

Antibiotics and Breast Cancer— What's the Meaning of This?

Roberta B. Ness, MD, MPH

Jane A. Cauley, DrPH

BREAST CANCER IS THE MOST FREQUENT CANCER diagnosed among women in the United States. Established risk factors include age, family history, reduced parity, earlier age at menarche, alcohol use, postmenopausal adiposity, and hormone therapy. In this issue of THE JOURNAL, Velicer and colleagues¹ report another potential risk factor: the use of prescribed antibiotics. Among 2266 women with breast cancer, as compared with 7953 controls, the use of antibiotics was more common; the risk of breast cancer was greater with longer duration of antibiotic use and was consistent across antibiotic classes. This observation is potentially worrisome in that antibiotic exposure is common and sometimes nonessential. Thus, if real, the risk of breast cancer attributable to the use of antibiotics could be large and partially preventable.

A number of strengths lend validity to the study's findings. Cases and controls were numerous and chosen from a single clinical source. Cancer diagnoses were confirmed using data from the Surveillance, Epidemiology, and End Results program. Among patients with the highest use of antibiotics, risk of breast cancer was similarly increased regardless of the indication (acne, rosacea, or respiratory tract infections). Computerized pharmacy records were used to validate antibiotic prescriptions and adjustment was made for a number of potentially confounding factors.

At the same time, the study methods engender certain concerns. A randomized clinical trial would have been the criterion standard design, since randomization generates an equivalent distribution of both known and unknown confounding factors across treatment groups. However, randomizing women to an intervention hypothesized to increase the risk of disease would have been unethical. The authors appropriately chose an observational design, specifically a case-control study. Yet case-control studies have important limitations; a major one is confounding.

Confounding by indication occurs if women using antibiotics differ from nonusers in ways that elevate their breast cancer risk. Women with greater cumulative use of antibiotics were older, had earlier age at menarche, had higher body mass indexes, were more likely to have a family history of breast can-

cer, and were more likely to report postmenopausal use of hormones, all of which could have increased their risk of breast cancer. The authors adjusted for these factors and state that doing so did not materially influence their results. Nevertheless, the frequency of missing data, especially among controls, limited the validity of this adjustment. Residual confounding may have occurred, for instance, because physicians may have prescribed more antibiotics to women of upper socioeconomic status, who may have been more likely to adhere to preventive health recommendations such as routine mammograms. Indeed, women with a greater cumulative exposure to antibiotics tended (albeit nonsignificantly) to report educational attainment beyond high school. Furthermore, restricting the analysis to women who filled at least 1 antibiotic prescription reduced the size of the associations.

Confounding by unknown or unmeasured factors also could have inflated observed associations. However, a confounding factor with a prevalence of 20% would have had to increase the relative odds of both outcome and exposure by factors of 4 to 5 before an observed relative risk of 1.57 would have been reduced to 1.00.² Thus, for residual confounding to explain the findings, the confounding would have to have a large impact on both use of antibiotics and risk of breast cancer.

Detection bias also may have inflated the observed risks. Mammography rates were quite low in the control group: only 42% had received a mammogram within 2 years of their reference date. Failure to detect breast cancer in the control group would lead to an underestimate of their breast cancer risk.

Beyond methodological considerations, the observed association, to be believable, must also be biologically plausible. Velicer et al raise 2 mechanistic possibilities: antibiotics may reduce the capacity of intestinal microflora to metabolize phytochemicals that might protect against carcinogenesis; and tetracyclines stimulate prostaglandin E₂, implicating an overexpression of cyclooxygenase 2, the enzyme that synthesizes prostaglandin E₂ and that has been associated with mammary carcinogenesis.^{1,3,4} Along this same line of reasoning, antibiotics reduce commensural bacteria in the gut, and thus may lower the absorption of cholesterol. Cholesterol lowering has been associated with a reduced risk of breast cancer in some studies⁵ but with an increased risk in others.

Author Affiliations: Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pa.

Corresponding Author: Roberta B. Ness, MD, MPH, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA 15261 (repro@pitt.edu).

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However, a biological explanation based on mechanisms attributed to a given class of antibiotics is difficult to reconcile with the observation by Velicer et al that the risk of breast cancer was elevated across multiple classes of antibiotics. Different antibiotics have different effects. Whereas tetracyclines stimulate prostaglandin E₂, presumably by mediation of cyclooxygenase 2, macrolides inhibit this pathway.⁶ With regard to microbiological mechanisms, antibiotic classes have various effects on intestinal microflora. For instance, in 1 study, phenoxymethylpenicillin had about half the effect on serum levels of the phytoestrogen enterolactone as did the macrolide class of antibiotics.⁷ Furthermore, sulfatrimethoprim and nalidixic acid have only a minor impact on intestinal microflora.⁸

Another possible explanation for the association between use of antibiotics and risk of breast cancer is that antibiotics are an epiphenomenon marking chronic infection and chronic inflammation. Inflammation, induced by infections or irritants, has been linked to a substantial proportion (one sixth to one third) of incident cancers worldwide.⁹ Compelling evidence for a link between inflammation and breast cancer comes from preclinical and epidemiologic observations suggesting that nonsteroidal anti-inflammatory drugs (NSAIDs) protect against the development of breast cancer. In both animal and in vitro models NSAIDs inhibit mammary carcinogenesis, and in case-control and cohort studies use of NSAIDs reduces the risk of breast cancer by 22% overall and by 28% in frequent users with 10 or more years of exposure.^{10,11}

Further support for the idea that inflammation plays a role in breast carcinogenesis comes from an evolving understanding that immune mechanisms may contribute to a variety of tumor-promoting actions when those mechanisms are not in balance.¹² This is the case in chronic inflammation. Chronic inflammation can produce DNA damage via reactive oxygen species, bypass key regulatory cellular mechanisms such as p53, activate extracellular matrix proteins (eg, matrix metalloproteinase 9) and endothelial growth factors (eg, vascular endothelial growth factor) that promote tumor invasion, and inhibit apoptosis.^{9,13} Cytokines, key regulators of inflammation, also stimulate the enzymes that convert androstenedione to estrogens in breast tissue. In turn, local and systemic elevations in estrogen levels have been consistently linked to risk of breast cancer.^{14,15}

However, there is a complexity to the explanation that chronic inflammation resulting from infection is the mediator of the association between use of antibiotics and risk of breast cancer. The multiple examples wherein chronic inflammation has been convincingly linked to cancer have involved inflammation and tumor development within the same tissue. Some examples include asbestos fibers and mesothelioma,¹⁶ schistosomiasis and bladder cancer,¹⁷ chronic *Helicobacter pylori* infection and stomach cancer,¹⁸ and mastitis and breast cancer.¹⁹ In addition, systemic inflammatory diseases, such as rheumatoid arthritis, have been linked to seemingly unrelated lymphoproliferative malignancies but not to breast cancer.²⁰ Moreover, the indications for chronic

use of antibiotics in the study by Velicer et al, such as rosacea and respiratory tract infections, have known effects on systemic immune activity.²¹

As is often true for reports of new associations, this study provides many (or more) questions than answers. Is the observed link between use of antibiotics and risk of breast cancer confounded by unmeasured factors? Is the effect due to use of antibiotics or to the indications for antibiotics? Does the link suggest caution in the use of antibiotics or suggest that infections at distant sites might promote inflammation localized to the breast? And, whether antibiotics are markers of inflammation or are themselves contributors to carcinogenesis, is use of antibiotics a risk factor for cancers at other sites? Time and further scrutiny will tell. While more research is needed, this study raises the possibility that long-term use of antibiotics may have harmful consequences, especially for patients for whom other therapeutic options are available.

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