Aspirin use and risk of breast cancer in African American women

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Abstract

Background: Use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) has been hypothesized to be associated with reduced risk of breast cancer; however, results of epidemiological studies have been mixed. Few studies have investigated these associations among African American women.

Methods: To assess the relation of aspirin use to risk of breast cancer in African American women, we conducted a prospective analysis within the Black Women's Health Study, an ongoing nationwide cohort study of 59,000 African American women. On baseline and follow-up questionnaires, women reported regular use of aspirin (defined as use at least 3 days per week) and years of use. During follow-up from 1995 through 2017, 1919 invasive breast cancers occurred, including 1112 ER+, 569 ER−, and 284 triple-negative (TN) tumors. We used age-stratified Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations of aspirin use with risk of ER+, ER−, and TN breast cancer, adjusted for established breast cancer risk factors.

Results: Overall, the HR for current regular use of aspirin relative to non-use was 0.92 (95% CI 0.81, 1.04). For ER+, ER−, and TN breast cancer, corresponding HRs were 0.98 (0.84, 1.15), 0.81 (0.64, 1.04), and 0.70 (0.49, 0.99), respectively.

Conclusions: Our findings with regard to ER− and TN breast cancer are consistent with hypothesized inflammatory mechanisms of ER− and TN breast cancer, rather than hormone-dependent pathways. Aspirin may represent a potential opportunity for chemoprevention of ER− and TN breast cancer.

Keywords: Aspirin, Non-steroidal anti-inflammatory drugs, Breast cancer, African American, Risk

Introduction

Relative to US white women, African American women have a disproportionately high incidence of aggressive breast cancer subtypes, such as estrogen receptor (ER)-negative tumors [1–3], and higher mortality from breast cancer [4]. Inflammation may play a role in breast cancer development, especially ER− breast cancer. Aspirin is an anti-inflammatory agent and a weak aromatase inhibitor [5, 6]. Experimental studies have demonstrated the chemopreventive properties of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) [7]. In population-based studies, there is consistent and compelling evidence that regular use of aspirin is inversely associated with colorectal cancer incidence [8]. The use of aspirin may also reduce the risk of breast cancer; however, results from epidemiologic studies are inconsistent [9, 10]. Few studies have investigated these associations among African American women. A previous Black Women’s Health Study (BWHS) analysis of aspirin use and 12-year risk of breast cancer showed a statistically significant inverse association [11]; however, that analysis did not consider ER+ and ER− breast cancer separately, nor have any previous studies in African American women evaluated whether associations differ by ER−.
subtype. The present analysis updates our previous report with an additional 10 years of follow-up and consideration of associations by ER status.

**Methods**

**Study population**

The BWHS is an ongoing prospective cohort of 59,000 African American women, who were ages 21 to 69 years (median age, 38 years) at baseline in 1995. Every 2 years, follow-up questionnaires are sent to participants to update information on incident cancer diagnoses and reproductive and behavioral factors, including medication use [12]. Notices of deaths are obtained from next-of-kin, the US Postal Service, and yearly searches of the National Death Index.

For this analysis, women were excluded if they had been diagnosed with breast cancer (n = 743) or any other type of cancer (except non-melanoma skin cancer) (n = 696) before baseline in 1995, or if they did not answer the question about aspirin use on the baseline questionnaire (n = 4399); the final analytic cohort included 53,126 women in the BWHS who were free from cancer and had available information on aspirin use at baseline, there were 1919 invasive breast cancers diagnosed through 2017. Information on ER status was available for 88% of these cases (569 ER− and 1112 ER+ tumors). Of the 569 ER− breast cancers, HER2 status was known for 368 (65%); 284 (77%) of these were classified as triple-negative (TN) cases.

**Case ascertainment**

Incident cases of breast cancer in the BWHS were ascertained through self-report on biennial follow-up questionnaires (95% of cases) or identified through death records or linkage to 24 cancer registries in states covering 95% of participants (5% of cases). Breast cancer diagnoses were confirmed by review of medical records, pathology reports, and cancer registry records. Data on tumor characteristics were also abstracted from these records.

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**Exposure and covariate assessment**

Regular medication use, defined as use at least 3 days per week, was queried on baseline and biennial follow-up questionnaires. On the baseline questionnaire, women reported current use of aspirin or acetaminophen, separately, at least 3 days per week. Current users were also asked to report the duration of use (<1, 1, 2, 3–4, ≥5 years). Popular brand names (e.g., Bayer, Anaclin, Tylenol) were given as a prompt. Regular use of other NSAIDs (e.g., ibuprofen) at least 3 days per week was queried beginning in 2009. Prior to 2009, non-aspirin NSAID use was reported via open-text response and coded using the Slone Drug Dictionary [13]; however, the duration of use was not recorded for open-text responses. Identical questions on medication use were included on follow-up questionnaires. Information on dose was not obtained.

The baseline questionnaire collected information on established and putative risk factors for breast cancer including adult height, weight, age at menarche, oral contraceptive use, parity, age at first birth, lactation, menopausal status, postmenopausal hormone use, alcohol consumption, physical activity, and breast cancer in first-degree relatives. Except for age at menarche, all data were updated on subsequent questionnaires.

**Statistical analyses**

Women contributed person-years from the beginning of follow-up in March 1995 until diagnosis of breast or other cancer, death, or end of follow-up in March 2017, whichever occurred first (970,189 total person-years). We used Cox proportional hazards regression models, stratified by age in 1-year intervals and questionnaire cycle such that age was the underlying time scale, to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for use of aspirin in relation to risk of overall, ER+, ER−, and TN breast cancer, separately. Aspirin use was treated as time-varying and modeled as a categorical exposure variable (non-use, past use, current use); over follow-up, current users were re-classified as past users if they no longer reported current regular use on subsequent questionnaires. In secondary analyses, we applied a 2-year lag to exposure classification, starting follow-up in 1997 and assigning aspirin use for each cycle according to that reported on the previous questionnaire. We also considered the duration of use among current users (<5 years, 5–10 years, or ≥10 years). Finally, we also evaluated possible associations with the use of acetaminophen, which is an analgesic but does not have anti-inflammatory properties.

Multivariable models included adjustment for established breast cancer risk factors and potential confounders: recent body mass index (BMI < 25, 25–29.9, 30–34.9, or ≥35 kg/m²), age at menarche (<11 years, 11 years, 12–13 years, or ≥14 years), recency of oral contraceptive use (never, <5 years ago, 5 to <10 years ago, or ≥10 years ago), parity (nulliparous, 1 birth, 2 births, or ≥3 births), age at first birth (<20 years, 20 to <25 years, or ≥25 years), lactation (never or ever), menopausal status (premenopausal or postmenopausal), duration of estrogen plus progestin use (never, <5 years, or ≥5 years), alcohol consumption (not current; current, 1–6 drinks/week; or current, ≥7 drinks/week), physical activity...
yses were performed using SAS 9.4 (Cary, NC).

At baseline, current regular users of aspirin were older (mean age, 44 years) and heavier (mean BMI, 29.1 kg/m²) than non-users (mean age, 38 years; mean BMI, 27.7 kg/m²). Compared to non-users, current users were also more likely to consume alcohol (39% vs. 28%) and less likely to have attained more than a high school education (72% vs. 83%). Current aspirin users and non-users generally had similar distributions of reproductive factors (Table 1).

Age- and multivariable-adjusted models produced similar results (Table 2). The multivariable-adjusted HR for overall breast cancer risk associated with current regular use of aspirin compared to non-use was 0.92 (95% CI 0.81, 1.04). Corresponding HRs for ER− and ER+ breast cancer were 0.81 (95% CI 0.64, 1.04) and 0.97 (95% CI 0.83, 1.13), respectively; however, there was no statistically significant heterogeneity by ER status (p = 0.20). Reductions in risk of ER+ breast cancer were noted for current users who had used aspirin regularly for at least 10 years (HR 0.81; 95% CI 0.60, 1.09). For ER−, there were no apparent trends in association with longer duration. Current regular use of aspirin was inversely associated with TN breast cancer (HR 0.70; 95% CI 0.49, 0.99), while there was no apparent trend in the duration of use (Table 3). Past use of aspirin was not associated with breast cancer risk overall, or by subtype (Tables 2 and 3). Further adjustment for the use of other NSAIDs did not change results (data not shown). Results were similar when exposure was lagged by 2 years (Additional Table 1) and when comparing current regular aspirin users to non-users of any NSAIDs (Additional Table 2).

Results

At baseline, current regular users of aspirin were older (mean age, 44 years) and heavier (mean BMI, 29.1 kg/m²) than non-users (mean age, 38 years; mean BMI, 27.7 kg/m²). Compared to non-users, current users were also more likely to consume alcohol (39% vs. 28%) and less likely to have attained more than a high school education (72% vs. 83%). Current aspirin users and non-users generally had similar distributions of reproductive factors (Table 1).

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Discussion

Previously, we reported a significant inverse association of current regular aspirin use with breast cancer in the BWHS (HR 0.79; 95% CI 0.66, 0.95) [11]. Results of the present analysis, updated with 10 additional years of follow-up and > 1900 incident invasive breast cancer cases in total, are in the same direction but weaker when considering breast cancer risk overall; however, they suggest that current regular aspirin use may be associated with a nearly 20% reduction in risk of ER− breast cancer and a 30% reduction in risk of TN breast cancer among African American women. These findings warrant confirmation in other studies that include large numbers of African American women.

A recent meta-analysis reported a small decreased risk of breast cancer associated with current regular aspirin use [relative risk (RR) 0.90; 95% CI 0.85, 0.95]; however, the association was primarily apparent among population-based case-control studies (RR 0.80; 95% CI 0.73, 0.88) and hospital-based case-control studies (RR 0.82; 95% CI 0.75, 0.91) with no association among cohort studies (RR 0.97; 95% CI 0.90, 1.04) or nested case-control studies (RR 0.91; 95% CI 0.82, 1.01) [15]. Epidemiologic studies that evaluated associations of aspirin use with ER+ and ER− breast cancer risk separately have had inconsistent findings. In the California Teachers Study (CTS), taking 3 or more tablets per week of low-dose aspirin (but not regular
strength aspirin) was associated with a reduced risk of breast cancer overall, and especially for the ER+/HER2− subtype (HR 0.80; 95% CI 0.66, 0.96) with no association for ER− breast cancer [16]; however, a prior analysis within the CTS showed a statistically significant increased risk of ER− breast cancer associated with daily, long-term use of aspirin (unspecified dose) [17]. A 20% reduction in risk of breast cancer associated with regular aspirin use was reported among postmenopausal women in the Iowa Women’s Health Study; similar decreased risks were noted for both ER+ and ER− breast cancer [18]. Among postmenopausal women enrolled in the VITamins And Lifestyle Study, a reduced risk of breast cancer was only apparent for women who used low-dose aspirin at least 4 times a week over 10 years (HR 0.65; 95% CI 0.43, 0.97); however, the corresponding HR for regular or extra-strength aspirin was 1.43 (95% CI 1.02, 2.00) [19]. No differences were seen by ER status [19]. Duration of aspirin use was inversely associated with breast cancer risk among postmenopausal women in the Women’s Health Initiative Observational Study (RR for ≥10 years of use vs. none 0.79; 95% CI 0.60, 1.03) [20]. These results are similar to our findings of an approximately 20% reduction in overall breast cancer risk with ≥10 years of aspirin use. In the NIH-AARP Study (primarily postmenopausal women), daily use of aspirin was associated with lower risk of ER+ breast cancer (RR 0.84; 95% CI 0.71, 0.98) whereas no association was noted for ER− disease [21]. In the Sister Study, a prospective cohort of women who had a sister with breast cancer, greater lifetime use of aspirin based on frequency and duration was associated with a significantly reduced risk of breast cancer among premenopausal women (but not among postmenopausal women); subtype-specific analyses were not carried out within strata defined by menopausal status [22].

There have also been large prospective studies that reported no association or a positive association between aspirin use and breast cancer risk. Among postmenopausal women in the Nurses’ Health Study (NHS) and among premenopausal women in the NHSII, there was no association between current regular aspirin use (at least 2 tablets per week) and breast cancer risk overall or by ER status [23–25]. Results were similarly null in the Multiethnic Cohort (MEC) [26], the Cancer Prevention Study II Nutrition Cohort [27], and the European Prospective Investigation into Cancer and Nutrition Cohort, which included 7379 breast cancer cases over a median of 13.1 years of follow-up [28]. Aspirin users in the Danish Diet, Cancer, and Health cohort, however, experienced a statistically significantly increased risk of breast cancer compared to non-users (RR 1.38; 95% CI 1.12, 1.69) [29]. Only a single randomized controlled trial has been published: the Women’s Health Study showed no association of low-dose aspirin every other day with risk of invasive breast cancer, overall or by subtype, over an average of 10 years of follow-up [30, 31]. Inconsistencies in results from prior epidemiologic studies may partly

| Table 1 Age-standardized baseline characteristics according to current aspirin use |
| Current aspirin use |
| No (n = 47,591) | Yes (n = 5535) |
| Age, years* | 37.8 (10.2) | 43.9 (11.7) |
| Current BMI, kg/m² | 27.7 (6.6) | 29.1 (7.2) |
| First-degree family history of breast cancer | 9 | 9 |
| Postmenopausal, % | 16 | 18 |
| Age at menarche | | |
| <13 years, % | 11 | 13 |
| 13–14 years, % | 17 | 16 |
| ≥14 years, % | 52 | 50 |
| Recency of oral contraceptive use | | |
| Never, % | 23 | 26 |
| <5 years ago, % | 28 | 24 |
| ≥5 years ago, % | 38 | 39 |
| Postmenopausal hormone use | | |
| Never used estrogen plus progestin (E+P), % | 96 | 96 |
| Used E+P, <5 years duration, % | 3 | 3 |
| Used E+P, ≥5 years duration, % | 1 | 1 |
| Parity | | |
| Nulliparous, % | 36 | 33 |
| Parous, 1 birth, % | 21 | 20 |
| Parous, 2 births, % | 23 | 22 |
| Parous, ≥3 births, % | 19 | 23 |
| Age at first birth (among parous) | | |
| <20 years, % | 33 | 41 |
| 20–25 years, % | 35 | 35 |
| ≥25 years, % | 30 | 21 |
| Ever lactation (among parous), % | 52 | 48 |
| Alcohol consumption | | |
| Not current drinker, % | 71 | 60 |
| Current, 1–6 drinks/week, % | 22 | 29 |
| Current, ≥7 drinks/week, % | 6 | 10 |
| Educational attainment | | |
| ≤12 years, % | 17 | 27 |
| 13–15 years, % | 36 | 39 |
| ≥16 years, % | 47 | 33 |

Values are means (SD) or percentages and are standardized to the age distribution of the study population
*Value is not age adjusted
reflect differences in exposure assessment and/or classification by frequency, duration, dose, or timing.

Besides the BWHS, the MEC is the only other prospective cohort study to report on the relation of aspirin use to breast cancer risk among African American women (HR for ≥ 6 years of use vs. non-use 0.98; 95% CI 0.64, 1.52); stratification by ER status was not reported [26]. In the Carolina Breast Cancer Study, a population-based case-control study, inverse associations of NSAID use and breast cancer risk were apparent among both white and African American women, but somewhat stronger among African American women [odds ratio (OR) for any use vs. no use of NSAIDs was 0.3 (95% CI 0.2, 0.6) for African American women compared to 0.5 (95% CI 0.3, 0.8) for whites]; that study did not consider subtypes of breast cancer [32]. No other studies have reported on these associations among African American women specifically, nor have any evaluated possible effect measure modification by race.

Aspirin and other NSAIDs could modulate breast cancer risk via their anti-proliferative, anti-angiogenic, and pro-apoptotic properties. Aspirin inhibits cyclooxygenase (COX), which is necessary for prostaglandin synthesis. Low-dose aspirin is specific for platelet COX-1, while the proposed anti-cancer effects are hypothesized to operate primarily through the COX-2 pathway [33]. Prostaglandins produced by COX-2 activity mediate inflammation and also increase aromatase expression, which leads to increased estrogen levels [5–7]. COX-2 inhibitors, including regular strength aspirin, may therefore reduce breast cancer risk by decreasing local

### Table 2

Multivariable-adjusted hazard ratios (95% CI) for associations of aspirin and acetaminophen use and risk of breast cancer in the BWHS, overall and by ER status, 1995–2017

|                        | All invasive (n = 1919) | ER-positive (n = 1112) | ER-negative (n = 566) |
|------------------------|-------------------------|------------------------|-----------------------|
|                        | Person-years            | Cases                  | HR^a 95% CI           | HR^a 95% CI           | Cases                  | HR^a 95% CI           | HR^a 95% CI           |
| **Aspirin use**        |                         |                        |                       |                       |                        |                       |                       |
| Non-use                | 676,158                 | 1226                   | 1.00 Reference        | 1.00 Reference        | 662                    | 1.00 Reference        | 1.00 Reference        |
| Past use               | 143,880                 | 325                    | 0.95 0.83, 1.08       | 0.97 0.85, 1.10       | 207                    | 0.97 0.83, 1.14       | 0.98 0.83, 1.16       |
| Current use            | 150,151                 | 368                    | 0.89 0.79, 1.01       | 0.92 0.81, 1.04       | 243                    | 0.97 0.83, 1.13       | 0.98 0.84, 1.15       |
| Duration of current use|                         |                        |                       |                       |                        |                       |                       |
| Current, < 5 years     | 73,790                  | 173                    | 0.91 0.77, 1.07       | 0.93 0.79, 1.09       | 108                    | 0.98 0.80, 1.21       | 1.00 0.81, 1.23       |
| Current, 5–10 years    | 41,940                  | 117                    | 0.96 0.79, 1.17       | 0.98 0.80, 1.19       | 82                     | 1.09 0.86, 1.38       | 1.09 0.86, 1.39       |
| Current, ≥ 10 years    | 34,422                  | 78                     | 0.77 0.61, 0.91       | 0.81 0.63, 1.03       | 53                     | 0.78 0.58, 1.05       | 0.81 0.60, 1.09       |
| **Acetaminophen use**  |                         |                        |                       |                       |                        |                       |                       |
| Non-use                | 681,495                 | 1340                   | 1.00 Reference        | 1.00 Reference        | 755                    | 1.00 Reference        | 1.00 Reference        |
| Past use               | 208,818                 | 439                    | 0.94 0.84, 1.05       | 0.96 0.86, 1.08       | 283                    | 0.98 0.85, 1.12       | 0.99 0.86, 1.15       |
| Current use            | 79,876                  | 140                    | 0.85 0.71, 1.02       | 0.88 0.74, 1.05       | 74                     | 0.86 0.67, 1.09       | 0.88 0.68, 1.12       |

*^aAdjusted for age
*bAdjusted for age, first-degree family history of breast cancer, menopausal status, recent BMI, duration of E+P use, parity, age at first birth, age at menarche, recency of OC use, alcohol consumption, physical activity, and lactation

### Table 3

Multivariable-adjusted hazard ratios (95% CI) for associations of aspirin use and risk of triple-negative breast cancer in the BWHS, 1995–2017

|                        | Triple negative (n = 284) |
|------------------------|---------------------------|
|                        | Person-years                  | Cases | HR^a 95% CI | HR^a 95% CI |
| **Aspirin use**        |                           |       |             |             |
| Non-use                | 674,961                    | 178   | 1.00 Reference | 1.00 Reference |
| Past use               | 143,603                    | 61    | 0.98 | 0.72, 1.32 | 0.99 | 0.72, 1.35 |
| Current use            | 149,804                    | 45    | 0.66 | 0.47, 0.94 | 0.70 | 0.49, 0.99 |
| Duration of current use|                           |       |             |             |
| Current, < 5 years     | 36,817                     | 14    | 0.48 | 0.28, 0.84 | 0.50 | 0.29, 0.87 |
| Current, 5–10 years    | 20,923                     | 18    | 0.92 | 0.56, 1.51 | 0.98 | 0.59, 1.61 |
| Current, ≥ 10 years    | 17,183                     | 13    | 0.70 | 0.39, 1.27 | 0.75 | 0.41, 1.37 |

*^aAdjusted for age
*bAdjusted for age, first-degree family history of breast cancer, menopausal status, recent BMI, duration of E+P use, parity, age at first birth, age at menarche, recency of OC use, alcohol consumption, physical activity, and lactation
| Table 4 | Multivariable-adjusted hazard ratios (95% CI) for associations of aspirin use and risk of breast cancer in the BWHS, overall and by ER status, stratified by selected risk factors, 1995–2017 |
|---------|-----------------------------------------------------------------------------------------------------|
|         | Person-years | Cases | HR | 95% CI | Cases | HR | 95% CI | Cases | HR | 95% CI |
| All invasive (n = 1127) | ER-positive (n = 626) | ER-negative (n = 353) |
| BMI < 30 kg/m² | | | | | | | | | | |
| Non-use | 435,269 | 768 | 1.00 | Reference | 397 | 1.00 | Reference | 250 | 1.00 | Reference |
| Past use | 76,978 | 176 | 1.01 | 0.85, 1.21 | 113 | 1.10 | 0.87, 1.37 | 51 | 0.89 | 0.64, 1.23 |
| Current use | 77,740 | 183 | 0.92 | 0.77, 1.09 | 116 | 1.00 | 0.80, 1.25 | 52 | 0.84 | 0.61, 1.16 |
| BMI ≥ 30 kg/m² | | | | | | | | | | |
| Non-use | 240,890 | 458 | 1.00 | Reference | 265 | 1.00 | Reference | 135 | 1.00 | Reference |
| Past use | 66,902 | 149 | 0.93 | 0.77, 1.13 | 94 | 0.89 | 0.70, 1.14 | 41 | 0.97 | 0.67, 1.38 |
| Current use | 72,411 | 185 | 0.91 | 0.76, 1.09 | 127 | 0.96 | 0.76, 1.20 | 40 | 0.77 | 0.53, 1.12 |
| WHR < 0.85 | | | | | | | | | | |
| Non-use | 358,866 | 635 | 1.00 | Reference | 336 | 1.00 | Reference | 201 | 1.00 | Reference |
| Past use | 60,791 | 136 | 0.98 | 0.80, 1.19 | 82 | 0.97 | 0.75, 1.25 | 41 | 0.91 | 0.64, 1.30 |
| Current use | 69,650 | 176 | 0.98 | 0.82, 1.17 | 114 | 1.07 | 0.85, 1.34 | 46 | 0.84 | 0.60, 1.19 |
| WHR ≥ 0.85 | | | | | | | | | | |
| Non-use | 137,202 | 273 | 1.00 | Reference | 145 | 1.00 | Reference | 87 | 1.00 | Reference |
| Past use | 36,330 | 96 | 1.04 | 0.81, 1.33 | 60 | 1.00 | 0.73, 1.38 | 31 | 1.15 | 0.74, 1.77 |
| Current use | 40,529 | 90 | 0.71 | 0.55, 0.92 | 54 | 0.67 | 0.48, 0.93 | 28 | 0.81 | 0.51, 1.28 |
| Premenopausal | | | | | | | | | | |
| Non-use | 436,127 | 577 | 1.00 | Reference | 290 | 1.00 | Reference | 185 | 1.00 | Reference |
| Past use | 52,186 | 76 | 1.01 | 0.79, 1.29 | 46 | 1.05 | 0.76, 1.46 | 26 | 1.02 | 0.67, 1.56 |
| Current use | 42,230 | 57 | 0.84 | 0.64, 1.11 | 34 | 0.95 | 0.66, 1.36 | 15 | 0.67 | 0.39, 1.15 |
| Postmenopausal | | | | | | | | | | |
| Non-use | 164,576 | 481 | 1.00 | Reference | 285 | 1.00 | Reference | 139 | 1.00 | Reference |
| Past use | 71,966 | 212 | 0.97 | 0.82, 1.16 | 139 | 0.96 | 0.77, 1.19 | 55 | 0.95 | 0.68, 1.32 |
| Current use | 93,480 | 273 | 0.91 | 0.78, 1.06 | 186 | 0.95 | 0.78, 1.15 | 67 | 0.87 | 0.64, 1.18 |
| Age < 50 | | | | | | | | | | |
| Non-use | 476,929 | 620 | 1.00 | Reference | 305 | 1.00 | Reference | 200 | 1.00 | Reference |
| Past use | 59,268 | 79 | 0.97 | 0.76, 1.24 | 44 | 0.96 | 0.69, 1.33 | 28 | 1.03 | 0.63, 1.55 |
| Current use | 45,174 | 67 | 0.98 | 0.76, 1.27 | 36 | 1.06 | 0.75, 1.51 | 21 | 0.95 | 0.60, 1.49 |
| Age ≥ 50 | | | | | | | | | | |
| Non-use | 199,229 | 606 | 1.00 | Reference | 357 | 1.00 | Reference | 185 | 1.00 | Reference |
| Past use | 84,612 | 246 | 0.96 | 0.82, 1.12 | 163 | 0.98 | 0.81, 1.20 | 64 | 0.85 | 0.63, 1.15 |
| Current use | 104,977 | 301 | 0.89 | 0.77, 1.03 | 207 | 0.96 | 0.80, 1.15 | 71 | 0.76 | 0.57, 1.01 |
Aspirin may also weakly inhibit aromatase through COX-2-independent pathways [34]. These mechanisms of action may be most relevant to hormone-dependent breast cancers. Compelling evidence suggests that inflammation may be a critical driver of ER$^-$ breast cancer [35–37] while higher levels of inflammatory cytokines [38] and genetic variants in cytokine-related genes [39] have been observed in African American women compared to white women. Inverse associations of aspirin with ER$^-$ and TN disease may therefore be driven by its anti-inflammatory effects rather than hormone-dependent mechanisms [40, 41]. Indeed, our observation of stronger associations among women 50 years and older, those with higher central adiposity, and parous women, groups with higher levels of systemic inflammation [42–46], is supportive of this theory; however, we were not able to evaluate potential mechanisms directly in this study.

An important limitation of this analysis is the lack of information on aspirin dose and possible misclassification of exposure based on self-report. Because we asked about regular use of aspirin defined as use at least 3 days per week, we were unable to distinguish whether more frequent use (e.g., daily use) shows stronger associations with breast cancer. Also, we did not evaluate non-aspirin NSAIDs separately because we did not consistently query the use of non-aspirin NSAIDs in the BWHS until 2009; however, adjustment for the use of non-aspirin NSAIDs reported on all questionnaires via open-text responses did not change effect estimates. Aspirin is a commonly used NSAID and may be expected to have a stronger protective effect on breast cancer because of its irreversible binding to COX-2 compared to non-aspirin NSAIDs [47]. We lacked information on reasons for use of aspirin; however, the lack of association for acetaminophen, which has a different mechanism of action than that of NSAIDs but is often used interchangeably with NSAIDs, suggests that the association of ER$^-$ or TN breast cancer with aspirin use is not likely explained by reasons for use. Temporal trends in aspirin use would not be expected to influence results since statistical models were adjusted for calendar time.

Strengths of this study include its prospective design and more than 20 years of follow-up, including repeated assessment of aspirin use over time which allowed us to update exposure information at each questionnaire cycle. Detailed characterization of breast cancer risk factors within the BWHS enabled careful control for potential confounding factors in our analyses. Finally, this is the largest study of aspirin use and breast cancer risk among African American women to date and we had a sufficient sample size to evaluate associations for subtypes of breast cancer defined by ER and HER2 status.

### Conclusions

The results of this study support the hypothesis that regular aspirin use is associated with reduced breast cancer risk, particularly for ER$^-$ and TN breast cancer, in African American women. If findings from this study are
confirmed, aspirin may represent a potential opportunity for chemoprevention of ER- and TN breast cancer.

Supplementary information
Supplementary information accompanies this paper at https://doi.org/10.1186/s13058-020-01335-1.

Additional file 1: Table S1. Multivariable-adjusted hazard ratios (95% CI) for associations of lagged aspirin use in the BWHS, overall and by ER status, 1997-2017. Table S2. Multivariable-adjusted hazard ratios (95% CI) for associations of current regular aspirin use relative to non-use of any NSAIDs in the BWHS, overall and by ER status, 1995-2017.

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Authors’ contributions
JRP and LR acquired the data; KAB, PFC, LR, and JRP conceived and designed the study; KAB and HG analyzed the data; KAB, TNB, HG, PFC, LB, LR, and JRP interpreted the results; KAB and JRP drafted the manuscript; all authors critically reviewed and revised the manuscript and approved the submitted version.

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Availability of data and materials
The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study protocol was approved by the Boston University Institutional Review Board. Consent to participate was implied by return of the baseline questionnaire.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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