

Antibiotic Use in Relation to the Risk of Breast Cancer

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FROM ABSTRACT

Context: Use of antibiotics may be associated with risk of breast cancer through effects on immune function, inflammation, and metabolism of estrogen and phytochemicals; however, clinical data on the association between antibiotic use and risk of breast cancer are sparse.

Objective: To examine the association between use of antibiotics and risk of breast cancer.

Design, Setting, and Participants

Case-control study among 2266 women older than 19 years with primary, invasive breast cancer (cases) enrolled in a large, nonprofit health plan for at least 1 year between January 1, 1993, and June 30, 2001, and 7953 randomly selected female health plan members (controls), frequency-matched to cases on age and length of enrollment. Cases were ascertained from the Surveillance, Epidemiology, and End Results cancer registry. Antibiotic use was ascertained from computerized pharmacy records.

Main Outcome Measure: Association between extent of antibiotic use and risk of breast cancer.

Results: Increasing cumulative days of antibiotic use were associated with increased risk of incident breast cancer, adjusted for age and length of enrollment.

Increased risk was observed in all antibiotic classes studied and in a subanalysis having breast cancer fatality as the outcome.

Among women with the highest levels of tetracycline or macrolide use, risk of breast cancer was not elevated in those using these antibiotics exclusively for acne or rosacea (indications that could be risk factors for breast cancer due to altered hormone levels), compared with those using them exclusively for respiratory tract infections, adjusted for age and length of enrollment.

Conclusions

Use of antibiotics is associated with increased risk of incident and fatal breast cancer.

It cannot be determined from this study whether antibiotic use is causally related to breast cancer, or whether indication for use, overall weakened immune function, or other factors are pertinent underlying exposures.

Although further studies are needed, these findings reinforce the need for prudent long-term use of antibiotics.

THESE AUTHORS ALSO NOTE:

The hypothesis that use of antibiotics may increase risk of cancer was first proposed in 1981.

[Setchell KD, Lawson AM, Borriello SP, et al. Lignan formation in man—microbial involvement and possible roles in relation to cancer. *Lancet*. 1981;2:4-7.]

“Use of antibiotics reduces the capacity of intestinal microflora to metabolize phytochemicals into compounds that may protect against cancer.”

“Use of antibiotics may be associated with cancer risk through effects on immune function and inflammation, although little is known about these mechanisms.”

“Understanding whether an association between antibiotic use and breast cancer exists is particularly important given the high incidence of breast cancer and widespread antibiotic use in many countries.”

Breast cancer is the second leading cause of cancer mortality in US women and the most common cancer in women worldwide, with more than 1 million cases diagnosed each year.

“Antibiotics are used extensively and overused in many countries.”

“In the United States, more than 22.6 million antibiotic prescriptions for nonbacterial acute respiratory infections were filled in 1995 alone.”

[Gonzales R, Malone DC, Maselli JH, Sande MA. Excessive antibiotic use for acute respiratory infections in the United States. *Clin Infect Dis*. 2001;33:757-762]

[This is crazy! And the medical establishment often has the gall to refer to chiropractors as quacks. This 22.6 million inappropriate prescriptions is likely the “tip of the iceberg,” as it does not include antibiotics prescribed for chronic nonbacterial respiratory infections, for other nonbacterial infections in the GI or elsewhere, or antibiotics prescribed for self limiting bacterial infections, etc.]

“Although the biological mechanisms through which antibiotics might alter cancer risk may also be relevant to other cancers, we selected breast cancer for this study because it is the topic of the only other epidemiologic study of antibiotic use and cancer risk, and it is an important cancer in women.” **[WOW! These authors are implying that antibiotic use may be associated with other cancers as well].**

These authors selected 2 measures of antibiotic exposure:

- 1) The cumulative number of days of antibiotic use
- 2) The total number of antibiotic prescriptions per participant

These authors also conducted a substudy of women to verify that it was antibiotic use, not the indication for antibiotic use, that was related to increased cancer rates.

RESULTS

A total of 110,191 antibiotic prescriptions were dispensed to study participants.

"Cumulative duration of antibiotic use ranged from 0 to 7600 days, and cumulative number of antibiotic prescriptions ranged from 0 to 194."

For all antibiotic classes, increasing cumulative days of use was associated with increased risk of incident breast cancer.

"The association between cumulative days of antibiotic use and death due to breast cancer was strong for all antibiotic classes, controlling for age, length of enrollment, and use of postmenopausal hormones."

COMMENT BY AUTHORS

"In this population-based case-control study, we found that increasing cumulative days of antibiotic use and increasing cumulative number of antibiotic prescriptions were associated with increased risk of incident breast cancer, after controlling for age and length of enrollment."

"Increasing cumulative days of antibiotic use was associated with death due to breast cancer, controlling for age, length of enrollment, and use of postmenopausal hormones."

"All classes of antibiotics were associated with increased risk."

"Our findings were robust."

"The hypothesis that some classes of antibiotics may increase risk of breast cancer is plausible; antibiotics have effects on intestinal microflora and on immune and inflammatory responses."

[Velicer CM, Lampe JW, Heckbert SR, Potter JD, Taplin SH. Hypothesis: is antibiotic use associated with breast cancer? *Cancer Causes Control*. 2003;14:739-747.]

"Antibiotic use may increase risk of breast cancer by decreasing phytochemical metabolism by intestinal microflora."

"Phytochemicals are hypothesized to play an inhibitory role at several points in the carcinogenesis pathway by modulating enzymes involved in carcinogen and steroid hormone metabolism."

"Use of tetracycline may be associated with increased production of prostaglandin E2, a hallmark of the inflammatory response, catalyzed by cyclooxygenase 1 and 2."
 [Attur MG, Patel RN, Patel PD, Abramson SB, Amin AR. Tetracycline up-regulates COX-2 expression and prostaglandin E2 production independent of its effect on nitric oxide. *J Immunol.* 1999;162:3160-3167]

[Hwang D, Scollard D, Byrne J, Levine E. Expression of cyclooxygenase-1 and cyclooxygenase-2 in human breast cancer. *J Natl Cancer Inst.* 1998;90:455-460.]
[Recall, prostaglandin E2 is derived from the omega-6 fatty acid arachidonic acid]

"Although this evidence suggests that antibiotics may be associated with breast cancer, it is also possible that a weakened immune system (either alone or in conjunction with use of antibiotics) is the biologically relevant basis of this association."

"The amount of antibiotic use at particularly sensitive times in breast development, such as adolescence, pregnancy, or during menopause, may be pertinent."

"In summary, we found that increased use of antibiotics was associated with increased risk of incident and fatal breast cancer for a variety of antibiotic classes."

KEY POINTS FROM DAN MURPHY

- 1) Antibiotics weaken the immune system, increase inflammation, and destroy microflora that metabolize estrogen and phytochemicals into compounds that may protect against cancer.
- 2) These compromises of physiology increase the risk of cancers. These authors only evaluated the relationship to breast cancer.
- 3) Increasing cumulative days of antibiotic use is associated with increased risk of breast cancer and fatal breast cancer.
- 4) All antibiotic classes studied increased the risk of breast cancer.
- 5) The greatest increased risk of breast cancer was associated with the use of antibiotics for respiratory tract infections. Ironically, most respiratory infections are viral, and antibiotics are contraindicated.
- 6) Antibiotics are extensively overused. In the US, more than 22.6 million antibiotic prescriptions for nonbacterial respiratory infections were filled in 1995.
- 7) Antibiotics, especially tetracycline, increased production of prostaglandin E2. Prostaglandin E2 is the pro-inflammatory derivative of the omega-6 fatty acid arachidonic acid, and it impairs immune system function.

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

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Roberta B. Ness, MD, MPH; Jane A. Cauley, DrPH

THESE AUTHORS NOTE IN THEIR EDITORIAL:

"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 colleagues 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. "

Among patients with the highest use of antibiotics, risk of breast cancer was 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."

Velicer et al raise 2 mechanistic possibilities:

- 1) Antibiotics may reduce the capacity of intestinal microflora to metabolize phytochemicals that might protect against carcinogenesis;
- 2) Tetracyclines stimulate prostaglandin E₂, implicating an overexpression of cyclooxygenase 2, the enzyme that synthesizes prostaglandin E₂ and that has been associated with mammary carcinogenesis.

Compelling evidence links inflammation and breast cancer.

"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."
[O'Byrne KJ, Dalglish AG. Chronic immune activation and inflammation as the cause of malignancy. *Br J Cancer*. 2001;85:473-483].

"Chronic inflammation can produce DNA damage via reactive oxygen species."

"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."

KEY POINTS FROM DAN MURPHY

- 1) Breast cancer is the most frequent diagnosed cancer among US women.
- 2) A potential risk factor for breast cancer is the use of prescribed antibiotics.
- 3) The risk of breast cancer is greater with longer duration of antibiotic use and is seen in all classes of antibiotics.
- 4) The risk of breast cancer attributable to the use of antibiotics could be large.
- 5) Antibiotics reduce the capacity of intestinal microflora to metabolize phytochemicals that protect against cancer.
- 6) Tetracyclines stimulate prostaglandin E2, implicating an over expression of cyclooxygenase 2. Remember that prostaglandin is derived from the omega-6 fatty acid arachidonic acid.
- 7) Compelling evidence links inflammation and breast cancer.
- 8) Chronic inflammation can produce DNA damage from free radicals.