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Non-steroidal Anti-inflammatory Drugs and Cancer Risk in Women: Results from the Women's Health Initiative

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Abstract

The use of non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with reduced risks of cancers at several sites in some studies; however, we recently reported no association between their use and total cancer risk in women in a prospective study. Here we examine the association between NSAIDs and total and site-specific cancer incidence in the large, prospective Women's Health Initiative (WHI). 129,013 women were recruited to participate in the WHI at 40 US clinical centers from 1993 to 1998 and followed prospectively. After 9.7 years of follow-up, 12,998 incident, first primary, invasive cancers were diagnosed. NSAID use was systematically collected at study visits. We used Cox proportional hazards regression models to estimate multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) for associations between NSAIDs use and total and site-specific cancer risk. Relative to non-use, consistent use (i.e., use at baseline and year 3 of follow-up) of any NSAID was not associated with total cancer risk (HR 1.00, 95% CI: 0.94–1.06). Results for individual NSAIDs were similar to the aggregate measure. In site-specific analyses, NSAIDs were associated with reduced risks of colorectal cancer, ovarian cancer, and melanoma. Our study confirms a chemopreventive benefit for

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Conflict of interest statement

The authors have no competing conflicts of interest to declare.

colorectal cancer in women and gives preliminary evidence for a reduction of the risk of some rarer cancers. NSAIDs' benefit on cancer risk was limited to specific sites and not evident when total cancer risk was examined. This information may be of importance when NSAIDs are considered as chemopreventive agents.

Keywords

Aspirin; cancer; ibuprofen; inflammation; naproxen; non-steroidal anti-inflammatory drug

Introduction

The use of non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with reduced risks of cancers at several sites, most consistently the colon and rectum [1]. Overall associations beyond those sites are less clear. A recent series of meta-analyses of randomized trials by Rothwell et al. [2–5], reported that aspirin to reduced cancer risk and mortality. It is noteworthy that women were underrepresented in those analyses and, in most cases, findings were not stratified on sex. Thus associations for women are not well studied. In the only randomized trial of aspirin among women, no overall effect on cancer risk was observed in the Women's Health Study (WHS) [6, 7], however these findings were based on a single, very low dose (100mg given every second day). In addition, few prospective observational studies of commonly available NSAIDs have examined associations with overall cancer risk in women and among them findings are inconsistent [8–14]. In the first study to examine specific non-aspirin formulations, we recently reported that NSAIDs, among participants of the VITamins And Lifestyle (VITAL) cohort study [10], reduced overall cancer incidence in men but not in women.

Given these discrepancies, we took advantage of the large, prospective, Women's Health Initiative (WHI) to study further the association between NSAIDs and overall as well as site-specific cancer risk in women.

Methods

Women's Health Initiative

The WHI is a large, prospective study that was designed to examine common causes of morbidity and mortality among postmenopausal women, including cancer, cardiovascular disease, and osteoporosis [15]. The study consists of a multifactorial clinical trial (CT) (Trial registration: clinicaltrials.gov identifier, NCT00000611) and an observational study (OS). Detailed methods of the study are given elsewhere [15–17]. Briefly, 161,808 women, ages 50–79 years, were recruited at 40 US clinical centers between September 1, 1993 and December 31, 1998. The WHI CT included 3 overlapping components: 2 placebo controlled hormone therapy trials [estrogen-alone (n=10,739) and estrogen plus progestin (n=16,608)]; a dietary modification compared to usual diet trial (n=48,836); and a calcium/vitamin D supplementation placebo controlled trial (n=36,282) [18–20]. Participants in the OS were 93,676 women who were screened for participation in the CT but were ineligible or unwilling to participate, or who were directly recruited [21]. After the original WHI study

ended in 2005, the WHI Extension Study (2005–2010) was carried out to collect an additional five years of follow-up data. Women provided written informed consent for participation in both the original and extension studies. Human Subjects Review Committees at all participating institutions approved the WHI study protocol.

For the present analysis, exclusions were made for women who: reported a positive history of cancer, other than non-melanoma skin cancer, prior to baseline enrollment or who were missing these data (n=16,255); had a cancer diagnosis between baseline and the third year of follow-up (n=3,705); or were missing NSAID exposure data from baseline or year 3 of follow-up (n=12,835) visits. After exclusions, there were 129,013 women available for inclusion in the analysis.

Data collection

WHI participants attended baseline screening visits, during which they completed self-administered questionnaires that collected detailed information on demographics, medical and reproductive history, family history of cancer, physical activity, and other risk factors. Height (cm) and weight (kg) were measured by clinic staff, and used to determine body mass index (BMI; kg/m^2).

A computer-driven medication-inventory system was developed to capture usual current medication use [16]. Participants were asked to bring prescription and over-the-counter medications used regularly (≥2 times/week) over the previous 2 weeks to their clinic visit to facilitate completion of a computer-assisted interview about current medication use. Women were asked about their current, regular use of NSAIDs, including aspirin, ibuprofen, naproxen, COX-2 inhibitors (e.g., celecoxib), and other NSAID preparations (e.g., indomethacin). Women provided medication data at baseline and year 3 (OS and CT) and additionally years 6 and 9 (CT only).

In an effort to minimize measurement error, use of individual NSAIDs was categorized as none, inconsistent, and consistent, corresponding to non-use at both baseline and the year 3 visits, use at baseline or year 3 only, and use at both baseline and year 3, respectively. Duration of NSAID use was reported at baseline and was dichotomized (<5y and ≥5y). Analyses of NSAID duration were restricted to non- and consistent users. Summary variables were created to account for uses of any NSAID (including prescription and over-the-counter preparations), any aspirin, and any non-aspirin NSAID. We defined low-dose aspirin as ≤100mg.

Follow-up for cancer and censoring

Incident, invasive cancer cases were reported by questionnaire annually in the OS and semi-annually in the CT. Medical records were obtained and reviewed, and cancer diagnoses confirmed by physician adjudicators [22]. Only confirmed, invasive cancer diagnoses after year 3, the adjusted “baseline”, were considered cases. After a median of 9.7 years of follow-up, 12,998 invasive cancers were identified. Cancers were additionally grouped by organ system or organ, and those with ≥150 cases were included in site-specific analyses.

Participants were right-censored from the analysis at the earliest date of the following events: end of original follow-up for participants who were not enrolled in the WHI Extension Study (n=24,392), withdrawal from the study (n=1,006), death (n=8,144), *in situ* diagnosis (n=2,718), loss of contact (n=479), or December 31, 2010, the last date of the WHI Extension study data adjudication (n=81,890). In site-specific analyses an invasive cancer at a given site was considered a "case" if it was the woman's first primary cancer. Incident cancers which were not the event of interest were censored at their respective times of diagnoses in order to avoid surveillance bias and to be consistent with exclusion criteria.

Statistical analyses

Cox proportional hazards regression models using baseline age as the time metric were used to estimate age- and multivariable-adjusted hazard ratios (HR) and 95% CI for associations between NSAID use and cancer incidence. All multivariable-adjusted regression models were adjusted for randomization/enrollment in the CT. In addition, we selected *a priori* potential confounders collected at baseline, including known and suspected risk factors of the most common cancers and indications/contraindications for NSAID use for inclusion in regression models (see footnote of Table 2). In order to control for the potential confounding of the association between an individual NSAID and cancer risk by use of another, regression analyses for any one NSAID exposure were further adjusted for the use of other NSAIDs. Tests for linear trend (P trend) across categories of NSAID duration were calculated by including 3-level ordinal variables for NSAID duration (non-use, <5y consistent use, ≥5y consistent use) in regression models.

We hypothesized *a priori* that associations between NSAID use and cancer risk would be modified by factors associated with inflammation, including BMI [23], cigarette smoking [24], history of arthritis [25], and use of cholesterol-lowering drugs [26]. P values for interaction (P interaction) were calculated by including a cross-product term in regression models. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA). All statistical tests are two-sided, and P<0.05 was considered statistically significant.

Results

Age-adjusted associations between characteristics of WHI women and consistent NSAID use are given in Table 1. Increasing age, BMI, smoking, and use of postmenopausal hormones were all positively associated with consistent NSAID use. Women who used multivitamins, had a family history of cancer, were screened for cancer, or had a personal history of hypertension, heart disease, or arthritis were also more likely to use NSAIDs consistently. Non-white women and women who reported gastric ulcers were less likely to use NSAIDs.

Age and multivariable-adjusted associations between NSAID use and total cancer incidence are given in Table 2. Results were similar in the OS and CT; therefore, findings are given in the combined cohort, adjusted for CT intervention assignment. Relative to non-use, consistent use of any NSAID (HR 1.00, 95% CI: 0.94–1.06) and increasing baseline duration of use among consistent users (≥5y: HR 0.99, 95% CI: 0.91–1.08) were not associated with total cancer risk. Use of individual NSAIDs, including low-dose and regular-

strength aspirin, ibuprofen, and naproxen were also not associated with cancer risk. Although long-term baseline use of naproxen was associated with a 45% increased risk of total cancer (HR 1.45, 95% CI: 1.02–2.06) among consistent users, this result was based on a small number of cases and there was no linear trend for duration of use (*P* trend=0.14).

We performed several sensitivity analyses in order to evaluate the robustness of our findings. In an analysis where use of individual NSAIDs was compared to a referent of non-users of any NSAID, results were not meaningfully changed (consistent use vs. non-use for any aspirin: HR 1.05, 95% CI: 0.98–1.13; for any non-aspirin NSAID: HR 1.02, 95% CI: 0.92–1.15). We also considered whether our censoring of *in situ* cancers had an effect on our results. In a separate sensitivity analysis, we examined associations between NSAID use and cancer risk, where a case was defined as incident *in situ* or invasive cancer. Results were changed only nominally (Supplemental Table 1). Lastly, in an effort to determine whether adjustment for correlates of NSAID use constituted over-adjustment, we examined associations in regression models adjusted only for cancer risk factors (Supplemental Table 2 and footnotes); here again, only very small changes were noticed in the results.

We further examined whether associations between consistent NSAID use and cancer risk were modified by factors known to affect inflammation (Figure 1). There was no effect-modification by BMI, cigarette smoking, history of arthritis, or use of cholesterol-lowering drugs.

Table 3 presents associations between NSAID use and risk of cancers of individual organs or organ systems. In-depth analyses of the associations between NSAIDs and colorectal [27], breast [28], endometrium [29], and skin [30] cancer in the WHI have been published previously. There was strong evidence for a reduction of the risk of GI tract cancers, and colorectal cancer in particular, with use of any NSAID (≥5y among consistent users vs. non-use: HR 0.74, 95% CI: 0.55–0.99). In addition, long-term consistent use of NSAIDs, primarily aspirin, was associated with a reduction of ovarian cancer risk and consistent aspirin use was inversely associated with melanoma incidence. Results were similar by aspirin dose (Supplemental Table 3). NSAID use was not associated with cancers of the urinary tract, lung, breast, endometrium, thyroid, or hematologic malignancies. There were no statistically significant increases in risk for any cancer site.

Discussion

In this large prospective study, we found little evidence to support the use of NSAIDs, in sum or individually, for cancer chemoprevention in postmenopausal women, beyond their suggested role in reducing colorectal cancer incidence. There was preliminary evidence for inverse associations with melanoma and ovarian cancers. Consistent NSAID use did not reduce the risks of breast, lung, endometrial, or thyroid cancers, the most common cancers in women aside from colorectal cancer [31].

NSAIDs are thought to reduce cancer risk through the inhibition of the cyclooxygenase (COX) enzymes, particularly the inducible isoform, COX-2. Inhibition of COX-2 reduces the downstream synthesis of pro-inflammatory prostaglandins (PG), particularly PGE_2, a

potent mitogen which has been considered a target for cancer prevention and therapy [32]. COX-2 and PGE_2 are also correlated with aromatase expression *in vitro* [33] and there is human evidence that their inhibition is associated with reduced estrogen metabolism [34].

There are relatively few observational studies with the capacity to adjust for potential confounding factors aside from age that have examined associations between NSAID use and total cancer risk in women [8–10]. Recently, we published findings from the VITAL cohort, which included 2,534 cases among 31,580 women followed for 7 years [10]. Similar to the current findings, use of NSAIDs was not associated with total cancer risk in women (≥4 days/week for ≥4 years vs. non-use: HR 1.10, 95% CI: 0.96–1.25) [10]. Reports from the Iowa Women's Health Study [(IWHS); *n* cases=3,487; 10y follow-up] [8] and the Cancer Prevention Study II Nutrition Cohort [(CPS); *n* female cases=7,196; 8y follow-up] [9] were suggestive of reduced risks of total cancer. In the IWHS, a prospective cohort of postmenopausal women, Bardia et al. [8], reported that current use of aspirin ≥6 days/week at baseline was associated with a 19% reduction in total cancer risk [Relative Risk (RR) 0.81, 95% CI: 0.73–0.90; *P* trend<0.001]. Use of non-aspirin NSAIDs was not associated with total cancer risk (RR 0.94, 95% CI: 0.83–1.06). To our knowledge, long-term NSAID exposure was not assessed. In the Cancer Prevention Study (CPS), current daily use of regular or extra-strength aspirin for ≥5 years was associated with a statistically non-significant 14% reduction in total cancer risk in women (RR 0.86, 95% CI: 0.73–1.03) [9]. In that study, use of non-aspirin NSAIDs was not assessed. Three earlier studies [11–13] reported only age-adjusted relative risks. Among them, findings were null for aspirin in the NHANES I cohort [12], and 8–10% increases in risk were reported for low-dose aspirin [11] or non-aspirin NSAIDs [13] in a cohort linked to the Danish Cancer Registry.

This study is only the second to examine associations of ibuprofen and naproxen with total cancer risk. Our current findings are consistent with our previous report among women in the VITAL cohort [10]. In it, we found no evidence of a reduction in cancer risk for long-term regular use of ibuprofen (≥4 days/week for ≥4 years vs. non-use: HR 1.05, 95% CI: 0.88–1.27) or naproxen (≥4 days/week for ≥4 years vs. non-use: HR 1.05, 95% CI: 0.77–1.44) relative to non-use [10].

Results from randomized trials are limited to aspirin, predominately conducted among men, and are conflicting. Recently, Rothwell et al. published a series of pooled analyses of randomized trials of aspirin on the short-term risk of cancer [4] and long-term risk of metastatic cancer [5]. In six trials of daily low-dose aspirin tested against a placebo, which included 642 incident cancers in approximately 16,400 women, aspirin was protective in women for total cancer after 3 years of follow-up (OR 0.75, 95% CI: 0.59–0.94) but not earlier (OR 1.13, 95% CI: 0.91–1.40) [4]. Aspirin (≥75mg/day) reduced the risk of distant metastasis in five trials (HR 0.64, 95% CI: 0.48–0.84) [5]; however less than a third of participants were women and findings were not stratified on sex. The WHS is the only randomized controlled trial of an NSAID, low-dose aspirin (100mg given every second day), for cancer prevention in women [6, 7]. The study included 39,876 women and 2,865 incident cancers after 10 years of follow-up [6]. Similar to our findings, no effect of low-dose aspirin on overall cancer risk was reported (HR 1.01, 95% CI: 0.94–1.08) [6, 7].

Only VITAL [10], IWHS [8], and the WHS [6] have examined whether associations between NSAIDs and cancer risk are modified by factors known to influence inflammation. Similar to this study, none has reported effect-modification.

Our site-specific findings are largely consistent with previous reports from the WHI in which the use of NSAIDs and risks of cancers of the breast [28], colon and rectum [27], skin [30], and endometrium [29], were examined. Our results differ with 2 prior publications [27, 28] among the WHI OS. Whereas we observed no reduction in breast cancer risk, Harris et al. [28], reported that long-term use of NSAIDs was associated with a linear reduction in breast cancer risk (RR 0.72, 95% CI: 0.56–0.91) after 3.6 years of follow-up. Conversely, whereas we found a strong reduction in colorectal cancer risk, Allison et al. [27], reported no association between aspirin use and colorectal cancer risk (HR 0.95, 95% CI: 0.69–1.31) after 6.4 years of follow-up. In an effort to explain these differences, we examined site-specific associations in the OS alone. The subgroup findings for breast and colorectal cancer did not differ from the combined OS + CT estimates (data not shown). Accrual of additional cases over a longer follow-up period may explain these differences in findings.

Our findings for a reduction in colorectal cancer risk are consistent with randomized trials and observational studies of NSAIDs, which have shown these medications to be chemoprotective for colorectal cancer risk [7, 35–37] and mortality [3, 38]. Evidence for the remaining cancer sites remains inconsistent and in the case of cancers shared between the sexes, few meta-analyses have stratified findings on sex. Nevertheless, our findings for lung cancer agree with those from a recent meta-analyses [39, 40] which reported reductions in lung cancer risk for men but not women. Our finding of a possible reduction of ovarian cancer risk and no association with endometrial cancer risk is also consistent with recent meta-analyses [41, 42]. Contrary to the current findings, meta-analyses have reported that use of NSAIDs are associated with small reductions in breast cancer risk [1, 43]. Our reported inverse association between aspirin use and melanoma risk, in conjunction with a recent report from the WHI-OS [30], is inconsistent with a recent meta-analysis of aspirin use among women [44], which found no association (RR 0.94, 95% CI: 0.72–1.22); however findings for women were not restricted to prospective studies, among which there are few.

This study has several strengths. It is by far the largest to prospectively examine the association between NSAID use and overall cancer risk in women. Follow-up of participants was nearly complete, thereby reducing the likelihood of attrition bias. Unlike most other studies, we were able to examine associations for specific, commonly available NSAID formulations. Lastly, we were able to adjust for a large number of potential confounding factors including correlates of NSAID use. The primary limitations of this study center on the measurement of NSAIDs. In addition to a long follow-up period which allows for participants to begin or cease NSAID use, we had limited data on non-aspirin NSAID dose and no data on the frequency of NSAID use or the number of pills taken per pill-taking event; each contributes to measurement error and may have contributed to the observed null results. Similarly, daily users may have been more likely to recall their use in the prior 2 weeks as compared to transient users, further contributing to error. Nevertheless, we attempted to create a more reliable measure of NSAIDs by combining baseline and year 3 data. The consistency of our findings measured against our previous report [10] and the inverse

associations observed for specific organ sites (e.g., colorectal cancer) provides evidence that our NSAID measurement was valid. Another limitation is that we included a large number of potential confounders for adjustment in multivariable regression models. For rarer cancers, this adjustment may have resulted in less precise estimates of hazard. Lastly, and in light of the reanalysis of the WHS trial data, which reported a protective effect for low-dose aspirin on colorectal cancer risk only after 10 years of follow-up [7], it is possible that the 10-year follow-up period in WHI was too short to observe an association overall or for other specific sites.

Our study confirms a chemopreventive benefit of NSAID use for colorectal cancer in women and gives preliminary evidence for a reduction in the risk of ovarian cancer and melanoma. NSAIDs' benefit on cancer risk was limited to specific sites in women and not evident when total cancer risk was examined. Use of NSAIDs for chemoprevention of colorectal cancer and perhaps other cancers in postmenopausal women warrants further consideration; however this research does not support the use of NSAIDs for overall cancer chemoprevention in postmenopausal women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Impact

The current report confirms that NSAIDs reduce colorectal cancer incidence in postmenopausal women but, importantly, they may not confer an overall cancer chemopreventive benefit. These findings challenge an unsubstantiated belief that NSAID use reduces cancer risk for women.

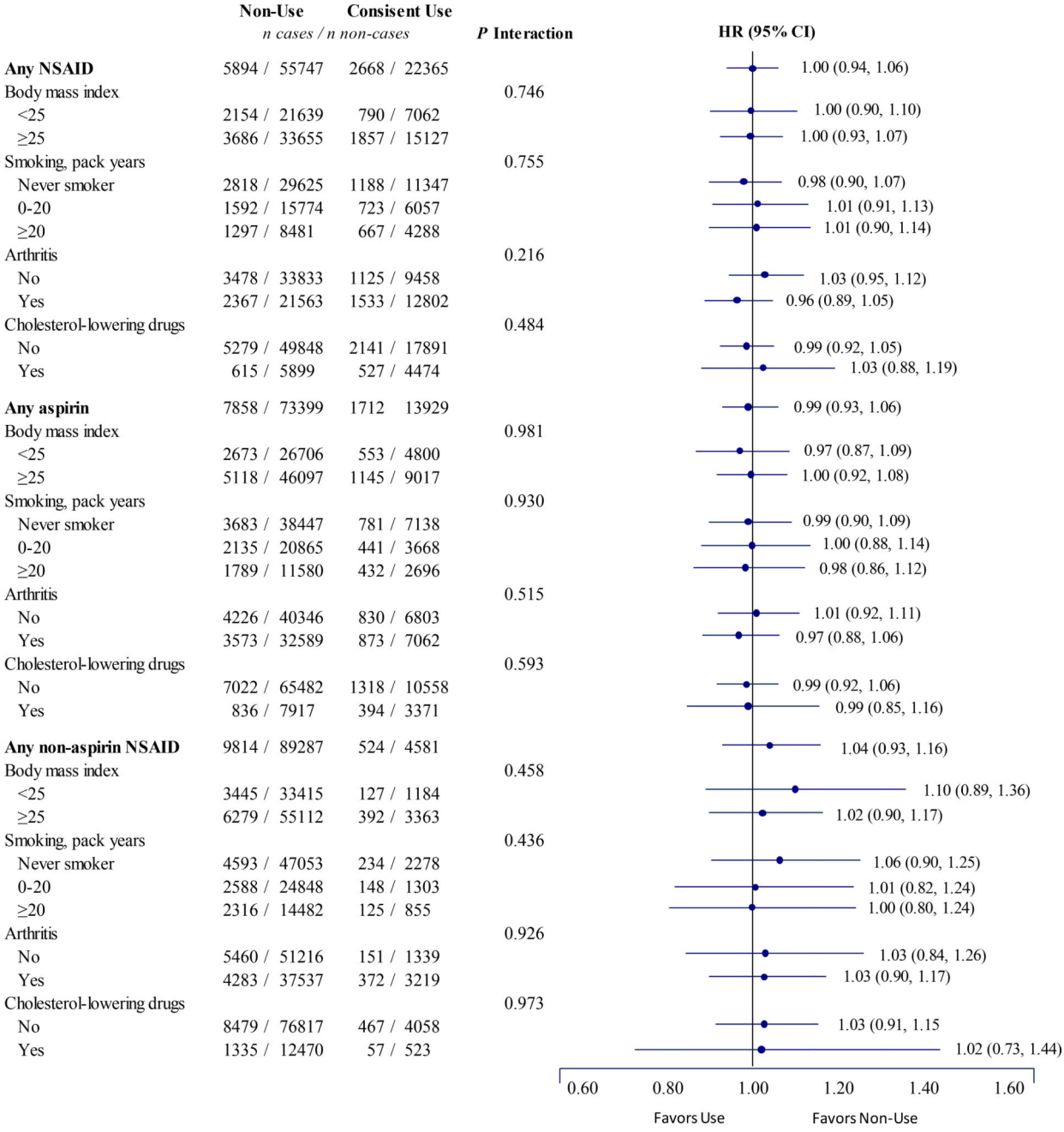

Figure 1.

Associations between NSAID use and invasive cancer risk, stratified on characteristics associated with inflammation, in the Women's Health Initiative observational study and clinical trial, *n*=129,013. Hazard ratios and 95% confidence intervals estimated using Cox proportional hazards regression models and are adjusted for age, observational study enrollment, hormone therapy trial enrollment, diet modification trial enrollment, calcium/vitamin D trial enrollment, US region, education, ethnicity, height, body mass index, physical activity, alcohol consumption, pack-years of smoking, fruit and vegetable consumption, red meat consumption, family histories of: breast cancer, cervical cancer,

endometrial cancer, and colorectal cancer (as separate terms); screening for: breast cancer, colon cancer, and cervical cancer (as separate terms); age at menarche, age at menopause, gravidity, age at 1st birth, duration of estrogen therapy, duration of combined postmenopausal hormone therapy, hysterectomy status, multivitamin use, use of anti-hypertensive medication, history of coronary heart disease, use of cholesterol-lowering medication, history of arthritis, history of migraine, history of ulcer, and other NSAID use. Consistent use is defined as NSAID use at baseline and the third year of follow-up.

Table 1

Associations between participant characteristics and NSAID use in the Women's Health Initiative observational study and clinical trial, n=129,013.

Characteristic	Non-user (*n*=61,641), *n*(%)	Inconsistent NSAID use[a] (*n*=42,339), *n*(%)	Consistent NSAID use (*n*=25,033), *n* (%)[b]
Demographics and anthropometrics			
Age, years			
50–54	9,794 (15.89)	5,426 (12.82)	2,110 (8.43)
55–59	13,995 (22.70)	8,014 (18.93)	4,006 (16.00)
60–64	14,410 (23.38)	9,877 (23.33)	5,935 (23.71)
65–69	12,556 (20.37)	9,420 (22.25)	6,340 (25.33)
70–74	7,824 (12.69)	6,741 (15.92)	4,707 (18.80)
75–79	3,062 (4.97)	2,861 (6.76)	1,935 (7.73)
Enrolled in WHI observational study			
No	29,183 (47.34)	18,619 (43.98)	10,509 (41.98)
Yes	32,458 (52.66)	23,720 (56.02)	14,524 (58.02)
Education			
≤ High school graduate	13,154 (21.51)	9,817 (23.34)	5,547 (22.29)
Some college	22,522 (36.83)	16,187 (38.48)	9,505 (38.20)
College or advanced degree	25,477 (41.66)	16,063 (38.18)	9,831 (39.51)
Ethnicity			
White	49,275 (79.94)	35,667 (84.24)	22,418 (89.55)
Black	5,983 (9.71)	3,673 (8.68)	1,477 (5.90)
Hispanic	2,824 (4.58)	1,524 (3.60)	457 (1.83)
Asian/Pacific Islander	2,395 (3.89)	719 (1.70)	323 (1.29)
Other	1,164 (1.89)	756 (1.79)	358 (1.43)
Height, inches			
<64	33,442 (54.56)	22,992 (54.65)	13,724 (55.11)
64–67.9	25,167 (41.06)	17,271 (41.05)	10,106 (40.58)
68–70.9	2,554 (4.17)	1,697 (4.03)	1,014 (4.07)
≥71	134 (0.22)	114 (0.27)	58 (0.23)
Body mass index, kg/m^2			
<25	23,793 (38.92)	13,551 (32.30)	7,852 (31.62)
25–29.9	21,361 (34.94)	14,516 (34.60)	8,809 (35.47)
≥30	15,980 (26.14)	13,883 (33.09)	8,175 (32.92)
Lifestyle characteristics			
Physical activity, MET-hrs/week			
Inactive	8,948 (15.29)	6,642 (16.45)	3,520 (14.60)
>0–6.8	16,145 (27.60)	11,647 (28.85)	6,832 (28.33)
6.8–16.6	16,019 (27.38)	10,946 (27.11)	6,964 (28.88)
≥16.7	17,394 (29.73)	11,141 (27.59)	6,801 (28.20)
Alcohol consumption, servings/week			

Characteristic	Non-user (*n*=61,641), *n*(%)	Inconsistent NSAID use[a] (*n*=42,339), *n*(%)	Consistent NSAID use (*n*=25,033), *n* (%)[b]
0	25,565 (41.60)	18,054 (42.76)	10,039 (40.18)
>0–0.9	12,686 (20.64)	8,488 (20.10)	4,987 (19.96)
0.9–3.6	11,272 (18.34)	7,472 (17.70)	4,680 (18.73)
≥3.7	11,938 (19.42)	8,210 (19.44)	5,280 (21.13)
Smoking, pack-years			
Never smoker	32,443 (54.45)	21,070 (51.53)	12,535 (51.65)
>0–4.9	8,792 (14.75)	5,940 (14.53)	3,302 (13.61)
5–19.9	8,574 (14.39)	5,871 (14.36)	3,478 (14.33)
≥20	9,778 (16.41)	8,005 (19.58)	4,955 (20.42)
Multivitamin use			
No	39,769 (64.52)	25,107 (59.30)	13,447 (53.72)
Yes	21,872 (35.48)	17,231 (40.70)	11,586 (46.28)
Family medical history			
Family history of breast cancer			
No	48,233 (82.35)	32,673 (81.49)	19,255 (81.24)
Yes	10,335 (17.65)	7,423 (18.51)	4,447 (18.76)
Family history of cervical cancer			
No	55,594 (96.13)	37,786 (95.61)	22,387 (95.82)
Yes	2,239 (3.87)	1,736 (4.39)	976 (4.18)
Family history of endometrial cancer			
No	54,587 (94.51)	37,160 (94.10)	21,953 (93.78)
Yes	3,172 (5.49)	2,331 (5.90)	1,457 (6.22)
Family history of ovarian cancer			
No	56,131 (97.63)	38,344 (97.58)	22,582 (97.25)
Yes	1,362 (2.37)	952 (2.42)	638 (2.75)
Family history of colorectal cancer			
No	47,491 (83.83)	32,318 (83.50)	19,068 (83.34)
Yes	9,159 (16.17)	6,387 (16.50)	3,813 (16.66)
Family history of prostate cancer			
No	52,130 (90.05)	35,662 (90.16)	21,011 (89.60)
Yes	5,757 (9.95)	3,891 (9.84)	2,438 (10.40)
Medications/medical history			
Duration of unopposed estrogen therapy, years			
<4	48,476 (78.64)	31,497 (74.39)	18,215 (72.76)
4–12	7,262 (11.78)	5,466 (12.91)	3,352 (13.39)
≥12	5,903 (9.58)	5,375 (12.70)	3,466 (13.85)
Duration of combined hormone therapy, years			
<2.5	50,849 (82.49)	34,758 (82.09)	20,184 (80.63)
2.5–7	5,847 (9.49)	3,814 (9.01)	2,331 (9.31)
≥8	4,944 (8.02)	3,767 (8.90)	2,517 (10.06)
Hysterectomy status			

Characteristic	Non-user (*n*=61,641), *n*(%)	Inconsistent NSAID use[a] (*n*=42,339), *n*(%)	Consistent NSAID use (*n*=25,033), *n* (%)[b]
No	38,348 (62.24)	24,386 (57.63)	14,464 (57.81)
Yes	23,267 (37.76)	17,931 (42.37)	10,554 (42.19)
Breast cancer screening			
No	2,386 (3.89)	1,417 (3.36)	591 (2.37)
Yes	58,910 (96.11)	40,733 (96.64)	24,353 (97.63)
Cervical cancer screening			
No	815 (1.43)	511 (1.30)	239 (1.02)
Yes	56,043 (98.57)	38,669 (98.70)	23,254 (98.98)
Colon cancer screening			
No	30,025 (51.43)	19,288 (47.90)	10,571 (43.94)
Yes	28,360 (48.57)	20,977 (52.10)	13,487 (56.06)
History of hypertension			
No	44,355 (72.30)	26,696 (63.43)	14,600 (58.64)
Yes	16,997 (27.70)	15,389 (36.57)	10,297 (41.36)
Use of anti-hypertensive medications			
No	44,443 (72.10)	26,125 (61.70)	13,735 (54.87)
Yes	17,198 (27.90)	16,214 (38.30)	11,298 (45.13)
History of coronary heart disease			
No	61,021 (99.03)	41,252 (97.46)	23,880 (95.47)
Yes	596 (0.97)	1,075 (2.54)	1,134 (4.53)
Use of cholesterol-lowering medications			
No	55,127 (89.43)	35,961 (84.94)	20,032 (80.02)
Yes	6,514 (10.57)	6,378 (15.06)	5,001 (19.98)
History of arthritis			
No	37,311 (62.26)	20,017 (48.92)	10,583 (43.52)
Rheumatoid	2,305 (3.85)	2,306 (5.64)	1,412 (5.81)
Osteoarthritis or other	20,307 (33.89)	18,595 (45.44)	12,324 (50.68)
History of migraine headaches			
No	51,825 (89.75)	35,186 (88.08)	21,013 (87.85)
Yes	5,921 (10.25)	4,760 (11.92)	2,906 (12.15)
History of gastric ulcer			
No	56,875 (93.50)	39,214 (93.61)	23,477 (94.57)
Yes	3,956 (6.50)	2,676 (6.39)	1,349 (5.43)

Abbreviations: NSAID, non-steroidal anti-inflammatory drug

[a] Inconsistent NSAID use is defined as use at baseline or the third year of follow-up.

[b] Consistent NSAID use is defined as NSAID use at baseline and at the third year of follow-up.

Table 2

Associations between NSAID use and invasive cancer risk in the Women's Health Initiative observational study and clinical trial, n=129,013.

NSAID	Cancer cases (n=12,998), n	Non-cases (n=116,015), n	Age & NSAID adjusted HR (95% CI)[a]	Multivariable-adjusted HR (95% CI)[b]
Any NSAID				
Non-user	5,894	55,747	1.00 reference	1.00 reference
Inconsistent use	4,436	37,903	1.11 (1.07–1.15)	1.07 (1.02–1.13)
Consistent use[c]	2,668	22,365	1.02 (0.97–1.07)	1.00 (0.94–1.06)
Duration among consistent users[d]				
<5y	1,612	13,670	1.00 (0.95–1.06)	0.99 (0.93–1.06)
≥5y	1,056	8,695	1.02 (0.96–1.09)	0.99 (0.91–1.08)
P trend[e]				0.822
Any aspirin				
Non-user	7,858	73,399	1.00 reference	1.00 reference
Inconsistent use	3,158	26,633	0.97 (0.93–1.01)	0.94 (0.89–0.99)
Consistent use[c]	1,712	13,929	0.99 (0.94–1.04)	0.99 (0.93–1.06)
Duration among consistent users[d]				
<5y	1,045	8,655	0.98 (0.92–1.05)	1.00 (0.92–1.08)
≥5y	667	5,274	1.00 (0.93–1.09)	0.98 (0.89–1.08)
P trend[e]				0.712
Low-dose aspirin (≤100mg)				
Non-user	10,657	97,012	1.00 reference	1.00 reference
Inconsistent use	1,278	11,146	0.93 (0.88–0.99)	0.92 (0.85–0.99)
Consistent use[c]	399	3,327	0.96 (0.87–1.06)	1.02 (0.90–1.14)
Duration among consistent users[d]				
<5y	321	2,604	0.99 (0.89–1.11)	1.05 (0.92–1.20)
≥5y	78	723	0.85 (0.68–1.06)	0.85 (0.65–1.11)
P trend[e]				0.754
Regular-strength aspirin (>100mg)				
Non-user	9,125	84,740	1.00 reference	1.00 reference
Inconsistent use	2,452	20,369	0.99 (0.95–1.04)	0.96 (0.90–1.02)
Consistent use[c]	1,027	8,161	1.02 (0.95–1.08)	1.01 (0.93–1.09)
Duration among consistent users[d]				
<5y	531	4,418	0.99 (0.91–1.08)	1.00 (0.89–1.11)
≥5y	496	3,743	1.06 (0.97–1.17)	1.05 (0.94–1.18)
P trend[e]				0.453
Any non-aspirin NSAID				
Non-user	9,814	89,287	1.00 reference	1.00 reference
Inconsistent use	2,142	18,980	1.04 (0.99–1.10)	1.03 (0.97–1.10)

NSAID	Cancer cases (*n*=12,998), *n*	Non-cases (*n*=116,015), *n*	Age & NSAID adjusted HR (95% CI)[a]	Multivariable-adjusted HR (95% CI)[b]
Consistent use[c]	524	4,581	1.06 (0.97–1.16)	1.04 (0.93–1.16)
Duration among consistent users[d]				
<5y	351	2,897	1.12 (1.01–1.25)	1.09 (0.96–1.25)
≥5y	173	1,684	0.96 (0.83–1.12)	0.94 (0.79–1.13)
P trend[e]				0.897
Ibuprofen				
Non-user	10,236	93,714	1.00 reference	1.00 reference
Inconsistent use	1,791	15,126	1.08 (1.03–1.14)	1.05 (0.98–1.12)
Consistent use[c]	424	3,646	1.08 (0.98–1.19)	1.07 (0.95–1.20)
Duration among consistent users[d]				
<5y	268	2,143	1.15 (1.02–1.30)	1.15 (0.99–1.33)
≥5y	156	1,503	0.98 (0.83–1.14)	0.96 (0.79–1.16)
P trend[e]				0.585
Naproxen				
Non-user	11,459	104,137	1.00 reference	1.00 reference
Inconsistent use	716	6,347	1.13 (1.01–1.27)	1.18 (1.03–1.37)
Consistent use[c]	115	955	1.09 (0.85–1.41)	1.22 (0.89–1.65)
Duration among consistent users[d]				
<5y	77	699	1.00 (0.80–1.25)	0.98 (0.75–1.27)
≥5y	38	256	1.26 (0.91–1.73)	1.45 (1.02–2.06)
P trend[e]				0.134

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; HR, hazard ratio; CI, confidence interval

[a]Analyses of individual NSAIDs, low-dose or regular-strength aspirin, ibuprofen, or naproxen are mutually adjusted for in regression models. Total aspirin is adjusted for individual non-aspirin NSAIDs, and total non-aspirin NSAIDs are adjusted for low-dose and regular-strength aspirin. Analyses of 'any NSAID' are age-adjusted only

[b]Adjusted for age, observational study enrollment, hormone therapy trial enrollment, diet modification trial enrollment, calcium/vitamin D trial enrollment, US region, education, ethnicity, height, body mass index, physical activity, alcohol consumption, pack-years of smoking, fruit and vegetable consumption, red meat consumption, family histories of: breast cancer, cervical cancer, endometrial cancer, and colorectal cancer (as separate terms); screening for: breast cancer, colon cancer, and cervical cancer (as separate terms); age at menarche, age at menopause, gravidity, age at 1st birth, duration of estrogen therapy, duration of combined postmenopausal hormone therapy, hysterectomy status, multivitamin use, use of anti-hypertensive medication, history of coronary heart disease, use of cholesterol-lowering medication, history of arthritis, history of migraine, history of ulcer, and other NSAID use

[c]Consistent use is defined as NSAID use at baseline and at the third year of follow-up

[d]Duration of use reported at baseline, restricted to analyses of non- and consistent users

[e]*P* trend is calculated across 3 categories: non-use, <5yrs use among consistent users, and ≥5yrs use among consistent users

Table 3

Associations between NSAID use and risk of individual invasive cancers in the Women's Health Initiative observational study and clinical trial.

	Non-user	Inconsistent use	Consistent use[c,d]			
			Overall	<5y	≥5y	*P* trend[e]
Gastrointestinal cancers (*n*=1,876)						
Any NSAID						
Cases / non-cases	866 / 60,775	676 / 41,663	334 / 24,699	206 / 1,507	128 / 9,623	
HR (95% CI)[a]	1.00 reference	1.13 (1.02–1.24)	0.83 (0.73–0.94)	0.84 (0.72–0.97)	0.80 (0.66–0.96)	0.003
HR (95% CI)[b]	1.00 reference	1.08 (0.95–1.23)	0.82 (0.69–0.96)	0.84 (0.69–1.02)	0.78 (0.62–0.99)	0.016
Any aspirin						
Cases / non-cases	1,139 / 80,118	463 / 29,328	208 / 15,433	126 / 9,574	82 / 5,859	
HR (95% CI)[a]	1.00 reference	0.90 (0.80–1.01)	0.77 (0.66–0.89)	0.76 (0.63–0.91)	0.79 (0.63–0.99)	0.002
HR (95% CI)[b]	1.00 reference	0.88 (0.76–1.02)	0.73 (0.61–0.89)	0.76 (0.61–0.96)	0.73 (0.54–0.97)	0.004
Any non-aspirin NSAIDs						
Cases / non-cases	1,377 / 97,724	351 / 20,771	57 / 5,048	42 / 3,206	15 / 1,842	
HR (95% CI)[a]	1.00 reference	1.11 (0.97–1.26)	0.79 (0.60–1.03)	0.93 (0.68–1.27)	0.57 (0.34–0.95)	0.044
HR (95% CI)[b]	1.00 reference	1.15 (0.97–1.35)	0.87 (0.63–1.20)	1.01 (0.70–1.46)	0.63 (0.35–1.15)	0.231
Colorectal cancer (*n*=1,287)						
Any NSAID						
Cases / non-cases	611 / 61,030	447 / 41,892	229 / 24,804	145 / 15,137	84 / 9,667	
HR (95% CI)[a]	1.00 reference	1.06 (0.94–1.20)	0.81 (0.70–0.95)	0.85 (0.71–1.02)	0.76 (0.60–0.95)	0.006
HR (95% CI)[b]	1.00 reference	1.00 (0.86–1.17)	0.78 (0.64–0.95)	0.84 (0.67–1.06)	0.74 (0.55–0.99)	0.023
Any aspirin						
Cases / non-cases	810 / 80,447	299 / 29,492	144 / 15,497	90 / 9,610	54 / 5,887	
HR (95% CI)[a]	1.00 reference	0.85 (0.74–0.99)	0.76 (0.64–0.91)	0.78 (0.63–0.97)	0.75 (0.57–0.99)	0.006
HR (95% CI)[b]	1.00 reference	0.83 (0.69–0.99)	0.71 (0.56–0.89)	0.75 (0.57–1.00)	0.69 (0.48–0.99)	0.010
Any non-aspirin NSAIDs						
Cases / non-cases	959 / 98,142	238 / 20,884	40 / 5,065	31 / 3,217	9 / 1,848	
HR (95% CI)[a]	1.00 reference	1.13 (0.97–1.31)	0.78 (0.57–1.08)	0.98 (0.69–1.41)	0.49 (0.25–0.95)	0.068

	Non-user	Inconsistent use	Consistent use[c,d]			*P* trend[e]
			Overall	<5y	≥5y	
HR (95% CI)[b]	1.00 reference	1.19 (0.98–1.44)	0.79 (0.53–1.19)	1.00 (0.63–1.56)	0.51 (0.23–1.14)	0.169
Pancreatic cancer (*n*=378)						
Any NSAID						
Cases / non-cases	160 / 61,481	151 / 42,188	67 / 24,966	40 / 15,242	27 / 9,724	
HR (95% CI)[a]	1.00 reference	1.34 (1.07–1.67)	0.87 (0.65–1.16)	0.84 (0.59–1.19)	0.86 (0.57–1.30)	0.324
HR (95% CI)[b]	1.00 reference	1.29 (0.97–1.70)	0.82 (0.57–1.17)	0.81 (0.53–1.24)	0.71 (0.42–1.21)	0.155
Any aspirin						
Cases / non-cases	211 / 81,046	108 / 29,683	39 / 15,602	23 / 9,677	16 / 5,925	
HR (95% CI)[a]	1.00 reference	0.97 (0.74–1.25)	0.74 (0.52–1.04)	0.71 (0.46–1.09)	0.78 (0.47–1.29)	0.114
HR (95% CI)[b]	1.00 reference	0.88 (0.64–1.23)	0.69 (0.45–1.06)	0.74 (0.44–1.24)	0.58 (0.29–1.15)	0.063
Any non-aspirin NSAIDs						
Cases / non-cases	259 / 98,842	77 / 21,045	11 / 5,094	7 / 3,241	4 / 1,853	
HR (95% CI)[a]	1.00 reference	1.20 (0.90–1.61)	0.83 (0.45–1.53)	0.83 (0.39–1.77)	0.81 (0.30–2.19)	0.582
HR (95% CI)[b]	1.00 reference	1.20 (0.83–1.72)	0.92 (0.46–1.83)	0.93 (0.41–2.12)	0.80 (0.25–2.53)	0.686
Urinary tract cancers (*n*=449)						
Any NSAIDs						
Cases / non-cases	204 / 61,437	153 / 42,186	92 / 24,941	54 / 15,228	38 / 9,713	
HR (95% CI)[a]	1.00 reference	1.09 (0.88–1.34)	0.98 (0.76–1.25)	0.93 (0.69–1.26)	1.01 (0.71–1.43)	0.888
HR (95% CI)[b]	1.00 reference	1.10 (0.84–1.43)	0.91 (0.66–1.25)	0.75 (0.50–1.12)	1.07 (0.70–1.63)	0.853
Any aspirin						
Cases / non-cases	269 / 80,988	111 / 29,680	62 / 15,579	35 / 9,665	27 / 5,914	
HR (95% CI)[a]	1.00 reference	1.07 (0.85–1.34)	0.99 (0.75–1.31)	0.89 (0.63–1.27)	1.10 (0.74–1.64)	0.898
HR (95% CI)[b]	1.00 reference	1.12 (0.85–1.49)	0.96 (0.68–1.37)	0.71 (0.44–1.16)	1.29 (0.82–2.05)	0.703
Any non-aspirin NSAIDs						
Cases / non-cases	352 / 98,749	74 / 21,048	14 / 5,091	9 / 3,239	5 / 1,852	
HR (95% CI)[a]	1.00 reference	1.07 (0.82–1.39)	0.80 (0.47–1.38)	0.81 (0.42–1.58)	0.78 (0.32–1.89)	0.455
HR (95% CI)[b]	1.00 reference	0.93 (0.66–1.31)	0.78 (0.41–1.48)	0.89 (0.42–1.91)	0.63 (0.20–1.98)	0.463
Kidney cancer (*n*=292)						

	Non-user	Inconsistent use	Consistent use[c,d]			*P* trend[e]
			Overall	<5y	≥5y	
Any NSAIDs						
Cases / non-cases	134 / 61,507	93 / 42,246	65 / 24,968	38 / 15,244	27 / 9,724	
HR (95% CI)[a]	1.00 reference	1.02 (0.78–1.33)	1.08 (0.80–1.45)	1.02 (0.71–1.46)	1.12 (0.74–1.69)	0.634
HR (95% CI)[b]	1.00 reference	1.03 (0.74–1.44)	0.86 (0.58–1.29)	0.62 (0.36–1.06)	1.15 (0.70–1.89)	0.942
Any aspirin						
Cases / non-cases	176 / 81,081	71 / 29,720	41 / 15,600	23 / 9,677	18 / 5,923	
HR (95% CI)[a]	1.00 reference	1.06 (0.80–1.41)	1.04 (0.74–1.47)	0.92 (0.60–1.43)	1.16 (0.71–1.89)	0.720
HR (95% CI)[b]	1.00 reference	1.08 (0.76–1.53)	0.89 (0.57–1.39)	0.57 (0.29–1.10)	1.34 (0.77–2.34)	0.854
Any non-aspirin NSAIDs						
Cases / non-cases	224 / 98,877	54 / 21,068	8 / 5,097	5 / 3,243	3 / 1,854	
HR (95% CI)[a]	1.00 reference	1.26 (0.92–1.72)	0.72 (0.35–1.47)	0.70 (0.29–1.71)	0.73 (0.23–2.29)	0.407
HR (95% CI)[b]	1.00 reference	1.08 (0.72–1.61)	0.56 (0.23–1.40)	0.55 (0.17–1.76)	0.62 (0.15–2.54)	0.318
Bladder cancer (*n*=157)						
Any NSAID						
Cases / non-cases	70 / 61,571	60 / 42,279	27 / 25,006	16 / 15,266	11 / 9,740	
HR (95% CI)[a]	1.00 reference	1.21 (0.86–1.71)	0.80 (0.51–1.24)	0.77 (0.45–1.33)	0.81 (0.43–1.54)	0.360
HR (95% CI)[b]	1.00 reference	1.23 (0.79–1.91)	0.99 (0.58–1.69)	1.00 (0.53–1.89)	0.92 (0.42–2.01)	0.859
Any aspirin						
Cases / non-cases	93 / 81,164	40 / 29,751	21 / 15,620	12 / 9,688	9 / 5,932	
HR (95% CI)[a]	1.00 reference	1.08 (0.74–1.58)	0.91 (0.57–1.47)	0.84 (0.46–1.53)	0.99 (0.50–1.97)	0.788
HR (95% CI)[b]	1.00 reference	1.22 (0.76–1.94)	1.12 (0.63–1.98)	1.01 (0.49–2.07)	1.24 (0.55–2.77)	0.665
Any non-aspirin NSAIDs						
Cases / non-cases	128 / 98,973	20 / 21,102	6 / 5,099	4 / 3,244	2 / 1,855	
HR (95% CI)[a]	1.00 reference	0.74 (0.44–1.24)	0.95 (0.41–2.18)	1.00 (0.37–2.73)	0.87 (0.21–3.51)	0.886
HR (95% CI)[b]	1.00 reference	0.61 (0.30–1.23)	1.20 (0.47–3.06)	1.55 (0.56–4.34)	0.63 (0.09–4.56)	0.318
Lung cancer (*n*=1,417)						
Any NSAID						
Cases / non-cases	569 / 61,072	553 / 41,786	295 / 24,738	185 / 15,097	110 / 9,641	

Int J Cancer. Author manuscript; available in PMC 2017 September 10.

	Non-user	Inconsistent use	Consistent use[c,d]			*P* trend[e]
			Overall	<5y	≥5y	
HR (95% CI)[a]	1.00 reference	1.40 (1.25–1.58)	1.12 (0.97–1.28)	1.14 (0.97–1.35)	1.05 (0.85–1.29)	0.324
HR (95% CI)[b]	1.00 reference	1.27 (1.09–1.48)	1.02 (0.85–1.22)	1.13 (0.92–1.40)	0.91 (0.70–1.18)	0.822
Any aspirin						
Cases / non-cases	777 / 80,480	407 / 29,384	199 / 15,422	127 / 9,573	72 / 5,869	
HR (95% CI)[a]	1.00 reference	1.09 (0.95–1.24)	1.09 (0.93–1.27)	1.14 (0.94–1.37)	1.03 (0.81–1.31)	0.430
HR (95% CI)[b]	1.00 reference	0.97 (0.82–1.16)	1.05 (0.86–1.28)	1.19 (0.94–1.50)	0.89 (0.65–1.22)	0.995
Any non-aspirin NSAIDs						
Cases / non-cases	1,030 / 9,807	234 / 20,888	52 / 5,053	37 / 3,211	15 / 1,842	
HR (95% CI)[a]	1.00 reference	1.10 (0.94–1.28)	1.07 (0.81–1.42)	1.19 (0.85–1.65)	0.83 (0.50–1.39)	0.940
HR (95% CI)[b]	1.00 reference	1.07 (0.88–1.30)	1.01 (0.70–1.45)	1.20 (0.79–1.82)	0.68 (0.35–1.33)	0.536
Breast and reproductive cancers (*n*=6,020)						
Any NSAID						
Cases / non-cases	2,796 / 58,845	1,973 / 40,366	1,251 / 23,782	764 / 14,518	487 / 9,264	
HR (95% CI)[a]	1.00 reference	1.06 (1.00–1.12)	1.05 (0.98–1.12)	1.04 (0.96–1.13)	1.03 (0.94–1.14)	0.324
HR (95% CI)[b]	1.00 reference	1.05 (0.97–1.12)	1.05 (0.97–1.14)	1.03 (0.93–1.14)	1.04 (0.92–1.17)	0.445
Any aspirin						
Cases / non-cases	3,723 / 77,534	1,403 / 28,388	802 / 14,839	505 / 9,195	297 / 5,644	
HR (95% CI)[a]	1.00 reference	0.98 (0.92–1.05)	1.04 (0.96–1.12)	1.06 (0.97–1.16)	1.01 (0.89–1.13)	0.509
HR (95% CI)[b]	1.00 reference	0.97 (0.89–1.05)	1.07 (0.97–1.17)	1.10 (0.98–1.23)	1.01 (0.87–1.16)	0.448
Any non-aspirin NSAIDs						
Cases / non-cases	4,632 / 94,469	964 / 20,158	252 / 4,853	168 / 3,080	84 / 1,773	
HR (95% CI)[a]	1.00 reference	1.02 (0.95–1.10)	1.07 (0.94–1.22)	1.13 (0.97–1.32)	0.98 (0.79–1.22)	0.544
HR (95% CI)[b]	1.00 reference	1.02 (0.93–1.11)	1.03 (0.88–1.20)	1.06 (0.87–1.28)	0.94 (0.73–1.23)	0.901
Breast cancer (*n*=4,815)						
Any NSAID						
Cases / non-cases	2,231 / 59,410	1,577 / 40,762	1,007 / 24,026	610 / 14,672	397 / 9,354	
HR (95% CI)[a]	1.00 reference	1.06 (1.00–1.13)	1.06 (0.98–1.14)	1.04 (0.95–1.14)	1.06 (0.95–1.18)	0.203

Int J Cancer. Author manuscript; available in PMC 2017 September 10.

	Non-user	Inconsistent use	Consistent use[c,d]			P trend[e]
			Overall	<5y	≥5y	
HR (95% CI)[b]	1.00 reference	1.07 (0.99–1.16)	1.07 (0.98–1.18)	1.06 (0.95–1.19)	1.07 (0.94–1.22)	0.213
Any aspirin						
Cases / non-cases	2,969 / 78,288	1,118 / 28,673	657 / 14,984	413 / 9,287	244 / 5,697	
HR (95% CI)[a]	1.00 reference	1.00 (0.93–1.07)	1.07 (0.98–1.16)	1.09 (0.98–1.21)	1.04 (0.91–1.18)	0.230
HR (95% CI)[b]	1.00 reference	0.99 (0.91–1.09)	1.11 (1.00–1.24)	1.15 (1.01–1.30)	1.05 (0.89–1.23)	0.162
Any non-aspirin NSAIDs						
Cases / non-cases	3,721 / 95,380	779 / 20,343	190 / 4,915	124 / 3,124	66 / 1,791	
HR (95% CI)[a]	1.00 reference	1.03 (0.95–1.12)	1.02 (0.88–1.18)	1.04 (0.87–1.25)	0.96 (0.75–1.23)	0.940
HR (95% CI)[b]	1.00 reference	1.05 (0.94–1.16)	0.97 (0.81–1.17)	0.99 (0.79–1.24)	0.89 (0.66–1.21)	0.466
Ovarian cancer (*n*=414)						
Any NSAID						
Cases / non-cases	191 / 50,797	152 / 33,998	71 / 20,150	53 / 12,283	18 / 7,867	
HR (95% CI)[a]	1.00 reference	1.22 (0.98–1.51)	0.88 (0.67–1.15)	1.07 (0.79–1.46)	0.57 (0.35–0.92)	0.082
HR (95% CI)[b]	1.00 reference	1.13 (0.87–1.46)	0.80 (0.57–1.12)	0.90 (0.62–1.32)	0.54 (0.32–0.94)	0.038
Any aspirin						
Cases / non-cases	251 / 66,438	108 / 24,015	43 / 12,675	35 / 7,851	8 / 4,824	
HR (95% CI)[a]	1.00 reference	0.94 (0.73–1.21)	0.80 (0.58–1.11)	1.08 (0.76–1.54)	0.40 (0.20–0.81)	0.047
HR (95% CI)[b]	1.00 reference	0.92 (0.68–1.24)	0.74 (0.50–1.10)	0.99 (0.64–1.54)	0.37 (0.16–0.84)	0.038
Any non-aspirin NSAIDs						
Cases / non-cases	304 / 81,164	66 / 16,879	17 / 4,027	12 / 2,562	5 / 1,465	
HR (95% CI)[a]	1.00 reference	0.96 (0.71–1.28)	1.09 (0.67–1.79)	1.27 (0.71–2.27)	0.93 (0.38–2.25)	0.797
HR (95% CI)[b]	1.00 reference	0.88 (0.62–1.26)	0.99 (0.56–1.76)	1.03 (0.50–2.10)	1.05 (0.43–2.57)	0.950
Endometrial cancer (*n*=774)						
Any NSAID						
Cases / non-cases	362 / 38,012	243 / 24,165	169 / 14,310	97 / 8,790	72 / 5,520	
HR (95% CI)[a]	1.00 reference	1.08 (0.92–1.28)	1.18 (0.98–1.41)	1.08 (0.86–1.35)	1.27 (0.99–1.64)	0.067
HR (95% CI)[b]	1.00 reference	0.90 (0.73–1.11)	1.08 (0.86–1.35)	0.92 (0.69–1.22)	1.19 (0.88–1.61)	0.449
Any aspirin						

Int J Cancer. Author manuscript; available in PMC 2017 September 10.

	Non-user	Inconsistent use	Consistent use[c,d]			P trend[e]
			Overall	<5y	≥5y	
Cases / non-cases	488 / 48,788	177 / 17,232	100 / 9,233	55 / 5,784	45 / 3,449	
HR (95% CI)[a]	1.00 reference	0.98 (0.82–1.18)	1.01 (0.81–1.25)	0.89 (0.68–1.18)	1.20 (0.89–1.64)	0.533
HR (95% CI)[b]	1.00 reference	0.90 (0.71–1.13)	1.01 (0.77–1.31)	0.86 (0.61–1.21)	1.17 (0.81–1.69)	0.727
Any non-aspirin NSAIDs						
Cases / non-cases	593 / 60,104	118 / 11,679	43 / 2,704	30 / 1,716	13 / 988	
HR (95% CI)[a]	1.00 reference	1.09 (0.89–1.34)	1.62 (1.19–2.23)	1.77 (1.23–2.57)	1.32 (0.76–2.29)	0.014
HR (95% CI)[b]	1.00 reference	0.94 (0.72–1.22)	1.32 (0.89–1.96)	1.36 (0.85–2.18)	1.21 (0.64–2.29)	0.228
Thyroid (*n*=208)						
Any NSAID						
Cases / non-cases	105 / 61,536	62 / 42,277	41 / 24,992	20 / 15,262	21 / 9,730	
HR (95% CI)[a]	1.00 reference	0.89 (0.65–1.23)	0.93 (0.65–1.34)	0.75 (0.46–1.21)	1.23 (0.77–1.97)	0.774
HR (95% CI)[b]	1.00 reference	1.01 (0.69–1.47)	1.03 (0.66–1.61)	0.81 (0.45–1.46)	1.45 (0.81–2.59)	0.413
Any aspirin						
Cases / non-cases	134 / 81,123	43 / 29,748	26 / 15,615	15 / 9,685	11 / 5,930	
HR (95% CI)[a]	1.00 reference	0.89 (0.62–1.27)	0.96 (0.63–1.47)	0.90 (0.52–1.53)	1.06 (0.57–1.96)	0.968
HR (95% CI)[b]	1.00 reference	0.92 (0.60–1.41)	0.90 (0.53–1.53)	0.76 (0.38–1.53)	1.20 (0.58–2.51)	0.956
Any non-aspirin NSAIDs						
Cases / non-cases	166 / 98,935	27 / 21,095	11 / 5,094	5 / 3,243	6 / 1,851	
HR (95% CI)[a]	1.00 reference	0.70 (0.44–1.09)	1.25 (0.67–2.32)	0.90 (0.37–2.19)	1.87 (0.83–4.25)	0.245
HR (95% CI)[b]	1.00 reference	0.86 (0.51–1.45)	1.61 (0.79–3.26)	1.32 (0.53–3.29)	1.96 (0.71–5.40)	0.149
Melanoma (*n*=531)						
Any NSAID						
Cases / non-cases	248 / 61,393	176 / 42,163	107 / 24,926	66 / 15,216	41 / 9,710	
HR (95% CI)[a]	1.00 reference	1.06 (0.87–1.29)	0.99 (0.79–1.25)	0.99 (0.76–1.31)	0.96 (0.69–1.34)	0.835
HR (95% CI)[b]	1.00 reference	0.96 (0.75–1.22)	0.83 (0.62–1.12)	0.86 (0.61–1.23)	0.76 (0.49–1.18)	0.173
Any aspirin						
Cases / non-cases	347 / 80,910	116 / 29,675	61 / 15,580	37 / 9,663	24 / 5,917	
HR (95% CI)[a]	1.00 reference	0.84 (0.67–1.05)	0.83 (0.63–1.09)	0.81 (0.58–1.14)	0.84 (0.55–1.27)	0.197

Int J Cancer. Author manuscript; available in PMC 2017 September 10.

	Non-user	Inconsistent use	Consistent use[c,d]			*P* trend[e]
			Overall	<5y	≥5y	
HR (95% CI)[b]	1.00 reference	0.71 (0.53–0.95)	0.66 (0.46–0.95)	0.63 (0.40–1.00)	0.69 (0.40–1.20)	0.043
Any non-aspirin NSAIDs						
Cases / non-cases	387 / 98,714	104 / 21,018	24 / 5,081	16 / 3,232	8 / 1,849	
HR (95% CI)[a]	1.00 reference	1.34 (1.07–1.68)	1.16 (0.76–1.76)	1.24 (0.75–2.05)	1.98 (0.53–2.18)	0.524
HR (95% CI)[b]	1.00 reference	1.24 (0.92–1.67)	1.18 (0.71–1.96)	1.28 (0.69–2.38)	1.15 (0.51–2.60)	0.492
Hematologic malignancies (*n*=1,354)						
Any NSAID						
Cases / non-cases	602 / 61,039	449 / 41,890	303 / 24,730	179 / 15,103	124 / 9,627	
HR (95% CI)[a]	1.00 reference	1.08 (0.96–1.22)	1.09 (0.95–1.25)	1.05 (0.89–1.25)	1.13 (0.93–1.37)	0.204
HR (95% CI)[b]	1.00 reference	1.04 (0.89–1.20)	1.03 (0.86–1.22)	1.02 (0.83–1.25)	0.99 (0.78–1.27)	0.997
Any aspirin						
Cases / non-cases	799 / 80,458	345 / 29,446	187 / 15,454	109 / 9,591	78 / 5,863	
HR (95% CI)[a]	1.00 reference	1.01 (0.88–1.16)	1.01 (0.86–1.19)	0.95 (0.78–1.16)	1.08 (0.86–1.37)	0.723
HR (95% CI)[b]	1.00 reference	0.99 (0.84–1.17)	1.00 (0.82–1.22)	0.97 (0.76–1.23)	1.00 (0.75–1.34)	0.918
Any non-aspirin NSAIDs						
Cases / non-cases	1,027 / 98,074	206 / 20,916	65 / 5,040	45 / 3,203	20 / 1,837	
HR (95% CI)[a]	1.00 reference	1.00 (0.85–1.17)	1.29 (1.00–1.66)	1.43 (1.06–1.93)	1.10 (0.70–1.71)	0.109
HR (95% CI)[b]	1.00 reference	0.94 (0.77–1.14)	1.17 (0.86–1.60)	1.24 (0.85–1.80)	1.11 (0.66–1.90)	0.426

[a] Adjusted for age and other NSAID use

[b] Adjusted for age, observational study enrollment, hormone therapy trial enrollment, diet modification trial enrollment, calcium/vitamin D trial enrollment, US region, education, ethnicity, height, body mass index, physical activity, alcohol consumption, pack-years of smoking, fruit and vegetable consumption, red meat consumption, family histories of: breast cancer, cervical cancer, endometrial cancer, and colorectal cancer (as separate terms); screening for: breast cancer, colon cancer, and cervical cancer (as separate terms); age at menarche, age at menopause, gravidity, age at 1st birth, duration of estrogen therapy, duration of combined postmenopausal hormone therapy, hysterectomy status, multivitamin use, use of anti-hypertensive medication, history of coronary heart disease, use of cholesterol-lowering medication, history of arthritis, history of migraine, history of ulcer, and other NSAID use

[c] Consistent use is defined as NSAID use at baseline and at the third year of follow-up

[d] Duration of use reported at baseline, restricted to analyses of non- and consistent users

[e] *P* trend is calculated across 3 categories: non-use, <5yrs use among consistent users, and ≥5yrs use among consistent users