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ORIGINAL ARTICLE

Personalizing Aspirin Use for Targeted Breast Cancer Chemoprevention in Postmenopausal Women

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Abstract

Objective: To evaluate the association of aspirin and other nonsteroidal anti-inflammatory drugs with the incidence of postmenopausal breast cancer for risk subgroups defined by selected nonmodifiable or difficult to modify breast cancer risk factors in order to better understand the potential risk-benefit ratio for targeted chemoprevention.

Patients and Methods: Postmenopausal women with no history of cancer on July 1, 1992 (N=26,580), were prospectively followed up through December 31, 2005, for breast cancer incidence (N=1581). Risk subgroups were defined on the basis of family history of breast cancer, age at menarche, age at menopause, parity/age at first live birth, personal history of benign breast disease, and body mass index. Hazard ratios (HRs) and 95% CIs adjusted for other breast cancer risk factors were estimated using Cox models.

Results: Aspirin use was associated with a lower incidence of breast cancer for women with a family history of breast cancer (HR, 0.62 for 6 or more times per week vs never use; 95% CI, 0.41-0.93) and those with a personal history of benign breast disease (HR, 0.69; 95% CI, 0.50-0.95) but not for women in higher-risk subgroups for age at menarche, age at menopause, parity/age at first live birth, or body mass index. In contrast, inverse associations with aspirin use were observed in all lower-risk subgroups. Nonsteroidal anti-inflammatory drug use had no association with breast cancer incidence.

Conclusion: On the basis of their increased risk of breast cancer, postmenopausal women with a family history of breast cancer or a personal history of benign breast disease could potentially be targeted for aspirin chemoprevention studies. Future studies are needed to confirm these findings.

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Breast cancer is the most common noncutaneous cancer and the second leading cause of cancer-related death among women in the United States.[1] In 2015, an estimated 231,840 new cases of invasive breast cancer will be diagnosed among women and more than 40,000 women will die of breast cancer.[2] Furthermore, 1 in 8 women in the United States will experience invasive breast cancer during their lifetime.[2] Thus, effective breast cancer prevention strategies, particularly among higher-risk women, could have tremendous public health impact.

Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) have been investigated extensively as potential cancer chemopreventive agents.[3-8] Nonsteroidal anti-inflammatory drugs may inhibit tumor growth by modulating cellular proliferation and apoptosis, predominantly via suppression of endogenous production of prostaglandin from inhibition of cyclooxygenase (COX) enzyme activity, particularly COX-2, which is overexpressed in cancer.[9-13] Nonsteroidal anti-inflammatory drugs can also inhibit aromatase, a critical enzyme involved in endogenous production of estrogens in postmenopausal women.[14] Most,[15-26] but not all,[27-30] epidemiological studies have observed an inverse association of either aspirin or other NSAIDs with breast cancer risk, including an earlier report of data from the cohort used in the current study.[31]

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Despite the consistent epidemiological observation, a causal association between aspirin and breast cancer has not been proven in randomized controlled trials, so it is not used in clinical practice as a chemopreventive agent. Furthermore, potential adverse effects, such as gastrointestinal bleeding and cerebral hemorrhage,[6,32] currently outweigh any putative benefits in the setting of breast cancer prevention in the general population. However, the risk-benefit ratio might be different for postmenopausal women at higher risk of breast cancer than those at average or lower risk, particularly based on nonmodifiable factors, such as a family history of breast cancer, a personal history of benign breast disease, reproductive history (age at menarche, age at menopause, parity and age at first live birth), or difficult to modify risk factors such as body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). "Personalizing" aspirin use to target specific higher-risk groups might be more broadly accepted for clinical trials and in clinical practice than universally treating all postmenopausal women with aspirin. Using a population-based cohort, we evaluated the association of aspirin and nonaspirin NSAIDs with breast cancer risk in postmenopausal women within risk subgroups defined by individual and total number of selected nonmodifiable or difficult to modify risk factors.

PATIENTS AND METHODS

Iowa Women's Health Study Cohort

The Iowa Women's Health Study is a prospective cohort study of postmenopausal women aged 55 to 69 years at study baseline in 1986.[31,33] Briefly, in 1986, a 16-page questionnaire was mailed to 98,030 women in Iowa randomly selected by driver's license. The questionnaire was returned by 41,836 women (42.7%), who constituted the original cohort. Compared with nonrespondents, respondents were on average 3 months younger, had a 0.4-kg/m^2 lower BMI, and were more likely to live in rural areas. The nonrespondents have been found to have a slightly higher mortality rate due to smoking-related diseases compared with respondents.[34] Follow-up questionnaires were conducted in 1987, 1989, 1992, 1997, and 2004.

Risk Factors of Interest

On the baseline survey (1986), information was collected on age, marital status, level of education, height, weight, age at menarche, age at menopause, number of live births, age at first live birth, family history of breast cancer, use of oral contraceptives or hormone therapy, physical activity, history of benign breast disease, history of cigarette smoking, alcohol consumption, and history of rheumatoid arthritis or osteoarthritis. The use of aspirin and nonaspirin NSAIDs in the cohort was ascertained on the 1992 follow-up questionnaire. Participants were asked, "How often do you take aspirin? Examples of aspirin include Bufferin, Anacin, enteric-coated aspirin, Ecotrin, and Excedrin (do not include acetaminophen, Tylenol, ibuprofen, Advil): never, less than once per week, once per week, 2 to 5 times per week, or 6 or more times per week." Use of nonaspirin NSAIDs was queried as, "How often do you take other nonsteroidal anti-inflammatory drugs or arthritis medicines? Examples include ibuprofen, Advil, Nuprin, Motrin, Naprosyn, Feldene, and Clinoril (do not include aspirin, acetaminophen, Tylenol, prednisone, cortisone, Deltasone): never, less than once per week, once per week, 2 to 5 times per week, and 6 or more times per week."

On the basis of the current literature, we defined a priori the nonmodifiable or difficult to modify breast cancer risk factors (and respective cut points) for postmenopausal women as age at menarche, less than 11 years; age at menopause, 55 years or older; nulliparous or age at first live birth, older than 30 years; BMI, 30 kg/m^2 or higher; any family history of breast cancer in a first-degree relative; and personal history of benign breast disease. Body mass index of 30 kg/m^2 or higher (the World Health Organization definition of obesity) was included because it is relatively difficult to modify in older women. All of these factors have consistently been reported to be associated with risk of breast cancer, including recent pooled results from 35,568 patients with breast cancer from 34 studies,[35] and many are also included in the Gail model for breast cancer risk,[36] for which we did not have individual elements.

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