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Regular Aspirin Use and Breast Cancer Risk in U.S. Black Women

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Abstract

Background—Epidemiologic studies have yet to provide consistent evidence to support a protective effect of aspirin and other non-steroidal anti-inflammatory drugs (NSAID) on the incidence of breast cancer.

Objective—We evaluated the relations of current use of aspirin, non-aspirin NSAIDs, and acetaminophen with breast cancer incidence in the Black Women's Health Study.

Methods—Biennial follow-up of 59,000 study participants began in 1995. During 558,600 person years of follow-up through 2007, 1,275 breast cancer cases were identified. Using Cox proportional hazards regression, we estimated incidence rate ratios (IRR) and 95% confidence intervals (CI) for associations of current and former use of aspirin, other NSAIDs, and acetaminophen with incident breast cancer.

Results—After adjustment for age, education, body mass index at age 18, physical activity, female hormone use, current smoking, and other NSAID use, the IRRs were 0.79 (95%CI=0.66, 0.95) for current aspirin use and 0.68 (95%CI=0.50, 0.92) for ≥ 5 years of aspirin use. Similar associations were observed for acetaminophen use.

Conclusions—Both aspirin and acetaminophen use were inversely associated with breast cancer incidence in the present study. Reasons for the association with acetaminophen use are unclear, given that acetaminophen has very weak anti-inflammatory effects.

Keywords

Aspirin; NSAIDs; breast cancer; incidence; epidemiology

INTRODUCTION

Aspirin, a non-steroidal anti-inflammatory drug (NSAID), has been consistently associated with a reduced risk of colon cancer (1-5), and it has been hypothesized that aspirin and non-aspirin NSAIDs might inhibit the development and progression of breast cancer tumors (3).

NSAIDs may act on cancer development through the cyclooxygenase (COX) enzyme system. While COX-1 is normally expressed in most human tissues, COX-2 is expressed in

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response to the inflammatory process (growth factors, oncogenes, and cytokines) (6). COX-2 concentrations are undetectable in normal breast tissue, but are over-expressed (7, 8) in breast tumors by approximately 40%, and in ductal carcinoma in-situ by as much as 80% (9). COX-2 promotes the production of prostaglandins and leads to an increase in the production of cyclic adenosine monophosphate (cAMP) in breast adipose stromal cells to induce aromatase activity (10). Aromatase activity enhances the synthesis of estrogen by converting androgen to estrogen in breast tissue (3), which increases cell proliferation in tumor cells (11). NSAIDs may block the COX-2 enzyme to decrease aromatase activity, which reduces levels of prostaglandin, estrogen, and prolactin (10), and could decrease carcinogenesis by increasing apoptosis and decreasing cell proliferation, angiogenesis, and metastasis (6).

Perhaps because of differences in the assessment of dose, duration, and induction period, epidemiologic studies have not provided consistent evidence to support or refute a protective effect of aspirin and other NSAIDs on the incidence of breast cancer. Several large prospective studies observed an inverse association of aspirin or NSAID use with breast cancer risk (12-15), while findings were null in several other large prospective studies (16-22), including a randomized controlled trial of low-dose aspirin and breast cancer (21, 22). Only two studies have specifically reported results among African American women (19, 23). In the Carolina Breast Cancer Study, a case-control study, there was a stronger inverse association between NSAID use and breast cancer among African American women than White women (23), whereas there was no association between aspirin and breast cancer among African American women in the Multiethnic Cohort study (19). Neither of these two studies evaluated aspirin or NSAID use that was updated over time nor did these studies evaluate the use of acetaminophen in African American women.

Given the inconsistent findings for the association between NSAID use and breast cancer, and the limited number of studies conducted in African American women, we evaluated the association of regular aspirin use with the incidence of breast cancer in prospective data from the Black Women's Health Study (BWHS). We also assessed non-aspirin NSAIDs and acetaminophen use.

MATERIALS AND METHODS

Study population

The BWHS is a prospective cohort study of 59,000 African American women aged 21 through 69 years at entry in 1995 (24). Women were recruited from 17 states across the mainland United States. Information on demographic and lifestyle factors, reproductive history, medical conditions, and medications was collected in the baseline questionnaire. Mortality information was obtained through the National Death Index, postal service, and friends and relatives. The cohort is followed biennially by mailed questionnaire and 80% of the original cohort had been followed through 2007.

Women who did not complete at least one follow-up questionnaire (n=53), had prevalent cancer at baseline (n=1,414), or did not complete the baseline question on aspirin use (n=4,409) were excluded from this study.

The Boston University Institutional Review Board approved this study.

Analgesic medication use

Self-reported regular aspirin use was collected in the baseline and in each follow-up questionnaire. On the baseline questionnaire women reported whether or not they were currently using aspirin ≥3 days per week (regular use) and for how many years they had

been taking it on a regular basis (<1, 1, 2, 3-4, ≥5 years). In a similar question, women were asked to report acetaminophen use. Other NSAIDs were identified through an open-text question that asked women to list any other medications they were taking ≥3 days per week; the question did not ask about the duration of such use. Each follow-up questionnaire specifically asked women to report aspirin and acetaminophen use ≥3 days per week and also included the open-text medication question. The 2005 follow-up questionnaire also specifically asked participants to report use of "baby aspirin" separate from other aspirin. Medications reported via the open-text question were coded with the Slone Drug Dictionary to identify NSAIDs other than aspirin (25). Information on dose was not obtained.

Potential confounding variables

Candidate confounding variables were identified *a priori* from the existing literature (26-32). At baseline and in follow-up questionnaires, participants were asked to report if a physician had told them that they had any of a list of medical conditions that included heart attack, angina, stroke, and deep vein thrombosis. In the follow-up questionnaires, they were also asked to report diagnoses of rheumatoid arthritis and osteoarthritis. Educational attainment at baseline was used as a surrogate for socioeconomic status. We used women's self-reported height and weight to calculate body mass index (BMI, weight in kilograms divided by height squared in meters). A woman was considered postmenopausal if she reported having natural menopause or bilateral oophorectomy or if she reported hysterectomy with retention of one or both ovaries and her current age was at least age 57 (90^{th} percentile of age at natural menopause in BWHS). She was considered premenopausal if she reported being premenopausal or if she reported a hysterectomy with retention of one or both ovaries and her current age was less than 43 (10^{th} percentile of age at natural menopause in BWHS). A woman who reported a hysterectomy with retention of one or both ovaries and was 43-56 years of age was classified as having uncertain menopausal status. Family history of breast cancer in a first degree relative (mother, sister) and age at menarche was reported at baseline. Information on parity, age at first birth, oral contraceptive use, female hormone use (*i.e.* postmenopausal hormone therapy), alcohol consumption, physical activity, smoking, and mammography receipt were collected at baseline and in each follow-up questionnaire.

Breast cancer ascertainment

Among the 59,000 women included in the BWHS cohort, a total of 1,429 breast cancer cases were reported on follow-up questionnaires from 1997 through 2007. To date, medical records or cancer registry data have been obtained to date for 1,151 of reported cases, of which 99.4% cases were confirmed. Because the confirmation rate was very high, we have included cases identified by self-report only.

Statistical Analysis

Women were followed from baseline in 1995 until breast cancer diagnosis, death from any cause, loss to follow-up, or the end of follow-up in 2007, whichever came first. Incidence rate ratios (IRR) and 95% confidence intervals (CI) for the associations of use of aspirin, other NSAIDs, and acetaminophen with breast cancer risk were estimated using Cox proportional hazards regression models (33). We examined current use at baseline (versus non-use) and time-varying use during follow-up (current, former, non-use). Time-varying, current aspirin use was compared with non-use of aspirin over the course of follow-up. For example, if a woman reported aspirin use in a particular questionnaire she was classified as a current user for that cycle. Women who reported aspirin use in the subsequent questionnaire remained current users, whereas women who did not report current use in the subsequent questionnaire were classified as former users. Former users could become current users in later questionnaire cycles. Women who did not report aspirin use on any questionnaire were

considered non-users. If a woman failed to complete a questionnaire cycle, medication use was coded as missing for that cycle.

Acetaminophen is not an NSAID and has only weak COX inhibiting properties (4), but our purpose in assessing acetaminophen use in relation to breast cancer risk was to determine whether any observed associations of NSAIDs with breast cancer were specific to NSAIDs or could be due to other factors associated with taking pain medication.

The proportional hazard models were jointly stratified by age (one-year intervals) and questionnaire cycle and included indicator variables to control for education (≤12, 13-15, and ≥16 years) BMI at age 18 (<20, 20-24, 25-29, and ≥ 30 kg/m^2), vigorous physical activity (none, <5 hours per week, ≥ 5 hours per week), current smoking status (yes, no), and female hormone use (ever, never). All of the variables except BMI at age 18 and years of education were updated in each questionnaire cycle and were treated as time-dependent variables in the analysis. Aspirin models were further adjusted for other NSAID use, other NSAID models were adjusted for aspirin use, and acetaminophen models were adjusted for both aspirin and other NSAID use. Adjustment for reproductive history, oral contraceptive use, cardiovascular events (myocardial infarction, angina, stroke, and deep vein thrombosis), and rheumatoid arthritis or osteoarthritis, did not appreciably change the results and these variables were not included in the final multivariable models. The Andersen-Gill data structure was used to account for the time-dependent nature of pain medication use and covariates in the time-varying analyses (34).

We stratified by menopausal status and obesity to evaluate whether the associations between aspirin use and breast cancer were modified by these variables.

We conducted several subanalyses. First, we assessed whether the results differed when comparing each of the specific pain medications to non-use of all pain medications (i.e. current aspirin use compared with non-use of aspirin, other NSAIDs, and acetaminophen). Second, we determined whether including low dose aspirin (i.e. “baby aspirin”) reported in the 2005 follow-up questionnaire altered the findings. Last, we accounted for failure to complete one or more questionnaires over follow-up by restricting the analysis to women who completed all of the follow-up questionnaires through 2005.

All statistical tests were two-sided and analyses were conducted using SAS, version 9.1 (Cary, North Carolina).

RESULTS

After exclusions, the final analytic sample consisted of 53,151 BWHS participants, among whom 1,275 incident breast cancer cases were reported over 558,600 person-years of follow-up through 2007. At baseline, there were 5,427 (10.2%) women who currently used aspirin, 2,257 (4.2%) who were users of other NSAIDs, 7,988 (15.0%) who were acetaminophen users, and 45,887 (86.3%) who did not use any NSAIDs (Table 1). Among aspirin users, 7.1 % also reported use of other NSAIDs and 52.3% reported acetaminophen use. Compared with non-users of aspirin or other NSAIDs, regular users of aspirin, other NSAIDs, and acetaminophen were older, less educated, heavier, less physically active, more likely to use female hormones, more likely to smoke, and had experienced more cardiovascular disease. Aspirin and acetaminophen users had similar distributions of baseline characteristics (Table 1). The point prevalence of aspirin use at two-year intervals from baseline through the 2003 follow-up questionnaire ranged from 9.8% to 13%; in 2005 the prevalence was 10% for baby aspirin and 5.9% for other aspirin. Spearman correlation coefficients for report of regular aspirin use in a particular questionnaire with the subsequent

questionnaire (i.e. 1995 with 1997, 1997 with 1999 etc.) between 1995 and 2005 were 0.44, 0.44, 0.45, 0.50, and 0.33, respectively.

Table 2 shows the associations of current use of aspirin, other NSAID, and acetaminophen at baseline with breast cancer risk, relative to non-use of each specific medication. The multivariable IRR (mIRR) for the association between current aspirin use at baseline and incident breast cancer was 0.90 (95%CI=0.75, 1.07); the mIRR for ≥5 years of use was 0.78 (95%CI=0.58, 1.05; p for trend=0.15). We observed similar associations for current use of other NSAIDs (mIRR=0.87; 95% CI 0.67, 1.13) and acetaminophen (mIRR=0.90; 95% CI 0.76, 1.07). The mIRR for ≥5 years of use of acetaminophen was 0.87 (95%CI=0.67, 1.12; p for trend=0.17). The results did not materially change for current aspirin use (mIRR=0.88; 95%CI=0.73, 1.06) or acetaminophen use (mIRR=0.90; 95%CI=0.74, 1.10) when the reference category was no aspirin, other NSAIDs, or acetaminophen use.

Table 3 shows the associations for time-varying use of aspirin, other NSAIDs, and acetaminophen with breast cancer risk during follow-up. The mIRRs were 0.79 (95%CI=0.66, 0.95) for current use of aspirin compared with non-use of aspirin and 0.80 (95% CI 0.65, 0.98) for current acetaminophen use, compared with non-use. The mIRRs for former use of aspirin and acetaminophen were compatible with 1.0. Longer duration (≥5 years) of aspirin (mIRR=0.68; 95%CI=0.50, 0.92; p for trend=0.03) and acetaminophen (mIRR=0.70; 95%CI=0.51, 0.97; p for trend=0.03) use were both associated with greater reductions in breast cancer risk. The mIRR for current other NSAID use was 0.75 (95%CI=0.55, 1.02).

Associations were little changed when we included baby aspirin use from the 2005 follow-up questionnaire in the time-varying analyses (data not shown). Results were similar among pre and postmenopausal women and among obese and non-obese women (data not shown).

The distribution of baseline characteristics by pain medication use among the subset of women who completed all questionnaire cycles was similar to that of the overall population. Among women who completed all questionnaire cycles, the associations for baseline current aspirin, other NSAIDs, and acetaminophen use were also similar to those in the overall population. For example, the mIRRs for ≥5 years use of aspirin and acetaminophen at baseline were 0.69 (95%CI=0.49, 1.03) and 0.73 (95%CI=0.53, 1.03), respectively, and the corresponding mIRRs for time-varying current aspirin and acetaminophen use were 0.76 (95%CI=0.61, 0.94) and 0.81 (95%CI=0.64, 1.02), respectively.

DISCUSSION

In the present study, we observed a reduced risk of breast cancer among current aspirin users and a stronger association when aspirin use was updated over follow-up. The lowest risks were observed for women who used aspirin regularly for at least five years. Use of other NSAIDs and use of acetaminophen were also associated with a decreased breast cancer risk.

Findings from our study for use of aspirin and other NSAIDs are consistent with several previous prospective studies (12-15), but not others (16, 18-21). The Women's Health Initiative Observational Study observed a similar decreased risk of breast cancer for regular-strength aspirin or any NSAID use for ≥5 years of duration (12). The Iowa Women's Health Study also observed a decreased risk of breast cancer for any aspirin use, particularly for frequent use (≥ 6 times per week) (13). The Vitamins and Lifestyle Cohort Study observed that regular strength aspirin used for 1-3 years was inversely associated with breast cancer (14). In addition, the large multicenter Case-Control Surveillance Study (35) and a case-control study of western New York (36) observed that NSAID use was associated with a reduced breast cancer risk. On the other hand, several large prospective studies have

observed no association between aspirin or NSAID use and breast cancer risk (16, 18-21). The Women's Health Study randomized controlled trial reported no association between low-dose aspirin (100 mg) taken every other day for 10 years and breast cancer (21). Compliance for taking low-dose aspirin or placebo was 67% over 10 years of follow-up (37). The Nurses' Health Study and the NIH-AARP cohort study did not observe an association of aspirin with breast cancer risk (16, 20). Two large nested case-control studies of the General Practices Research Database (38) and of Northern Denmark (39), did not observe an association between aspirin and breast cancer. Among premenopausal women in the Nurses' Health Study II, current use of aspirin and other NSAIDs was not associated with breast cancer (17).

As in the present study, the Nurses' Health Study updated aspirin use over the course of follow-up (16). The Nurses' Health Study assessed regular aspirin use as two or more aspirin pills taken per week, whereas our study assessed aspirin use at least three days per week. However, the Nurses' Health Study did not collect information on non-aspirin NSAIDs. While the inclusion of women with lower frequency of use per week and women who used other NSAIDs in the reference group could have biased their results towards the null, in our study the results did not materially change when we compared aspirin, other NSAID, and acetaminophen use to the absence of use of all three pain medications.

Mixed findings have also observed specifically among African American women. The Carolina Breast Cancer Study reported an inverse association between all NSAIDs combined with breast cancer among African American women (379 cases), which was a stronger association than in White women (23). An analysis of the Multiethnic Cohort Study data (289 cases), observed a null association for current and former aspirin use, and a non-significant inverse association between non-aspirin NSAIDs use and breast cancer (19).

In follow-up studies with repeated data collection, there is a question as to how to treat missing data from cycles in which data were not provided. The relatively low correlation between aspirin use from one questionnaire cycle to the subsequent cycle in our study suggested that pain medication use varies considerably over time. Therefore, we assigned missing indicators for medication use for person-time in which a questionnaire was not completed. We also carried out an analysis confined to women who had completed all the questionnaires. The two methods gave similar results.

A limitation of our analysis was the absence of information on dose. Among the few existing studies that evaluated aspirin dose (3, 22, 40), doses of >100 mg (12) and ≥325 mg (22) were associated with lower rates of incident breast cancer, whereas low-dose aspirin was not (21, 38, 39). We asked about use of low dose ("baby") aspirin in 2005 only. Analyses that incorporated data on baby aspirin use gave similar results to analyses that did not include baby aspirin use in the exposure definition. We also lacked information on duration of analgesic medication use before 1995. Women who did not report current use in 1995, but had long-term use prior to 1995 would have been misclassified as non-aspirin, non-NSAID, or non-acetaminophen users, attenuating our results towards the null. Another limitation is that we defined "regular" use as use for three or more days per week, but this definition does not encompass the patterns of use that may be common among young to middle-aged women. For example, women may use analgesic medications for menstrual symptoms or intermittently for headaches or muscle aches. If these lower levels of use are also associated with a reduced risk of breast cancer, then inclusion of such women in the "unexposed" group would attenuate associations of analgesic use with breast cancer risk.

BWHS questionnaires did not include a specific question on non-aspirin NSAID medications; therefore, non-aspirin NSAIDs may have been underreported in our study.

Ibuprofen (12) and prescription NSAIDs (39, 41) have COX 2 inhibiting actions and have been associated with reduced breast cancer risk in some studies (12, 39, 41). Inclusion of non-aspirin NSAID users in the reference group would have attenuated associations.

Our study found an inverse association between acetaminophen use and breast cancer, similar in magnitude to that for aspirin. While acetaminophen is not an NSAID, use was associated with reduced estradiol levels in a cross-sectional analysis of the Nurses' Health Study (45). In addition, acetaminophen has been shown to have anti-inflammatory properties in laboratory studies (46-48). Although most previous studies have not observed an association between acetaminophen use and breast cancer (12, 18, 19, 43, 49), two studies reported that acetaminophen was associated with a decreased breast cancer risk (4, 50). In our study, the baseline descriptive characteristics for aspirin and acetaminophen use were similar and half of aspirin users at baseline also reported use of acetaminophen. This suggests that there may be other explanations for our inverse findings. The inverse associations observed in our study might reflect certain behaviors or characteristics associated with taking analgesic medications that are also associated with reduced breast cancer risk. Control for common conditions associated with pain medication use, such as rheumatoid arthritis, osteoarthritis, and cardiovascular disease, did not appreciably alter our results. However, unknown confounding may have distorted the results.

Our study is the largest to have assessed the associations of aspirin, other NSAIDs, and acetaminophen with incident breast cancer in African American women. Strengths include high participation rates over 12 years of follow-up, prospective data collection, detailed information on potential confounding variables, accurate breast cancer reporting, and a large number of breast cancer cases. Unlike the majority of studies examining the association between aspirin or NSAIDs and breast cancer (12-14, 18-20, 23, 44, 51), we incorporated multiple observations per subject to allow for changes in medication use over follow-up. Our results were consistent, regardless of the method used to account for missing questionnaires over follow-up. Because of the potential for non-differential misclassification of medication use, our results may have underestimated the effect of these pain medications on breast cancer risk.

In conclusion, we observed that longer duration (≥ 5 years) of current aspirin use is associated with a decreased risk of breast cancer in African American women. A similar inverse association with breast cancer incidence was observed for acetaminophen use. The reasons for the association with acetaminophen use are unclear. Further research may elucidate whether those results indicate that other factors such as indication for use of pain medications are responsible for the associations with both NSAIDs and acetaminophen or whether there is a beneficial biological effect of acetaminophen.

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REFERENCES

1. Rosenberg L, Louik C, Shapiro S. Nonsteroidal antiinflammatory drug use and reduced risk of large bowel carcinoma. Cancer. 1998; 82:2326–33. [PubMed: 9635524]

2. Rosenberg L, Palmer JR, Zauber AG, Warshauer ME, Stolley PD, Shapiro S. A Hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large-bowel cancer. Journal of the National Cancer Institute. 1991; 83:355–8. [PubMed: 1759994]
3. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. Journal of the National Cancer Institute. 2002; 94:252–66. [PubMed: 11854387]
4. Meier CR, Schmitz S, Jick H. Association between acetaminophen or nonsteroidal antiinflammatory drugs and risk of developing ovarian, breast, or colon cancer. Pharmacotherapy. 2002; 22:303–9. [PubMed: 11898889]
5. Bosetti C, Gallus S, La Vecchia C. Aspirin and cancer risk: an updated quantitative review to 2005. Cancer Causes and Control. 2006; 17:871–88. [PubMed: 16841255]
6. DuBois RN. Aspirin and Breast Cancer Prevention. JAMA: The Journal of the American Medical Association. 2004; 291:2488–9. [PubMed: 15161901]
7. The Endogenous Hormones Breast Cancer Collaborative Group. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. Journal of the National Cancer Institute. 2002; 94:606–16. [PubMed: 11959894]
8. Hwang D, Scollard D, Byrne J, Levine E. Expression of cyclooxygenase-1 and cyclooxygenase-2 in human breast cancer. Journal of the National Cancer Institute. 1998; 90:455–60. [PubMed: 9521170]
9. Diaz-Cruz ES, Shapiro CL, Brueggemeier RW. Cyclooxygenase inhibitors suppress aromatase expression and activity in breast cancer cells. Journal of Clinical Endocrinology & Metabolism. 2005; 90:2563–70. [PubMed: 15687328]
10. Howe LR, Lippman SM. Modulation of breast cancer risk by nonsteroidal anti-inflammatory drugs. Journal of the National Cancer Institute. 2008; 100:1420–3. [PubMed: 18840814]
11. Harris RE, Namboodiri KK, Stellman SD, Wynder EL. Breast cancer and NSAID use: heterogeneity of effect in a case-control study. Preventive Medicine. 1995; 24:119–20. [PubMed: 7597011]
12. Harris RE, Chlebowski RT, Jackson RD, et al. Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative. Cancer Research. 2003; 63:6096–101. [PubMed: 14522941]
13. Johnson TW, Anderson KE, Lazovich D, Folsom AR. Association of aspirin and nonsteroidal anti-inflammatory drug Use with breast cancer. Cancer Epidemiology Biomarkers & Prevention. 2002; 11:1586–91.
14. Ready A, Velicer C, McTiernan A, White E. NSAID use and breast cancer risk in the VITAL cohort. Breast Cancer Research and Treatment. 2008; 109:533–43. [PubMed: 17674199]
15. Jacobs EJ, Thun MJ, Connell CJ, et al. Aspirin and other nonsteroidal anti-inflammatory drugs and breast cancer incidence in a large U.S. cohort. Cancer Epidemiology Biomarkers & Prevention. 2005; 14:261–4.
16. Egan KM, Stampfer MJ, Giovannucci E, Rosner BA, Colditz GA. Prospective study of regular aspirin use and the risk of breast cancer. Journal of the National Cancer Institute. 1996; 88:988–93. [PubMed: 8667430]
17. Eliassen AH, Chen WY, Spiegelman D, Willett WC, Hunter DJ, Hankinson SE. Use of aspirin, other nonsteroidal anti-inflammatory drugs, and acetaminophen and risk of breast cancer among premenopausal women in the Nurses' Health Study II. Archives of Internal Medicine. 2009; 169:115–21. [PubMed: 19171806]
18. Marshall SF, Bernstein L, Anton-Culver H, et al. Nonsteroidal anti-inflammatory drug use and breast cancer risk by stage and hormone receptor status. Journal of the National Cancer Institute. 2005; 97:805–12. [PubMed: 15928301]
19. Gill JK, Maskarinec G, Wilkens LR, Pike MC, Henderson BE, Kolonel LN. Nonsteroidal antiinflammatory drugs and breast cancer risk: The Multiethnic Cohort. American Journal of Epidemiology. 2007; 166:1150–8. [PubMed: 17698973]
20. Gierach G, Lacey J, Schatzkin A, et al. Nonsteroidal anti-inflammatory drugs and breast cancer risk in the National Institutes of Health-AARP Diet and Health Study. Breast Cancer Research. 2008; 10:R38. [PubMed: 18447943]

21. Cook NR, Lee IM, Gaziano JM, et al. Low-dose aspirin in the primary prevention of cancer: The Women's Health Study: a Randomized Controlled Trial. Journal of the American Medical Association. 2005; 294:47–55. [PubMed: 15998890]
22. Zhang SM, Cook NR, Manson JE, Lee I-M, Buring JE. Low-dose aspirin and breast cancer risk: results by tumour characteristics from a randomised trial. British Journal of Cancer. 2008; 98:989–91. [PubMed: 18268496]
23. Moorman P, Grubber J, Millikan R, Newman B. Association between non-steroidal anti-inflammatory drugs (NSAIDs) and invasive breast cancer and carcinoma in situ of the breast. Cancer Causes and Control. 2003; 14:915–22. [PubMed: 14750530]
24. Palmer JR, Rao SR, Adams-Campbell LL, Rosenberg L. Height and breast cancer risk: results from the Black Women's Health Study (United States). Cancer Causes and Control. 2001; 12:343–8. [PubMed: 11456230]
25. Kelley KE, Kelley TP, Kaufman DW, Mitchell AA. The Slone Drug Dictionary: A research driven pharmacoepidemiology tool. Pharmacoepidemiology and Drug Safety. 2003; 12(S1):S168–S98.
26. Stephenson GD, Rose DP. Breast cancer and obesity: an update. Nutrition and Cancer. 2003; 45:1–16. [PubMed: 12791499]
27. Monninkhof EM, Elias SG, Vlems FA, et al. Physical activity and breast cancer: a systematic review. Epidemiology. 2007; 18:137–57. [PubMed: 17130685]
28. Band PR, Le ND, Fang R, Deschamps M. Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer. The Lancet. 2002; 360:1044–9.
29. Boffetta P, Hashibe M. Alcohol and cancer. The Lancet Oncology. 2006; 7:149–56. [PubMed: 16455479]
30. Kelsey JL. Breast cancer epidemiology: summary and future directions. Epidemiologic Reviews. 1993; 15:256–63. [PubMed: 8405209]
31. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiologic Reviews. 1993; 15:36–47. [PubMed: 8405211]
32. Kelsey JL, Horn-Ross PL. Breast cancer: magnitude of the problem and descriptive epidemiology. Epidemiologic Reviews. 1993; 15:7–16. [PubMed: 8405214]
33. Cox DR. Regression models and life-tables. Journal of the Royal Statistical Society: Series B (Methodological). 1972; 34:187–220.
34. Therneau, TM.; Grambsch, PM. Modeling survival data: extending the Cox model. Springer-Verlag New York, Inc.; 2000.
35. Coogan PF, Rao SR, Rosenberg L, et al. The Relationship of Nonsteroidal Anti-inflammatory Drug Use to the Risk of Breast Cancer. Preventive Medicine. 1999; 29:72–6. [PubMed: 10446030]
36. Brasky TM, Bonner MR, Moysich KB, et al. Non-steroidal anti-inflammatory drug (NSAID) use and breast cancer risk in the Western New York Exposures and Breast Cancer (WEB) Study. Cancer Causes and Control. 2010; 21:1503–12. [PubMed: 20499154]
37. Pedersen, ATn; Ottesen, B. Issues to debate on the Women's Health Initiative (WHI) study. Epidemiology or randomized clinical trial - time out for hormone replacement therapy studies? Human Reproduction. 2003; 18:2241–4. [PubMed: 14585866]
38. Garcia Rodriguez LA, Gonzalez-Perez A. Risk of breast cancer among users of aspirin and other anti-inflammatory drugs. British Journal of Cancer. 2004; 91:525–9. [PubMed: 15226764]
39. Cronin-Fenton D, Pedersen L, Lash T, Friis S, Baron J, Sørensen HT. Prescriptions for selective cyclooxygenase-2 inhibitors, non-selective non-steroidal anti-inflammatory drugs, and risk of breast cancer in a population-based case-control study. Breast Cancer Research. 2010; 12:R15. [PubMed: 20193065]
40. Harris R, Beebe-Donk J, Alshafie G. Reduction in the risk of human breast cancer by selective cyclooxygenase-2 (COX-2) inhibitors. BMC Cancer. 2006; 6:27. [PubMed: 16445867]
41. Rahme E, Ghosn J, Dasgupta K, Rajan R, Hudson M. Association between frequent use of nonsteroidal anti-inflammatory drugs and breast cancer. BMC Cancer. 2005; 5:159. [PubMed: 16343343]
42. Terry MB, Gammon MD, Zhang FF, et al. Association of frequency and duration of aspirin use and hormone receptor status with breast cancer risk. Journal of the American Medical Association. 2004; 291:2433–40. [PubMed: 15161893]

43. Gallicchio L, Visvanathan K, Burke A, Hoffman SC, Helzlsouer KJ. Nonsteroidal anti-inflammatory drugs and the risk of developing breast cancer in a population-based prospective cohort study in Washington County, MD. International Journal of Cancer. 2007; 121:211–5.
44. Friis S, Thomassen L, Sørensen HT, et al. Nonsteroidal anti-inflammatory drug use and breast cancer risk: a Danish cohort study. European Journal of Cancer Prevention. 2008; 17:88–96. [PubMed: 18287865]
45. Gates MA, Tworoger SS, Eliassen AH, Missmer SA, Hankinson SE. Analgesic use and sex steroid hormone concentrations in postmenopausal women. Cancer Epidemiology Biomarkers & Prevention. 2010; 19:1033–41.
46. Graham GG, Scott KF. Mechanism of action of paracetamol. American Journal of Therapeutics. 2005; 12:46–55. [PubMed: 15662292]
47. Anderson BJ. Paracetamol (Acetaminophen): mechanisms of action. Pediatric Anesthesia. 2008; 18:915–21. [PubMed: 18811827]
48. Aronoff DM, Oates JA, Boutaud O. New insights into the mechanism of action of acetaminophen: Its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. Clinical Pharmacology & Therapeutics. 2006; 79:9–19. [PubMed: 16413237]
49. Thun MJ, Namboodiri MM, Calle EE, Flanders WD, Heath CW Jr. Aspirin use and risk of fatal cancer. Cancer Research. 1993; 53:1322–7. [PubMed: 8443812]
50. Garcia Rodriguez LA, Gonzalez-Perez A. Risk of breast cancer among users of aspirin and other anti-inflammatory drugs (NSAIDs) and invasive breast cancer and carcinoma in situ of the breast. Cancer Causes and Control. 2004; 91:525–9.
51. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology. 1994; 5:135–46. [PubMed: 8172987]

Table 1

Frequencies and age-standardized percentages[a] of descriptive demographic, reproductive, and behavioral characteristics for baseline use of aspirin, non-aspirin NSAID, acetaminophen, and no NSAIDs in the Black Women's Health Study (N=53,151)

Baseline Characteristics	No NSAIDs[b] N=45,887		Aspirin[c] N=5,427		Other NSAID[d] N=2,257		Acetaminophen[e] N=7,988	
	N	%	N	%	N	%	N	%
Age (years)								
< 30	11,321	24.7	687	12.7	290	12.9	1,452	18.2
30-39	16,382	35.7	1,314	24.2	617	27.3	2,764	34.6
40-49	12,241	26.7	1,695	31.2	691	30.6	2,314	29.0
≥50	5,943	13.0	1,731	31.9	659	29.2	1,458	18.3
Education (years)								
<12	7,792	17.4	1,562	27.5	517	20.4	6,901	27.1
13-15	16,513	35.7	1,973	39.3	840	38.5	15,312	41.0
≥16	21,505	46.8	1,874	32.9	895	40.9	20,905	31.7
Age at menarche (years)								
≤11	12,905	28.0	1,549	29.3	698	31.9	2,293	28.9
12-13	24,135	52.6	2,682	49.6	1,101	48.9	3,994	50.1
≥14	8,644	19.0	1,168	20.6	439	18.5	1,659	20.5
Age at first birth (years)								
Nulliparous	17,411	36.7	1,404	33.8	652	37.9	2,260	30.5
<20	9,317	20.8	1,654	27.7	659	25.5	2,357	28.6
20-29	16,007	35.6	2,061	33.5	819	31.8	2,948	35.9
≥30	2,799	6.2	239	3.9	110	4.2	328	3.9
BMI in 1995 (kg/m^2)								
<24	18,666	40.1	1,474	30.9	587	30.2	539	30.6
25-29	14,137	31.2	1,757	31.0	650	27.8	2,462	30.6
≥30	12,572	27.6	2,075	36.0	985	40.8	3,045	37.4
BMI at age 18 (kg/m^2)								
<20	18,481	40.7	2,146	37.5	875	37.2	3,116	38.3
20-24	20,406	44.4	2,327	43.2	943	41.4	3,413	42.9

Baseline Characteristics	No NSAIDs[b] N=45,887		Aspirin[c] N=5,427		Other NSAID[d] N=2,257		Acetaminophen[e] N=7,988	
	N	%	N	%	N	%	N	%
≥25	6,302	13.9	796	16.6	400	19.8	1,297	16.8
≥1 alcoholic drink/week	10,870	23.8	1,731	33.1	612	27.9	2,429	30.6
Vigorous activity (hours/week)								
None	13,770	30.8	2,208	35.6	913	35.9	3,021	36.5
<5	24,213	52.2	2,314	46.6	1,011	48.9	3,688	47.2
≥5	6,340	13.6	594	12.8	249	12.4	920	12.1
Female hormone use	6,059	14.4	1,343	16.9	602	18.6	1,536	17.6
Oral contraceptive use (years)								
Nonuse to <1	18,687	41.6	2,841	46.9	1,087	44.0	3,696	45.1
1-4	12,364	26.5	1,235	25.8	555	26.9	2,097	27.1
≥5	14,836	31.9	1,351	27.3	615	29.2	2,197	27.8
Positive family history of breast cancer	2,895	6.5	387	6.3	158	6.1	516	6.2
Current smoking	6,802	15.0	1,231	22.9	471	20.2	1,858	22.8
Mammogram recency								
None	20,935	43.5	1,561	41.9	667	42.1	3,148	43.1
< 1 year ago	11,945	27.6	2,096	29.0	858	28.7	2,386	27.6
≥ 1 years ago	12,474	27.8	1,680	27.6	702	28.1	2,335	2.4
Myocardial infarction	212	0.5	201	2.5	58	1.6	142	1.6
Angina	1,560	3.6	615	9.0	239	8.6	702	8.3
Stroke	213	0.5	168	2.2	49	1.7	116	1.3
Deep vein thrombosis	973	2.2	271	4.0	111	4.0	351	4.1
Rheumatoid arthritis	1,125	2.6	425	5.9	407	15.1	613	7.1
Osteoarthritis	1,724	4.0	560	7.6	503	17.9	787	9.1
Aspirin	-	-	-	-	420	7.1	2,536	52.3
Other NSAID	-	-	420	16.7	-	-	731	33.3
Acetaminophen	4,937	10.9	2536	31.4	731	8.9	-	-

[a] Percentages are standardized to the age distribution of the overall analytic population at baseline

[b] No reported aspirin or other NSAID use at baseline

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[c] Any aspirin use at baseline is defined as women who reported aspirin use at baseline regardless of use of other NSAIDs or acetaminophen

[d] Any other NSAID use at baseline reported in the open-text question at baseline regardless of report of aspirin or acetaminophen

[e] Any acetaminophen use at baseline is defined as women who reported acetaminophen use in the baseline questionnaires regardless of use of aspirin or other NSAIDs

Table 2

Incidence rate ratios (IRR) and 95% confidence intervals (CI) of incident breast cancer according to baseline medication use in the Black Women's Health Study, 1995-2007

Regular Medication use	Total # of Cases 1,275	Total # of Person Years 558,600	Age Adjusted		Multivariable Adjusted[a]	
			IRR	95%CI	IRR	95%CI
Aspirin						
Nonuse in 1995	1,124	503,142	1.00	-	1.00	-
Current use in 1995	151	55,458	0.87	(0.73, 1.04)	0.90	(0.75, 1.07)
Duration[b]						
< 1 year	43	16,430	0.93	(0.69, 1.27)	0.95	(0.70, 1.30)
1 to < 2 years	12	4,910	0.81	(0.46, 1.43)	0.83	(0.47, 1.47)
2 to < 3 years	15	5,331	0.90	(0.54, 1.50)	0.93	(0.55, 1.54)
3 to < 5 years	30	8,339	1.09	(0.76, 1.57)	1.12	(0.78, 1.61)
≥ 5 years	46	18,328	0.76	(0.57, 1.03)	0.78	(0.58, 1.05)
Other NSAIDs						
Nonuse in 1995	1,215	534,924	1.00	-	1.00	-
Current use in 1995	60	23,676	0.85	(0.65, 1.10)	0.87	(0.67, 1.13)
Acetaminophen						
Nonuse in 1995	1,037	456,468	1.00	-	1.00	-
Current use in 1995	178	82,155	0.85	(0.73, 1.00)	0.90	(0.76, 1.07)
Duration[c]						
< 1 year	57	24,407	1.03	(0.79, 1.34)	1.09	(0.83,1 .42)
1 to < 2 years	8	6,083	0.54	(0.27, 1.08)	0.57	(0.28, 1.14)
2 to < 3 years	14	6,582	0.88	(0.52, 1.49)	0.93	(0.55, 1.58)
3 to < 5 years	27	11,554	0.87	(0.60, 1.28)	0.93	(0.63, 1.36)
≥ 5 years	66	29,902	0.82	(0.64, 1.05)	0.87	(0.67, 1.12)

[a] Models were jointly stratified by age (one-year intervals) and questionnaire cycle and adjusted for education, BMI at age 18, vigorous activity, female hormone use, and smoking. Models for aspirin adjusted further for other NSAIDs, other NSAIDs adjusted for aspirin, and acetaminophen for aspirin and other NSAIDs

[b] p for trend = 0.15 in multivariable model

[c] p for trend = 0.17 in multivariable model

Table 3

Incidence rate ratios (IRR) and 95% confidence intervals (CI) of incident breast cancer according to time-dependent current and former medication use in the Black Women's Health Study, 1995-2007

Regular Medication use	Total # of Cases 1,275	Total # of Person Years 558,600	Age Adjusted		Multivariable Adjusted[a]	
			IRR	95%CI	IRR	95%CI
Aspirin						
Nonuse	941	442,199	1.00	-	1.00	-
Former use	141	42,217	1.12	(0.93, 1.35)	1.15	(0.95, 1.38)
Current use	147	56,794	0.77	(0.65, 0.92)	0.79	(0.66, 0.95)
Duration[b]						
< 1 year	9	4,106	0.81	(0.40, 1.65)	0.84	(0.41, 1.70)
1 to < 2 years	1	956	0.36	(0.05, 2.54)	0.37	(0.05, 2.66)
2 to < 3 years	59	22,025	0.87	(0.67, 1.13)	0.89	(0.68, 1.16)
3 to < 5 years	32	11,156	0.82	(0.58, 1.16)	0.84	(0.59, 1.19)
≥ 5 years	46	18,551	0.67	(0.49, 0.89)	0.68	(0.50, 0.92)
Other NSAIDs						
Nonuse	1,135	507,745	1.00	-	1.00	-
Former use	81	26,164	1.01	(0.80, 1.27)	1.02	(0.81, 1.29)
Current use	43	19,417	0.73	(0.54, 0.99)	0.75	(0.55, 1.02)
Acetaminophen						
Nonuse	909	401,576	1.00	-	1.00	-
Former use	138	57,446	0.93	(0.78, 1.11)	0.94	(0.78, 1.12)
Current use	108	56,144	0.76	(0.63, 0.93)	0.80	(0.65, 0.98)
Duration[c]						
< 1 year	7	6,059	0.50	(0.22, 1.13)	0.55	(0.24, 1.23)
1 to < 2 years	1	1,170	0.37	(0.05, 2.64)	0.41	(0.06, 2.94)
2 to < 3 years	41	19,557	0.90	(0.66, 1.22)	0.93	(0.68, 1.27)
3 to < 5 years	22	9,375	0.88	(0.58, 1.34)	0.92	(0.60, 1.39)
≥ 5 years	37	19,983	0.67	(0.49, 0.93)	0.70	(0.51, 0.97)

[a] Models were jointly stratified by age (one-year intervals) and questionnaire cycle and adjusted for education, BMI at age 18, vigorous activity, female hormone use, and smoking. Models for aspirin adjusted further for other NSAIDs, other NSAIDs adjusted for aspirin, and acetaminophen for aspirin and other NSAIDs

[b] p for trend=0.03 in multivariable model

[c] p for trend=0.03 in multivariable model