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The impact of aspirin use on breast cancer subtype and clinical course

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ABSTRACT

Background: The use of aspirin has been associated with improved survival in patients with breast cancer, but the results have been mixed. We aim to analyze the impact of aspirin use before or after breast cancer diagnosis on breast cancer clinical characteristics and outcomes.
Materials and Methods: We performed a single-institution, retrospective analysis of 1113 women diagnosed with operable breast cancer between 1995 and 2015. Patients were grouped according to their aspirin use: never (944), before diagnosis (79), and after diagnosis (90). Clinical variables, overall survival (OS), and disease-free survival (DFS) were compared between groups.
Results: Women using aspirin before diagnosis were older, more likely to be black, and to have associated medical comorbidities than patients in other groups (all $P < 0.001$). These patients were also more likely to present with hormone receptor–negative cancers, including triple-negative breast cancer ($P = 0.002$). Aspirin use before diagnosis was associated with a worse OS in univariate and multivariate analyses (both $P < 0.001$), but there were no other differences in OS or DFS related to aspirin use.
Conclusions: Despite a potential impact on tumor subtype in patients using aspirin before their breast cancer diagnosis, aspirin use does not appear to alter breast cancer–related survival.

Introduction

Aspirin is a common medication used by millions of patients for its well-known role in primary and secondary preventions of cardiovascular events such as myocardial infarction.[1] This widespread use has allowed investigators to examine the impact of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) on the incidence and effects on other disease states, such as cancer. Epidemiologic studies have demonstrated an association between aspirin use and a decrease in both all-cancer incidence and mortality.[2,3] The most well-established link to emerge from these studies is a decrease in incidence, metastasis, and mortality from colorectal cancer after prolonged aspirin use.[4,5]

For decades, the impact of cyclooxygenase (COX) prostaglandin expression and the effect of NSAIDs on breast cancer have been under consideration in the laboratory.[6-9] Several mechanisms, mostly related to inhibition of COX synthesis of prostaglandins, have been considered for the link between NSAIDs and breast cancer incidence and outcomes. Under normal circumstances, prostaglandins stimulate aromatase activity, thereby promoting production of estrogen (ER)

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precursors, indicating a potential link to hormone receptor (HR) positivity.[10] They also stimulate angiogenesis,[11] inhibit epithelial apoptosis,[12] and inhibit platelet aggregation, known to be important in metastatic tumor cell adhesion,[13] all of which can impact the carcinogenesis and metastatic potential of breast tumors. COX expression in tumors has been associated with a worse prognosis in most immunohistochemical studies;[14-17] however, the survival benefit of aspirin was not different in tumors expressing or not expressing COX indicating that COX inhibition is unlikely the sole mechanism behind the benefit.[18] Despite the lack of definitive mechanism, the impact of aspirin and other NSAIDs on breast cancer incidence and outcome are of interest.

Many prospective and retrospective investigations have been conducted to elucidate the impact of aspirin use on breast cancer, and these epidemiologic studies have yielded mixed results.[19] Observational and randomized studies evaluating whether aspirin affects the incidence of breast cancer have either shown a moderate decrease in incidence or no statistical difference when comparing users to nonusers.[2,20-23] Other authors have stratified patients or focused on populations based on NSAID/aspirin dosing and duration of use, and underlying breast cancer risk factors such as age and family history, and still the results are mixed.[24-26] Most of the recent work has examined the impact of aspirin use on the risk of recurrence, breast cancer death, and death from other causes after a breast cancer diagnosis. These results have also been mixed with some groups reporting a decrease in recurrence and improved survival for aspirin users[21,27-29] and others unable to demonstrate a benefit.[30-32] Definitive results will await completion of the ABC trial (NCT02927249), a randomized phase III double-blinded placebo controlled trial of aspirin as adjuvant therapy for node-positive *HER2/neu* (Her2)-negative breast cancer.

The results from large-scale population analyses studying the impact of aspirin on breast cancer outcome have been inconsistent, possibly due to study heterogeneity, limitations in power and sample size, and challenges in statistical analysis. Moreover, such large data sets are typically not as clearly annotated to address more complex questions such as whether a patient with a specific breast cancer subtype may derive the most benefit from aspirin. A single-institution study may offer more data granularity, homogeneity, and consistency in terms of data collection and treatment patterns including the use of standard diagnostic imaging modalities, pathology results reporting, and oncology care practices.

Overall, we hypothesized that aspirin use is associated with improved breast cancer outcomes. We tested our hypothesis using data derived from a large retrospective breast cancer patient cohort treated at a single institution.

Materials and methods

Study population

After obtaining Institutional Review Board approval, we identified all patients with primary operable breast cancer (stages I-III) in our electronic medical record (EMR) treated between 2005 and 2013 at our institution. Patients with an Internation Classification of Diseases-9 diagnosis code of invasive breast cancer on at least two separate in-person visits and who underwent definitive surgery and were followed up at our institution were included.

To be included for analysis, age at diagnosis, height, and weight from within 3 mo of breast cancer diagnosis and postoperative clinical follow up of greater than 30 d must be available. Clinical covariates collected also included self-reported race, diagnosis of diabetes mellitus, and the presence of cardiovascular comorbidities (diabetes, coronary artery disease, and cerebrovascular disease).

Aspirin use was also abstracted from the EMR, which includes a comprehensive list of prescribed and over-the-counter medications reviewed and updated by clinicians at each outpatient visit. Patients were stratified into three groups according to their use of aspirin: never users designated as "never" subgroup, those who began use at least 30 d before their breast cancer diagnosis designated as "before" subgroup, and those who began use after breast cancer diagnosis designated as "after" subgroup. The "never" and "after" groups were combined and compared to the "before" group to analyze differences in tumor characteristics at the time of breast cancer diagnosis.

Tumor pathology data collected included tumor size, grade (Nottingham histologic score), lymphovascular invasion (LVI), ER, progesterone, and Her2 receptor status as determined by immunohistochemical staining and nodal status. We classified breast cancer into four main molecular subtypes based on HR, which includes ER and/or progesterone status and Her2 expression: (1) HR+ Her2−; (2) HR− Her2+; (3) HR+ Her2+ or triple-positive breast cancer; and (4) HR− Her2−or triple-negative breast cancer (TNBC).[33,34] Outcomes, including overall survival (OS), disease-free survival (DFS), local-regional recurrence, and distant metastasis, were ascertained based on records within the EMR and by use of the Social Security Death Certificate Index. Length of the follow-up was determined by duration from the date of breast cancer diagnosis to the last follow-up date listed in their EMR as of December 31, 2016. Disease status of each patient was classified as no evidence of disease, alive with disease, death of disease, death from other causes, or death from cause unknown.

Statistical analyses

Association between aspirin use, clinical, and pathologic covariates, and disease status was performed using two-tailed Fisher's exact or chi-square test. *P*-values less than or equal to 0.05 were accepted as statistically significant.

Univariate and multivariate survival analyses for OS and DFS were also performed using Kaplan–Meier and Cox proportional hazard models. Forward-backward stepwise regression was used to determine independent covariates contributing to the final survival models on multivariate analysis.

Results

Cohort and aspirin use

A total of 1515 women with diagnoses of stage I-III invasive breast cancer were initially identified from the EMR; 263 patients were excluded due to missing information such as