Published in final edited form as:

Mayo Clin Proc. 2016 January ; 91(1): 71–80. doi:10.1016/j.mayocp.2015.10.018.

Personalizing Aspirin Use for Targeted Breast Cancer Chemoprevention Among Postmenopausal Women

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Abstract

Objective—To better understand the potential risk/benefit ratio for targeted chemoprevention, we evaluated the association of aspirin and other NSAIDs with incidence of postmenopausal breast cancer for risk subgroups defined by selected non-modifiable or difficult-to-modify breast cancer risk factors.

Patients and Methods—Postmenopausal women with no history of cancer on July 1, 1992 (N=26,580) were prospectively followed through December 31, 2005 for breast cancer incidence (N=1581). Risk subgroups were defined on family history of breast cancer, age at menarche, age at menopause, parity/age at first live birth, history of benign breast disease, and body mass index (BMI). Hazard ratios (HRs) and 95% confidence intervals (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 family history of breast cancer (HR=0.62 for 6+ per week vs. never use; 95%CI 0.41-0.93) and 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 BMI. In contrast, inverse associations with aspirin use were observed in all lower risk subgroups. NSAID use had no association with breast cancer incidence.

Conclusion—Based on their increased risk of breast cancer, postmenopausal women with a family history of breast cancer or a 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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Potential competing Interests: None.

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Breast cancer is the most common non-cutaneous 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 over 40,000 women will die of breast cancer.² Furthermore, one in eight women in the U.S. will develop 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 non-steroidal anti-inflammatory drugs (NSAIDs) have been extensively investigated as potential cancer chemopreventive agents.³⁻⁸ NSAIDs 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 over-expressed in cancer.⁹⁻¹³ NSAIDs can also inhibit aromatase, a critical enzyme involved in endogenous production of estrogens in postmenopausal females.¹⁴ Most¹⁵⁻²⁶ but not all²⁷⁻³⁰ epidemiologic studies have observed an inverse association of either aspirin or other NSAIDs with breast cancer risk, including an earlier report from this cohort.³¹

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 non-modifiable factors, such as family history of breast cancer, 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). "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 non-aspirin NSAIDs with breast cancer risk among postmenopausal women within risk subgroups defined by individual and total number of selected non-modifiable or difficult-to-modify risk factors.

Methods

Iowa Women's Health Study (IWHs) Cohort

The IWHs is a prospective cohort study of postmenopausal women aged 55–69 years at study baseline in 1986.^{31,33} Briefly, in 1986 a 16-page questionnaire was mailed to 98,030 randomly selected women in Iowa based on drivers' license, and was returned by 41,836 women (42.7%) who constituted the original cohort. Compared to non-respondents, respondents were on average 3 months younger, had a 0.4 kg/m² lower body mass index, and were more likely to live in rural areas. The non-respondents have been demonstrated to have a slightly higher mortality rate due to smoking-related diseases compared to respondents.³⁴ Follow-up questionnaires (response rates) were conducted in 1987 (91%), 1989 (90%), 1992 (83%), 1997 (79%), and 2004 (70%).

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 non-aspirin 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 one per week, one per week, 2–5 per week, and 6+ per week. " Use of non-aspirin 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 one per week, one per week, 2–5 per week, and 6+ per week. "

Based on current literature, we defined *a priori* the non-modifiable or difficult-to-modify breast cancer risk factors (and respective cutpoints) for postmenopausal women as age at menarche <11 years; age at menopause ≥55 years; nulliparous or age at first live birth >30 years; BMI of ≥30 kg/m²; any family history of breast cancer in a first degree relative; and history of benign breast disease. BMI ≥30 kg/m² (the WHO 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 breast cancer patients 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.

Cohort Follow-Up

Incident breast cancers were identified through 2005 by linking the cohort to the Iowa Cancer Registry, a member of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program.³⁷ Cohort members were matched against registry files according to name, maiden name, zip code, birth date, and social security number. Deaths were identified through annual linkage to Iowa state death certificates, supplemented by linkage to the National Death Index. Estrogen and progesterone receptor status of the tumor was obtained from registry records.³⁸

Data Analysis

Among 41,836 participants, women were excluded if they were premenopausal at enrollment in 1986 (n=569); had a diagnosis of cancer (excluding nonmelanoma skin cancer) at the 1986 baseline (n=3830) or at the 1992 follow-up (n=2949); had a total or partial mastectomy (n=1884); did not return the 1992 follow-up questionnaire due to death or non-response (n=8819); or skipped the aspirin or NSAIDs questions (n=681). After exclusions, 26,580 women remained in the at-risk cohort (exclusions were not mutually exclusive).

Follow-up for each woman began on July 1, 1992, the approximate date of the 1992 questionnaire, and ended on the date of breast cancer diagnosis, move out of Iowa, death or, if none of these events occurred, on December 31, 2005. The outcome of interest was defined as time from the 1992 questionnaire to the development of breast cancer or censorship.

The association of aspirin and NSAID use with risk of breast cancer was assessed using a Cox proportional hazards regression analysis, modeling age as the time-scale.³⁹ The lowest risk category for each established breast cancer risk factor was modeled as the referent category. For analyses of aspirin and NSAIDs, never users were the referent category and hazard ratios (HRs) were assessed for categories of use: 1, 2-5, or 6+ per week. Tests for trend were implemented for the frequency of use variables, ordering them from lowest (never) to highest, and including a one degree of freedom linear term in the Cox proportional hazards model. Multivariate analyses for the frequency of use variables included the following variables as covariates: oral contraceptive use (never, ever); use of hormone replacement therapy (never, ever); smoking status (never, former, current); alcohol use (never, former, and current by frequency of use); physical activity level (low, moderate, high); history of rheumatoid arthritis (no, yes); and history of osteoarthritis (no, yes). Covariates were collected from the 1986 and 1992 questionnaires.

Aspirin and NSAID use were examined among all women, as well as within subgroups defined by risk level for each of selected risk factors. We dichotomized these factors into risk categories based on *a priori*, commonly-defined cutpoints that also ensured adequate sample size to assess aspirin/NSAID associations within each subgroup.

To model the potential clinical impact of prescribing aspirin or NSAID use for specific risk groups, the number needed to treat (NNT) was calculated based on cumulative incidence at 10 years of follow up, using a time-based method, with corresponding 95% confidence intervals.⁴⁰

All statistical analyses were carried out using SAS (SAS institute, Inc., Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria) software systems. All p-values were two-sided, and $P < .05$ was declared statistically significant.

Results

A total of 26,580 women were included in the analytical cohort, of whom 11,089 (42%) had zero, 10,592 (40%) had one, 4045 (15%) had two, and 854 (3%) had three or more risk factors. Through 2005 (307,178 person-years of follow-up), there were 1581 incident breast cancers. Each of the risk factors was positively associated with an increased risk of breast cancer, although not all were statistically significant (Table 1). The strongest association was observed for women having a family history of breast cancer (HR=1.50; 95% CI 1.30-1.73).

As a main effect, aspirin use was inversely associated with breast cancer risk after multivariate adjustment (HR=0.72 for use 6+ times/week versus never use; 95% CI

0.61-0.84; P -trend<.001), while there was no association for other (non-aspirin) NSAIDs at the same frequency of use (HR=1.04; 95% CI 0.87-1.23; P -trend=.78) (Table 1).

We next evaluated the association of aspirin use with breast cancer risk for each of the selected risk factors, adjusted for other breast cancer risk factors and for each other (Table 2 and Figure 1). Aspirin use was inversely associated with risk of breast cancer for women in both risk categories of family history of breast cancer and history of benign breast disease. Specifically, aspirin use was associated with a lower risk of breast cancer for women with (HR=0.62 for 6+ per week vs. never use; 95% CI 0.41-0.93) and without (HR=0.73; 95% CI 0.61-0.88) a family history of breast cancer, and for women with (HR=0.69; 95% CI 0.50-0.95) and without (HR=0.72; 95% CI 0.60-0.87) a history of benign breast disease. For age at menarche, aspirin use was only associated with a lower risk of breast cancer for women with an age of menarche age 11 years and older (HR=0.70; 95% CI 0.59-0.83) but not for higher risk women with an age at menarche for age <11 years (HR=1.14; 95% CI 0.49-2.62). For age at menopause and parity/age at first live birth, inverse associations of aspirin use with breast cancer risk was observed in both risk groups, but were only statistically significant in the lower risk subgroups (i.e., age at menopause <55 years and parity/age at first live birth 1+/- 30 years). Finally, for BMI, the inverse association with aspirin use was only observed for lower risk women with a BMI <30 kg/m² (HR=0.62; 95% CI 0.51-0.75) but not for the women with a BMI of 30+ (HR=0.98; 95% CI 0.73-1.32).

There were no associations for use of other NSAIDs with breast cancer risk for any of the subgroups defined in Table 2 (data not shown).

Given that only family history of breast cancer and benign breast disease had statistically significant inverse associations for aspirin use in the higher risk groups (i.e., family history positive or history of benign breast disease), one could argue that the risk-benefit ratio for using aspirin chemoprevention might be more favorable for these women. To better quantify this strategy, we calculated the number needed to treat (NNT) with 6+ aspirin per week to prevent one additional breast cancer in 10 years of follow-up. For women with a negative family history the NNT was 83 (95% CI 49-282), but among women with a positive family history the NNT was substantially lower at 38 (95% CI 19-∞). The NNT among women with no history of benign breast disease was 83 (95% CI 48-305), while for women with a history of benign breast disease the NNT was 40 (95% CI 22-192). These estimates would need to be balanced against the absolute risks for the negative outcomes of regular aspirin use over 10 years, which was not available from our study.

Discussion

To understand the potential risk/benefit ratio for targeted chemoprevention using aspirin or other NSAIDs, we characterized the association of aspirin use with breast cancer in higher risk groups of postmenopausal women defined by non-modifiable or difficult-to-modify risk factors. We found regular aspirin use, but not other NSAIDs, was inversely associated with breast cancer incidence for postmenopausal women at higher risk as defined by a positive family history of breast cancer or a history of benign breast disease. In contrast, use of aspirin or other NSAIDs was not protective among women at higher risk as defined by age

at menarche and body mass index, and to a lesser extent parity/age of first live birth and age at menopause. This may have implications for mechanistic pathways that aspirin chemoprevention targets, as well as clinical implications for the design of future trials and clinical management. For example, our analysis found that the NNT to prevent one additional breast cancer among women with a positive family history or with a personal history of benign breast disease is about one-half the NNT for those without such a history, perhaps changing the risk/benefit balance for aspirin chemoprevention in this setting.

This study adds to the literature by investigating the effect of aspirin on breast cancer risk among higher risk subgroups of women, namely postmenopausal women with non-modifiable or difficult-to-modify breast cancer risk factors. Its strengths include the prospective cohort design, ascertainment of cancer incidence using high-quality SEER cancer registry data, virtually complete follow-up for mortality, and availability of information on multiple risk and protective factors to evaluate potential confounding. The study was population-based, which enhances its external validity.

This study also has limitations. Our questionnaire did not assess the type, dose, or duration of aspirin or non-aspirin NSAID use, although we were able to distinguish between use of two major classes of agents and ascertain frequency of use. The majority of the population was Caucasian, and these associations may vary among other racial and ethnic groups. The observational study design has the potential for lower internal validity than an experimental (i.e., randomized controlled trial) design would have, particularly with respect to potential bias due to self-selection and confounding. However, we did adjust for multiple known confounders, although there may be residual confounding or other unknown confounders. Finally, while all of the *a priori* defined risk factors were positively associated with a higher risk of breast cancer in our cohort, not all were statistically significant. Similarly, small numbers in some of the higher risk subgroups resulted in limited power to identify subgroup effects and may have contributed to the observed null associations.

A majority,^{15-24,26} but not all,^{27,28,41,42} studies have reported an inverse association of aspirin with post-menopausal breast cancer. In a meta-analysis of 33 studies (19 cohort studies, 13 case-control studies, and 1 randomized controlled trial [RCT]) that included 1,916,448 subjects, aspirin use was found to be associated with a 14% lower risk of breast cancer (OR=0.86; 95% CI 0.81-0.92).⁴³ Similar to our study, multiple studies have also suggested that a higher frequency (daily) and duration (>5 years) of aspirin use is associated with lower risk of breast cancer.^{20-22,24,26} However, in the meta-analysis, cohort studies also showed a slightly weaker effect (OR=0.91; 95% CI 0.84-0.98) and there was substantial heterogeneity ($I^2=80.5\%$), which could be due to differences in study populations, exposure measurement, and adjustment factors or perhaps differences in the prevalence in risk factors in the study population, given our findings of differential effects of aspirin across some breast cancer risk factors. In the only randomized study, the Women's Health Study trial⁴⁴ did not find a protective effect of aspirin (RR=0.98; 95% CI 0.89-1.08) suggesting lack of efficacy and bias in observational studies, although the lack of association might be due to the lower frequency (alternate day aspirin use) and low dose of aspirin (100 mg) used in the trial.

There has been much less assessment of the association of aspirin and breast cancer risk by other risk factors that are largely non-modifiable in post-menopausal women, and this is one of the first studies to compressively look into this issue. However, studies have reported reduced risk of breast cancer recurrence and improved survival among breast cancer survivors with aspirin use or combined aspirin and NSAID use.^{45,46} In a prospective observational study based on the Nurses' Health Study, aspirin use was associated with a decreased risk of breast cancer recurrence (RR=0.57 for aspirin use 6-7 times/week versus no use; 95% CI 0.39-0.82) and death (RR=0.36 for aspirin use 6-7 times/week versus no use; 95% CI 0.24-0.54), suggesting a potential role of aspirin in the secondary prevention of breast cancer.⁴⁵ Similarly, a recent meta-analysis showed that ASA and NSAID use after but not before breast cancer diagnosis was associated with improved breast cancer survival.⁴⁷ Given our finding that aspirin was associated with reduced breast cancer risk in all lower risk subgroups, future studies should explore the potential chemopreventive effect of aspirin on breast cancer recurrence among women with lower risk profiles.

Aspirin use was inversely associated with risk among women with a family history of breast cancer or a personal history of benign breast disease, factors predominantly associated with increased risk of both estrogen receptor positive and negative breast cancer, but not among women in the higher risk groups for early age at menarche or high BMI, factors predominantly associated with increased risk of estrogen receptor positive breast cancer.^{35,48} These results raise the hypothesis that the association of aspirin with reduced breast cancer may not be directly related to estrogen receptor mediated signaling pathways but may be through other pathways, such as cyclooxygenase pathway,⁴⁹ phosphatidylinositol 3-kinase downregulation,⁵⁰ B-cell lymphoma 2 mediated apoptosis,⁵¹ or epidermal growth factor receptor inhibition, and p53 acetylation.⁵² It is also possible that certain risk factors that induce chronic inflammation to various degrees (e.g., obesity or smoking), alone or on combination, may create a threshold above which anti-inflammatory drugs such as aspirin at standard doses fail to provide benefit. In such a scenario, a higher dose of aspirin may be required, which would increase the risk of adverse events. This could be addressed by analogs of aspirin chemically modified to have reduced gastrointestinal toxicity, which have shown promising results for breast cancer inhibition in animal models.⁵² Additional *in vivo* and *in vitro* studies are needed to further elucidate the biological mechanisms underlying the association of aspirin with reduced breast cancer risk among women with lower levels of hormone exposure.

Consistent with our prior observations in the IWHS cohort,³⁸ and those of others,^{20,21,30} but not all,^{23,24} non-aspirin NSAID use was not associated with breast cancer incidence. The observed differences between aspirin and NSAIDs could be due to the additional biologic effects of aspirin, such as the irreversible inhibition of COX enzymes (as compared to reversible inhibition by non-aspirin NSAIDs) or the potential cancer-preventive effects from inhibition of platelet activation (not seen with non-aspirin NSAIDs).⁷ In addition, the heterogeneity in the literature could be due to greater variability in the dose, type, and duration of non-aspirin NSAID use. Indeed a meta-analysis of epidemiological studies,⁵³ reported that the inverse association between non-aspirin NSAIDs and breast cancer was

weaker than that of aspirin, and there was significant heterogeneity in the results based on study design, population studied, and exposure assessment for the non-aspirin NSAIDs.

Our results could have important implications for designing clinical trials of aspirin chemoprevention by focusing on higher risk women given the need to maximize the risk/benefit profile. Our study suggests that women with a family history of breast cancer or a personal history of benign breast disease might be targeted, although this concept needs confirmation in other studies. Ideally, a randomized controlled clinical trial needs to be conducted to confirm the epidemiological findings before aspirin can be recommended for clinical use. Given the negative results of the Women's Health Study⁴⁴ and other large chemoprevention studies,⁵⁴⁻⁵⁷ it is unlikely that a large randomized trial assessing general chemopreventive effects of aspirin would be conducted in the near future among unselected women.^{7,58,59} Instead, targeted chemoprevention in selected populations based on individual risk profile and other risk biomarkers should be pursued.^{60,61} For example, findings from a cohort study have suggested that aspirin may reduce the risk of progression to breast carcinoma among women with benign breast disease and the association might vary with COX-2 polymorphisms.⁴⁹

Conclusion

Our results raise the hypothesis that aspirin chemoprevention may only be effective in certain higher risk groups and not others, which may provide insight into mechanistic pathways underlying these observations and also would have implications for the design of trials to target higher risk women. Additional work in this area is warranted.

Acknowledgments

We thank Sondra Buehler for editorial assistance.

Grant Support: This work was supported by a grant from the National Institutes of Health (R01 CA39742).

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Abbreviations and Acronyms

NSAIDs	non-steroidal anti-inflammatory drugs
Cox	cyclooxygenase
BMI	body mass index
IWHS	Iowa Women's Health Study
NNT	number needed to treat
OR	odds ratio

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RR relative risk

Figure 1. Association of aspirin use with risk of post-menopausal breast cancer risk for subgroups defined by individual risk factors, Iowa Women's Health Study 1992-2005

Table 1
Association of Aspirin, Non-Aspirin NSAIDs And Non-Modifiable or Difficult-To-Modify Factors with Risk of Post-Menopausal Breast Cancer, Iowa Women's Health Study, 1992-2005

Risk Factor	N	%	Cases	Person-years	HR (95% CI)^a	HR (95% CI)^b
First degree relative with breast cancer						
Negative	22744	88%	1290	263537	1.00 (reference)	1.00 (reference)
Positive	3122	12%	259	35656	1.48 (1.29, 1.69)	1.50 (1.30, 1.73)
Age at menarche						
11+ years	25506	97%	1518	294879	1.00 (reference)	1.00 (reference)
<11 years	811	3%	53	9313	1.11 (0.85, 1.46)	1.11 (0.83, 1.50)
Age at menopause						
<55 years	23001	89%	1353	266202	1.00 (reference)	1.00 (reference)
55+ years	2745	11%	184	31517	1.13 (0.98, 1.33)	1.21 (1.04, 1.45)
Parity/Age at first live birth						
Age at 1 st live birth 30 y	22829	87%	1344	264613	1.00 (reference)	1.00 (reference)
Nulliparous or age at 1 st live birth >30 y	3460	13%	221	39254	1.10 (0.96, 1.27)	1.10 (0.94, 1.29)
Benign breast disease						
No	21254	80%	1187	245150	1.00 (reference)	1.00 (reference)
Yes	5182	20%	386	60339	1.33 (1.18, 1.49)	1.29 (1.13, 1.47)
Body mass index						
<30 kg/m ²	20557	77%	1175	239158	1.00 (reference)	1.00 (reference)
30+ kg/m ²	6024	23%	406	68021	1.22 (1.09, 1.36)	1.25 (1.10, 1.42)
Aspirin use						
Never	7475	28%	489	84529	1.00 (reference)	1.00 (reference)
1 / week	8817	33%	535	104210	0.89 (0.79, 1.01)	0.88 (0.77, 1.01)
2-5 / week	4685	18%	268	55018	0.84 (0.73, 0.98)	0.79 (0.67, 0.94)
6+ / week	5603	21%	289	63422	0.79 (0.68, 0.91)	0.72 (0.61, 0.84)
<i>P</i> -trend					<.001	<.001
NSAID use						
Never	16085	61%	948	185464	1.00 (reference)	1.00 (reference)
1 / week	4882	18%	275	57750	0.94 (0.82, 1.07)	0.90 (0.78, 1.05)

Risk Factor	N	%	Cases	Person -years	HR (95% CI) ^a	HR (95% CI) ^b
2-5 / week	2152	8%	136	25057	1.07 (0.89, 1.28)	1.03 (0.84, 1.26)
6+ / week	3461	13%	222	38907	1.12 (0.97, 1.29)	1.04 (0.87, 1.23)
P-trend					.17	.78

^a Hazard ratios (HR) and 95 confidence intervals (CI), adjusted for age.

^b Each factor in the table is adjusted for age, use of oral contraceptives, use of hormone replacement therapy, smoking, alcohol use, physical activity level, history of rheumatoid arthritis, history of osteoarthritis, and except for the Summary Index, all other risk factors listed in the table.

^c The non-modifiable or difficult-to-modify breast cancer risk factors included family history of breast cancer in a first degree relative, age at menarche <11 years, age at menopause ≥ 55 years, nulliparous or age at first live birth >30 years, history of benign breast disease, and BMI of ≥ 30 kg/m².

Table 2
Association of Aspirin Use with Risk of Post-Menopausal Breast Cancer for Subgroups Defined By Individual Risk Factors, Iowa Women's Health Study 1992-2005^a

Subgroup	Use of Aspirin				P-trend
	Never	1 / week	2-5/week	6+/week	
First degree relative with breast cancer					
Negative	Cases / p-years	396 / 72492	439 / 89744	215 / 47012	240 / 54288
	HR (95% CI)	1.00 (reference)	0.89 (0.77, 1.03)	0.78 (0.65, 0.94)	0.73 (0.61, 0.88)
Positive	Cases / p-years	85 / 9543	83 / 11986	45 / 6443	46 / 7683
	HR (95% CI)	1.00 (reference)	0.82 (0.59, 1.14)	0.84 (0.57, 1.24)	0.62 (0.41, 0.93)
Age at menarche					
11+ years	Cases / p-years	472 / 81000	513 / 100705	260 / 52514	273 / 60660
	HR (95% CI)	1.00 (reference)	0.87 (0.76, 0.99)	0.79 (0.67, 0.94)	0.70 (0.59, 0.83)
<11 years	Cases / p-years	12 / 2764	19 / 2610	7 / 1826	15 / 2112
	HR (95% CI)	1.00 (reference)	1.52 (0.71, 3.25)	0.79 (0.29, 2.13)	1.14 (0.49, 2.62)
Age at menopause					
<55 years	Cases / p-years	424 / 73159	452 / 89964	226 / 47270	251 / 55809
	HR (95% CI)	1.00 (reference)	0.89 (0.77, 1.02)	0.79 (0.66, 0.94)	0.70 (0.59, 0.83)
55+ years	Cases / p-years	56 / 8653	66 / 11042	31 / 5923	31 / 5899
	HR (95% CI)	1.00 (reference)	0.84 (0.57, 1.23)	0.82 (0.52, 1.31)	0.82 (0.52, 1.30)
Parity/Age at first live birth					
1+ / 30 years	Cases / p-years	417 / 72193	444 / 89485	236 / 48228	247 / 54706
	HR (95% CI)	1.00 (reference)	0.85 (0.74, 0.99)	0.80 (0.67, 0.95)	0.71 (0.59, 0.84)
0/>30 years	Cases / p-years	69 / 11462	82 / 13667	30 / 6154	40 / 7971
	HR (95% CI)	1.00 (reference)	1.07 (0.75, 1.52)	0.73 (0.44, 1.20)	0.76 (0.48, 1.19)
Benign breast disease					
No	Cases / p-years	367 / 68162	400 / 83408	211 / 43971	209 / 49609
	HR (95% CI)	1.00 (reference)	0.90 (0.77, 1.05)	0.87 (0.72, 1.05)	0.72 (0.60, 0.87)
Yes	Cases / p-years	118 / 15858	135 / 20380	55 / 10650	78 / 13451
	HR (95% CI)	1.00 (reference)	0.83 (0.63, 1.08)	0.57 (0.40, 0.82)	0.69 (0.50, 0.95)
Body mass index					

Subgroup	Use of Aspirin					P-trend
		Never	1 / week	2-5/week	6+/week	
<30 kg/m ²	Cases / p-years	366 / 63464	412 / 84158	204 / 43806	193 / 47730	
	HR (95% CI)	1.00 (reference)	0.83 (0.71, 0.97)	0.75 (0.62, 0.91)	0.62 (0.51, 0.75)	<.001
30 kg/m ²	Cases / p-years	123 / 21065	123 / 20052	64 / 11212	96 / 15692	
	HR (95% CI)	1.00 (reference)	1.02 (0.77, 1.33)	0.94 (0.67, 1.31)	0.98 (0.73, 1.32)	.81

^a Adjusted for age, use of oral contraceptives, use of hormone replacement therapy, smoking, alcohol use, physical activity level, history of rheumatoid arthritis, history of osteoarthritis all other factors in the table.