of increasing cumulative days of use (1–50, 51–100, 101–500, and ≥ 501 days), the corresponding odds ratios were 1.0 (95 percent confidence interval (CI): 0.9, 1.1), 1.0 (95 percent CI: 0.8, 1.1), 0.9 (95 percent CI: 0.7, 1.0), and 1.2 (95 percent CI: 0.9, 1.6) ($p = 0.31$ for trend) (see table 1). In an alternative analysis, we used the number of antibiotic prescriptions (1–10, 11–25, and ≥ 26) instead of cumulative days of exposure. The corresponding odds ratios were 1.0 (95 percent CI: 0.9, 1.1), 0.9 (95 percent CI: 0.8, 1.1), and 1.0 (95 percent CI: 0.8, 1.3), respectively. In addition, we were able to examine whether the effect would vary according to the treatment indication, since this information is usually recorded by the general practitioner in the General Practice Research Database. This enabled us to perform an analysis similar to the one performed by Velicer et al. (2) analyzing all women with 100 or more cumulative days of antibiotic use (2,611 antibiotic users). As table 2 shows, no specific antibiotic indication was associated with an elevated risk of breast cancer. However, use of antibiotics to treat skin disorders was associated with increased risk of breast cancer in comparison with use of antibiotics to treat respiratory diseases (odds ratio = 1.5, 95 percent CI: 1.1, 2.1).

The results were similar for younger (<55 years) and older (≥ 55 years) women (data not shown).

DISCUSSION

We could not find a clear association between breast cancer and antibiotic use, either overall or when we performed subanalyses according to treatment duration or prescription indication. There was only a suggestion of a small increased risk among users of antibiotics prescribed to treat skin disorders. The reasons behind this modestly increased risk are unclear and warrant further investigation with data from alternative sources. The results of this study contrast with those of two previous reports. Knekt et al. (7) found that young women exposed to antibiotics for

TABLE 1. Odds ratios for breast cancer according to cumulative duration of use of antibiotics, General Practice Research Database, United Kingdom, 1995–2001

Cumulative duration (days) of antibiotic use	Controls (n = 20,000)		Cases (n = 3,708)		OR*,†	95% CI*	OR‡	95% CI
	No.	%	No.	%				
No use	3,253	16.3	596	16.1	1		1	
1–50	11,663	58.3	2,153	58.1	1.0	0.9, 1.1	1.0	0.9, 1.1
51–100	2,878	14.4	554	14.9	1.1	0.9, 1.2	1.0	0.8, 1.1
101–500	1,946	9.7	345	9.3	1.0	0.8, 1.1	0.9	0.7, 1.0
≥501	260	1.3	60	1.6	1.3	0.9, 1.7	1.2	0.9, 1.6

* OR, odds ratio; CI, confidence interval.

† Adjusted for age and calendar year.

‡ Adjusted for age, calendar year, body mass index, alcohol intake, hormone replacement therapy, use of nonsteroidal antiinflammatory drugs, prior benign breast disease, time under observation, and utilization of health-care services.

treatment of urinary tract infection had an elevated risk of breast cancer (odds ratio = 1.74, 95 percent CI: 1.13, 2.68). Velicer et al. (2) found that cumulative exposure to antibiotics for more than 500 days was associated with an approximately twofold relative risk of breast cancer.

There are some potential confounders for which we were not able to obtain information through our database, including age at menarche, parity, family history, age at first childbirth, and germ-line mutation. However, it seems highly unlikely that this limitation of our study would have changed these results significantly. Indeed, one would expect these potential confounders to be rather evenly distributed between users of antibiotics and nonusers.

Since we based exposure ascertainment on computerized prescription data, we are aware that a few patients will have either not filled their prescription (this was not an issue in the study by Velicer et al. (2), since they used filled prescriptions as the exposure measure) or not taken the

pills once their prescription was filled (less likely with chronic treatment, which is the relevant exposure). Therefore, patients who did not take their medicine would have been incorrectly classified as users, and this would have tended to dilute any effect of antibiotics on breast cancer risk, biasing the results toward the null. This limitation is common to studies performed with most automated databases, like the study by Velicer et al. (2).

Durations of time since first registration in the database were very similar among cases and controls (median, 7 years), even though we did not match participants on this variable. In any case, to remove any possible confounding, we adjusted for length of observation in the final analysis.

In summary, we did not find convincing evidence of an increased risk of breast cancer among women exposed frequently to antibiotics. The finding of a small increased risk among users of antibiotics for skin disorders warrants further investigation.

TABLE 2. Odds ratios for breast cancer according to indication for use of antibiotics, General Practice Research Database, United Kingdom, 1995–2001

Indication for antibiotic use*	Controls (n = 20,000)		Cases (n = 3,708)		OR†,‡	95% CI†	OR§	95% CI
	No.	%	No.	%				
No use	3,253	16.3	596	16.1	1		1	
Respiratory infection	1,252	6.3	204	5.5	0.9	0.8, 1.1	0.8	0.7, 1.0
Urinary tract infection	302	1.5	57	1.5	1.0	0.8, 1.4	0.9	0.6, 1.2
Skin infection	275	1.4	68	1.8	1.4	1.0, 1.8	1.2	0.9, 1.6
Other	377	1.9	76	2.1	1.1	0.9, 1.4	1.0	0.8, 1.3

* Among participants with 100 or more days of cumulative use.

† OR, odds ratio; CI, confidence interval.

‡ Adjusted for age and calendar year.

§ Adjusted for age, calendar year, body mass index, alcohol intake, hormone replacement therapy, use of nonsteroidal antiinflammatory drugs, prior benign breast disease, time under observation, and utilization of health-care services.

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