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Non-steroidal Anti-inflammatory Drugs and Cancer Incidence by Sex in the VITamins And Lifestyle (VITAL) Cohort

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Abstract

Use of NSAIDs may reduce the risk of several cancers. A recent meta-analysis of randomized trials of aspirin reported a reduction in cancer mortality; however few studies have investigated whether aspirin or other NSAIDs reduce overall cancer risk. 64,847 residents of western Washington State, ages 50-76 years, completed a baseline questionnaire in 2000-2002 and reported on their use of individual NSAIDs over the past 10 years. Behavior was categorized as non-use, low (<4 days/week or <4 years), and high (≥4 days/week and ≥4 years). Over 7 years of follow-up 5,946 incident invasive cancer cases were identified. Multivariable proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). Relative to non-use, high 10-year use of regular-strength NSAIDs was inversely associated with total cancer risk in men (HR 0.88, 95% CI: 0.79-0.97) and suggestive of a positive association in women (HR 1.10, 95% CI: 0.96-1.25; *P* interaction <0. 01). Use of regular-strength NSAIDs was strongly and inversely associated with colorectal cancer risk in men and women, but differentially associated

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with sex-specific risk of shared cancer sites other than colorectal cancer (men: HR 0.84, 95% CI: 0.72-0.97; women: HR 1.18, 95% CI: 0.97-1.44; *P* interaction <0.01). Long-term use of NSAIDs reduces the risk of total cancer among men and colorectal cancer among both sexes. Our findings do not support NSAID use for overall cancer prevention among women. Additional high-quality studies with long-term follow-up for cancer among women are needed before a public health recommendation can be made.

Introduction

Use of non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with reduced risks of cancers at several sites (1). NSAIDs are thought to reduce cancer risk through inhibition of cyclooxygenase (COX) enzymes, particularly the inducible isoform, COX-2, and downstream prostaglandins including PGE_2, a potent mitogen. A recent meta-analysis of randomized trials of aspirin and cancer mortality found that assignment to aspirin versus placebo conferred a 21% reduction in cancer death (OR 0.79, 95% CI: 0.68-0.92) (2). In contrast, few have examined the association between NSAID use and total cancer incidence (3-7). Although cohort studies have reported reductions in total cancer incidence for aspirin (4, 7) and non-aspirin NSAIDs (5), these findings are not supported by results of the Women's Health Study, a randomized trial that found no effect of aspirin on cancer risk (3). Inferences from these studies are limited. Randomized trials used only aspirin, some at very low doses (2, 3), whereas observational studies measured only current aspirin or NSAID use. No study has addressed individual types of commonly used non-aspirin NSAIDs (4-6).

Here we address the associations between NSAIDs and total cancer risk in a large, prospective cohort of men and women living in western Washington State. Unique aspects of this study include data on frequency and duration of NSAID use, which is used to generate a quantitative measure of long-term exposure, and a sample size large enough to give results stratified by sex.

Materials and Methods

Study population

Participants were members of the VITamins And Lifestyle (VITAL) cohort, a prospective study designed to investigate the associations of dietary supplements and other behaviors, including medication use, with cancer risk. Details of the study design and cohort enumeration are given in White et al. (8). Briefly, men and women, ages 50 to 76 years at baseline, who lived in the 13-county region in western Washington State covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry were eligible to participate. Using names purchased from a commercial mailing list, we mailed baseline questionnaires and post-card reminders two weeks later to 364,418 individuals between October 2000 and December 2002. Of these, 77,719 (21.3%) were returned and considered eligible. Participants with a positive or missing history of any cancer other than non-melanoma skin cancer (n=11,463) at baseline, missing baseline on use of NSAIDs (n=1,388), or for whom a post-baseline cancer diagnosis was available only from the death certificate without a date of diagnosis (n=21) were excluded, leaving 64,847 participants for analysis. All participants gave informed consent and study procedures were approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center.

Data collection

The baseline questionnaire included questions on participants' regular use of NSAIDs, defined as ≥1 day/week for ≥1 year, including frequency (days/week) and duration of use (years) in the past 10 years of low-dose aspirin, regular or extra-strength aspirin, ibuprofen,

naproxen, and celecoxib/rofecoxib. Use of each drug over the 10 years prior to baseline was categorized as none; low, <4 days/week or <4 years; and high, ≥4 days/week and ≥4 years. Additional variables included 'non-aspirin NSAIDs', defined as the maximum of 10-year use of ibuprofen, naproxen, and celecoxib/rofecoxib, and 'regular-strength NSAIDs', defined as the maximum of 10-year use of regular or extra-strength aspirin, ibuprofen, naproxen, and celecoxib/rofecoxib. Both variables were categorized as none, low, and high use as for individual NSAIDs. Low-dose aspirin use was excluded from the 'regular-strength NSAIDs' variable as it is not thought to have strong anti-inflammatory activity (9, 10). The analgesic, acetaminophen, was excluded from all analyses as it has weak anti-inflammatory properties.

Data were also collected on known or suspected cancer risk factors and correlates of NSAID use. Participants reported their demographic and health-related characteristics, including height, weight, education, and marital status; multivitamin use; smoking history; alcohol consumption at age 30, 45, and at baseline; and medical history, including cancer screening and family history of cancer. Participants who reported having had a heart attack, angina, angioplasty, or bypass surgery were considered to have a positive history of coronary artery disease (CAD). Female participants additionally reported their ages at menarche, menopause, and first birth, as well as their use of hormone therapy. From these data, we computed several variables: body mass index (BMI; kg/m^2); pack-years of smoking; and MET-hours/week of activity over the past 10 years (11). Regular diet was measured using a 120-item food-frequency questionnaire (8). Dietary patterns that may be risk factors for cancer were based on two factors identified by the World Cancer Research Fund/American Institute for Cancer Research extensive review of diet and cancer risk (12): total fruit and vegetable (excluding potatoes) intake; and total consumption of red or processed meats (bacon or breakfast sausage, hot dogs or sausage, lunch meats, beef, pork, ham, lamb, ground meat, and organ meats).

Case ascertainment

Cohort members were followed for incident invasive cancer diagnoses from baseline to December 31, 2008, with a mean follow-up time of 7 years. Incident cancers were ascertained by linking the study cohort to the western Washington SEER cancer registry, which is maintained by the Fred Hutchinson Cancer Research Center. All cancer cases, except non-melanoma skin cancer, diagnosed within the 13-county area of western Washington State are reported to SEER along with stage, histologic subtype, and other tumor characteristics. Cases were ascertained through all area hospitals, offices of pathologists, oncologists, and radiotherapists, and from state death certificates. Extensive quality-control procedures ensure that registry data are accurate and complete. Linkage to SEER is based on ranking of the agreement between characteristics common to VITAL and SEER including name, social security number, date of birth, etc.; matches with high concordance were made automatically, while visual inspection was performed for matches in which some, but not all criteria matched. 5,946 incident, invasive cancer cases were diagnosed among eligible participants between baseline and December 2008.

Follow-up for censoring

Excluding the 9.2% of the cohort with incident cancer diagnoses, the remaining participants were right-censored from the analysis at the earliest date of the following events: requested removal from the study (0.03%), death (3.4%), emigration out of the SEER catchment area (7.5%), or December 31, 2008, the most recent date of SEER linkage (89.0%). Deaths that occurred in the cohort were ascertained by linkage to the Washington State death file, using procedures similar to the SEER linkage. The National Change of Address System and active

follow-up by telephone calls and mailings were used to identify participants who had moved out of the SEER catchment area.

Statistical analysis

Because total cancer incidence is comprised partly of tumors of differing sites for men and women, analyses for cancer incidence were performed stratified by sex. Cox proportional hazards regression models with age as the time metric were used to estimate age and covariate-adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for sex-stratified associations of participant characteristics and NSAID use with cancer incidence.

We selected *a priori* potential confounders (including known and suspected risk factors of the most common cancers) for inclusion in regression models. Proportional hazards models were adjusted for age (time variable: years); education (≤high school, some college, ≥college graduate); race (White, African-American, Asian or Pacific Islander, Hispanic, Native American, other race); marital status (married or living together, never married, separated or divorced, widowed); height (inches: quartiles); BMI (<25.0, 25.0-29.9, ≥30.0); 10-year physical activity (MET hours/week: 0, and tertiles of activity); smoking (pack-years: never and tertiles of pack-years); alcohol consumption at 45 years (drinks/day: 0, <1, 1-2, ≥2); fruit and vegetable consumption (servings/day: tertiles); red or processed meat consumption (servings/day: tertiles); multivitamin use (never, former, current); self-rated health (excellent, very good, good, fair, poor); number of first-degree relatives with histories of: colon cancer, lung cancer, or hematologic malignancy (each coded as 0, 1, ≥2); and sigmoidoscopy in the last 10 years (yes/no). Alcohol consumption at 45 years was used as a covariate in the statistical models because it was the best predictor of total cancer incidence among the three time periods of alcohol use collected.

We also adjusted regression models for the following measures among women: number of first degree relatives with a history of breast cancer (0, 1, ≥2); mammogram in the past 2 years (yes/no); age at menarche (≤11, 12, 13, ≥14 years); age at menopause (≤44, 45-49, ≥50 years); age at first birth (≤19, 20-24, 25-34, ≥35 years, nulligravid); years of estrogen-only hormone therapy (0, 1-4, 5-9, ≥10); years of combined hormone therapy (0, 1-4, 5-9, ≥10); and history of hysterectomy (none, simple, total or bilateral oophorectomy). We adjusted models for the following measures among men: number of first-degree relatives with a history of prostate cancer (0, 1, ≥2); and prostate-specific antigen (PSA) test in the past 2 years (yes/no).

We additionally adjusted regression models for indications/contraindications of NSAID use, including histories of coronary artery disease; risk factors for coronary heart disease, including history of diabetes, use of cholesterol-lowering medication, and use of blood pressure medication; osteoarthritis or chronic joint pain; migraine or chronic headaches; and history of gastric ulcers (each coded as yes/no). Regression analyses for any one exposure were further adjusted for use of other NSAIDs.

In addition to differences by sex, we hypothesized *a priori* that the association between NSAID use and cancer incidence would be modified by factors found to be associated with markers of inflammation, including smoking status (13), BMI (14), history of coronary artery disease (15), and use of cholesterol-lowering drugs (16). *P* values for interaction (*P* interaction) between NSAIDs and potential effect-modifiers were computed by including a multiplicative term using the ordinal 10-year (non-user, low, high) NSAID variables in multivariable models.

In order to interrogate differences in the association of NSAIDs and cancer incidence between men and women, we categorized solid tumors into mutually exclusive categories:

colorectal (n=451); shared (between the sexes) cancers other than colorectal (n=2,551; including lung, head and neck, pancreas, skin, kidney, bladder, brain, hematologic malignancies, etc.); cancers of the female breast and reproductive system ("female cancers"; n=1,269); and cancers of the male reproductive system ("male cancers"; n=1,636). Hematologic cancers (n=595) were defined using the World Health Organization Classification of Hematopoietic and Lymphoid Neoplasms (17, 18) and included among cancers of shared sites. Breast cancer was restricted to female breast and excluded from shared sites. We separated colorectal cancers from other cancers shared by the sexes to show that the association in VITAL is consistent with that of the literature and to remove its strong effect from that of other shared cancer sites.

In supplemental analyses, we additionally classified cancers by mutually exclusive sites: gastrointestinal cancers other than colorectal ([GI]; n=357; including esophagus, stomach, liver, pancreas, gall bladder, small intestines, and anus); lung cancer (n=648); and other shared solid non-GI cancers (n=951), defined as all solid, non-GI cancers shared by men and women except lung and hematologic cancers. The major cancers included in this classification were cancers of the skin, kidney, bladder, and thyroid. Excluded from these classifications were those whose primary site was unknown (n=39) and hematologic malignancies. Supplemental analyses of melanoma were additionally adjusted for skin cancer risk factors: freckles, ≥3 sunburns, and red or blond hair (all between the ages 10-20 years); reaction to 1 hour in strong sunlight; family history of melanoma; and personal histories of non-melanoma skin cancer and mole biopsy.

All analyses were done using SAS 9.2 for the PC (Cary, NC, USA). All reported *P* values are two-sided. *P* values for trend (*P* trend) were calculated by treating categorical exposures as ordinal in proportional hazards models.

Results

Age-adjusted associations between selected characteristics of VITAL study participants and total cancer incidence are given in Table 1. Increasing height, pack-years of smoking, and consumption of alcohol or red or processed meats were positively associated with cancer risk in men and women. In men and women, better self-perceived health, attainment of a college degree, high physical activity, and high consumption of fruits and vegetables were associated with reduced cancer risk. High BMI was associated with increased cancer risk in women only.

Table 2 gives multivariable-adjusted associations between NSAID use and total cancer incidence. Relative to non-use, high 10-year use of regular-strength NSAIDs was associated with a 12% reduction in cancer incidence among men (HR 0.88, 95% CI: 0.79-0.97; P trend=0.01) and a 10% statistically non-significant increase in cancer risk among women (HR 1.10, 95% CI: 0.96-1.25; *P* trend=0.16). The *P* for interaction for sex was <0.01. Among men, high 10-year use of regular-strength aspirin (HR 0.90, 95% CI: 0.80-1.00; *P* trend=0.07) and ibuprofen (HR 0.85, 95% CI: 0.69-1.03; *P* trend=0.01) were associated with reduced risk. In women, high 10-year use of regular-strength aspirin appeared to primarily contribute to the increased risk in a non-linear fashion, although the individual finding did not achieve statistical significance. Neither low-dose aspirin nor naproxen use was associated with cancer risk in men or women. Findings were similar when we restricted cases to those diagnosed >4 years after baseline (data not shown). The associations between NSAID use and cancer risk were not modified by body mass index, smoking status, history of heart disease, or use of cholesterol-lowering drugs (data not shown).

Table 3 gives the association between NSAID use and cancer incidence categorized into mutually exclusive groups: colorectal cancer (the site with the strongest evidence for an association with NSAID use (19, 20)), other sites of cancer shared between men and women, female cancers, and male cancers. In men and women, high use of regular-strength NSAIDs (HR 0.60, 95% CI: 0.38-0.92 and HR 0.60, 95% CI: 0.37-0.96, respectively) and low-dose aspirin (HR 0.55, 95% CI: 0.33-0.92 and HR 0.55, 95% CI: 0.31-0.97, respectively) were strongly associated with reduced risk of colorectal cancer. In men, regular-strength aspirin but not non-aspirin NSAIDs was inversely associated with colorectal cancer risk, while in women non-aspirin NSAIDs but not regular-strength aspirin were inversely associated with risk. In contrast, high use of regular-strength NSAIDs was associated with reduced risks of cancer of shared sites other than colorectal cancer in men (HR 0.84, 95% CI: 0.72-0.97; *P* trend=0.02) and statistically non-significant increased risks in women (HR 1.18, 95% CI: 0.97-1.44; *P* trend=0.09) relative to non-use (*P*-interaction<0.01). There were no statistically significant associations between NSAID use and risks of sex-specific cancers (analyses of the association between NSAID use and breast (21) and prostate cancers (22) in the VITAL cohort were reported previously); however, there was a suggestion of an association between regular-strength NSAID use and risk of female cancers (HR 1.13, 95 CI: 0.94-1.36; *P* trend=0.13).

Results for individual cancers at shared sites other than colorectal are given in Supplemental Table 1. Analyses of the association between NSAID use and lung cancer (23), melanoma (24), and hematologic malignancies (25) in the VITAL cohort are published elsewhere. We observed decreased risks for men and increased risks for women with regular-strength aspirin use and gastrointestinal cancers other than colorectal (HR 0.66, 95% CI: 0.42-1.04, *P* trend=0.03; and HR 1.98, 95% CI: 1.19-3.29, *P* trend=0.08; respectively; *P* interaction<0.01), regular aspirin use and hematologic cancers (HR 0.72, 95% CI: 0.51-1.03, *P* trend=0.14; HR 1.27, 95% CI: 0.77-2.09, *P* trend=0.11, respectively; *P* interaction=0.02) and non-aspirin NSAID use and risk of other shared solid non-GI tumors (HR 0.81, 95% CI: 0.52-1.24, *P* trend=0.32; and HR 1.63, 95% CI: 1.11-2.39, *P* trend=0.02, respectively; *P* interaction=0.04). In women, this latter association was partly explained by substantial increases in risks of malignant melanoma (n_{cases} = 289; high vs. non-use: HR 3.14, 95% CI: 1.61-6.15; *P* trend<0.001) and renal cancer (n_{cases} = 166; high vs. non-use: HR 2.15, 95% CI: 0.93-4.97; *P* trend=0.07) with use of non-aspirin NSAIDs. There were no statistically significant associations between NSAID use and melanoma or renal cancers in men. In our previous analysis of melanoma, we did not stratify on sex (24). Lastly, there were no sex differences for NSAID use and lung cancer risk.

Discussion

In this large, prospective study of men and women, long-term NSAID use was inversely associated with total cancer incidence in men only. There was little support for a chemopreventive role of NSAIDs in women, apart from the well-established chemopreventive properties for colorectal cancers (19, 20), and limited evidence of an increased risk.

In men, long-term use of regular-strength NSAIDs, aspirin and ibuprofen in particular, was associated with reduced risk of cancer. No studies have investigated individual non-aspirin NSAIDs and total cancer risk in men or women. Three observational studies have examined the association between either aspirin or non-aspirin NSAIDs and cancer risk in men (4, 6, 7). In 1994, Schreinemachers et al (7), reported that ever use of aspirin in the 30 days prior to baseline was associated with a reduction of cancer risk in men (IRR 0.79, 95% CI: 0.67-0.93), using data from the National Health and Nutrition Examination Survey I (NHANES). Findings from this study should be interpreted with caution, however, as many

cancer risk factors were not included for multivariable adjustment. Jacobs et al. (4), reported a similar finding for aspirin in the Cancer Prevention Study II Nutrition Cohort (hereafter, "CPSII"), a nationwide study of diet and lifestyle and cancer incidence among 146,113 men and women. The authors reported that relative to non-use, current, daily use of aspirin for ≥5 years was associated with a 16% reduction in cancer risk (HR 0.84, 95% CI: 0.76-0.93) in men. In contrast, using data from the North Jutland County Prescription Database and linking them to the Danish Cancer Registry, Sørensen et al. (6), reported no association between prescriptions for non-aspirin NSAIDs and cancer incidence (SIR 1.0, 95% CI: 1.0-1.1) in men. These findings may be due, in part, to confounding and measurement error – the Danish study was age-standardized only and analyses were not adjusted for other major cancer risk factors. Additionally, NSAIDs available over-the-counter were not included, and the authors were unable to account for prescription compliance, potentially adding to measurement error (6). Recently, Rothwell et al. (2), published a meta-analysis of 8 randomized trials of aspirin and cancer mortality. The authors reported that allocation to aspirin reduced the risk of cancer death by 21% (HR 0.79, 95% CI: 0.68-0.92) compared to placebo (2). Sixty-eight percent of participants in the 8 trials were men. Although these findings only reflect the most fatal types of cancer, they provide supporting evidence that aspirin reduces cancer risk in men.

In contrast to our findings in men, we found that use of NSAIDs was associated with small increases in overall cancer risk among women. This result is inconsistent with those from the few prior studies of NSAID use and total cancer risk in women (4-7). In the aforementioned CPSII (4), aspirin use was associated with a small, statistically non-significant reduction in cancer risk among women (RR 0.86, 95% CI: 0.73-1.03). A similar risk reduction was reported from the Iowa Women's Health Study (IWHS). In the IWHS, Bardia et al. (5), reported use of aspirin ≥6 times per week was also associated with decreased cancer incidence (RR 0.81, 95% CI: 0.73-0.90) relative to non-use. Authors of the NHANES study reported no association between recent aspirin use and total cancer risk among women (7), and authors of the IWHS (5) and Danish prescription linkage study (6) reported no association between non-aspirin NSAIDs and total cancer risk among women. We can offer little explanation as to the differences between our results and those of the IWHS and CPSII. In the IWHS, investigators did not separate the effects of regular-strength aspirin and low-dose aspirin, even though the latter is strongly associated with other healthy behaviors. The reported reductions in risk may partly reflect the confounding effect of such behaviors. Both studies assessed short-term use of either aspirin or NSAIDs, and although it is possible that short-term and long-term effects of these drugs may differ, we would not expect a reversal in the direction of the association.

Neither the use of low-dose aspirin nor naproxen was associated with overall cancer risk in either men or women. To our knowledge, the Danish prescription linkage study is the only observational study to examine the association between low-dose aspirin and cancer risk (26). Different from our findings, the authors reported statistically significant increases in risk for men (SIR 1.10, 95% CI: 1.04-1.16) and women (SIR 1.08, 95% CI: 1.01-1.14). Cook et al. (3), reported no effect of low-dose aspirin (100mg) taken every other day on cancer incidence in the Women's Health Study randomized trial, and Rothwell et al. (2), observed reductions in cancer mortality regardless of aspirin dose in their pooled-analysis of aspirin trials in men. To our knowledge no study has examined the associations of naproxen with cancer incidence. Further high-quality studies are needed to better understand the association between these drugs with cancer incidence.

Our findings of a reduction of colorectal cancer incidence for men and women are highly consistent with randomized trials and observational studies of aspirin and other NSAIDs,

which have established these medications as chemoprotective agents against colorectal cancer incidence and mortality (2, 19, 20, 27).

The different associations that we observed between NSAID use and total cancer risk in men and women are somewhat inconsistent with the literature. Differences were primarily driven by findings for female cancers and for shared anatomic sites (other than colorectal cancer), especially melanoma, kidney, and hematologic cancers. Our finding of a statistically non-significant increased risk of cancers of the female breast and reproductive system differs from the literature. There is evidence that use of NSAIDs, particularly aspirin, may reduce the risk of breast (28), but not ovarian cancer in women (29). Although comparisons for this classification of cancers are challenging, NSAIDs have generally been associated with reduced risks of solid tumors, including cancers of the lung (30), the gastro-intestinal tract (31), and less common sites (1). There is limited support of an increased risk of hematologic malignancy among female NSAID users in this (25) and other studies (32, 33), as well as an overall increased risk for kidney cancer (34). Findings for melanoma have thus far been inconsistent (1, 4, 24).

We know of little reason why the use of NSAIDs may be differentially associated with cancer incidence between the sexes. Although the biologic mechanisms are not understood, there is some evidence that the protective effect of aspirin on cardiovascular disease may also differ by sex, based on meta-analyses of the randomized trials of these effects (35-37).

Strengths of the VITAL cohort include its large sample size, prospective design, inclusion of both men and women, availability of information on a large number of potential confounding factors including indications/contraindications for NSAID use, and near-complete follow-up using the population-based SEER cancer registry. Different from previous studies, we were able to collect exposure data on the use of individual NSAIDs, allowing us to report on the association between the most commonly available over-the-counter NSAIDs and cancer risk.

The primary limitation of this study is that we were unable to ascertain information on NSAID dose (other than for aspirin). As available formulations vary, it is possible that participants classified as “high” users (i.e., frequent and long-term users) may have used the lowest doses to avoid adverse effects. We expect that introduction of this measurement error would result in attenuation of point-estimates. It may be possible that NSAID use was the result of early cancer-related pain (“protopathic bias”). However, restricting the analysis to cancers diagnosed >4 years after baseline did not materially change point estimates. We considered the possibility of confounding by indication and we adjusted analyses for known indications/contraindications of NSAID use as well as predictors of cancer risk; however, some residual confounding may remain.

In conclusion, we provide strong evidence in support of a chemopreventive role of NSAIDs for total cancer in men and colorectal cancer in both sexes. However, our findings do not support the limited evidence that NSAID use is associated with reduced risk of total cancer among women. Additional prospective studies with high-quality data on NSAID exposure and long-term follow-up for cancer among women are needed before a public health recommendation can be made.

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Table 1

Select characteristics of VITAL participants and risk of total cancer.

Characteristic	Women (*n*=33,299)			Men (*n*=31,548)		
	Cancer Cases (*n*=2,534), *n* (%)	Non-cases (*n*=30,765), *n* (%)	Cancer HR (95% CI)[a]	Cancer Cases (*n*=3,412), *n* (%)	Non-cases (*n*=28,136), *n* (%)	Cancer HR (95% CI)[a]
Age (years)						
<55	350 (13.8)	8,071 (26.2)		370 (10.8)	7,382 (26.2)	
55 to 59.9	480 (18.9)	7,473 (24.3)		575 (16.9)	6,818 (24.2)	
60 to 64.9	486 (19.2)	5,410 (17.6)		674 (19.8)	5,223 (18.6)	
65 to 69.9	538 (21.2)	4,494 (14.6)		774 (22.7)	4,439 (15.8)	
≥70	680 (26.8)	5,317 (17.3)		1,019 (29.9)	4,274 (15.2)	
Education						
≤High school graduate	687 (27.9)	6,820 (22.6)	1.00 (referent)	644 (19.1)	4,189 (15.1)	1.00 (referent)
Some college	996 (40.4)	12,542 (41.6)	0.92 (0.83-1.01)	1,172 (34.7)	9,721 (34.9)	0.96 (0.87-1.06)
College or advanced degree	783 (31.8)	10,770 (35.7)	0.90 (0.81-1.00)	1,561 (46.2)	13,916 (50.0)	0.90 (0.82-0.99)
Race						
White	2,345 (94.9)	28,022 (92.9)	1.00 (referent)	3,168 (944.0)	25,891 (93.2)	1.00 (referent)
African-American	26 (1.1)	386 (1.3)	0.83 (0.57-1.22)	53 (1.6)	332 (1.2)	1.40 (1.07-1.84)
Asian or Pacific Islander	51 (2.1)	840 (2.8)	0.74 (0.56-0.98)	61 (1.8)	688 (2.5)	0.76 (0.59-0.98)
Hispanic	8 (0.3)	293 (1.0)	0.38 (0.19-0.77)	24 (0.7)	250 (0.9)	0.94 (0.63-1.40)
Native American	30 (1.2)	456 (1.5)	0.84 (0.59-1.21)	45 (1.3)	412 (1.5)	0.95 (0.71-1.27)
Other race/not reported	11 (0.5)	155 (0.5)	0.92 (0.51-1.66)	21 (0.6)	218 (0.8)	0.88 (0.57-1.34)
Marital status						
Married/Living Together	1,622 (65.9)	21,406 (71.2)	1.00 (referent)	2,908 (86.1)	23,808 (85.7)	1.00 (referent)
Never married	101 (4.1)	1,020 (3.4)	1.46 (1.20-1.79)	89 (2.6)	943 (3.4)	0.95 (0.77-1.17)
Separated or divorced	382 (15.5)	4,526 (15.1)	1.16 (1.04-1.29)	258 (7.6)	2,325 (8.4)	1.06 (0.93-1.20)
Widowed	358 (14.5)	3,119 (10.4)	1.13 (1.00-1.27)	122 (3.6)	715 (2.6)	1.00 (0.83-1.20)
Height (inches)						
<64.0	735 (29.8)	9,750 (32.4)	1.00 (referent)	17 (0.5)	165 (0.6)	} 1.23 (1.08-1.39)
64.0-67.9	1,386 (56.1)	16,385 (54.4)	1.13 (1.03-1.23)	330 (9.8)	3,057 (11.0)	
68.0-70.9	325 (13.2)	3,560 (11.8)	} 1.00 (referent)	1,188 (35.3)	10,015 (36.1)	1.11 (0.98-1.25)
≥71	24 (1.0)	408 (1.4)		1,835 (54.5)	14,522 (52.3)	1.22 (1.08-1.36)

Characteristic	Women (*n*=33,299)			Men (*n*=31,548)		
	Cancer Cases (*n*=2,534), *n* (%)	Non-cases (*n*=30,765), *n* (%)	Cancer HR (95% CI)[a]	Cancer Cases (*n*=3,412), *n* (%)	Non-cases (*n*=28,136), *n* (%)	Cancer HR (95% CI)[a]
P-trend			<0.001			<0.001
Body mass index (kg/m^2)						
<25.0	889 (37.7)	11,911 (41.4)	1.00 (referent)	936 (28.2)	7,420 (27.2)	1.00 (referent)
25.0-29.9	818 (34.7)	9,662 (33.6)	1.12 (1.01-1.23)	1,656 (49.9)	13,266 (48.5)	1.03 (0.95-1.12)
≥30.0	654 (27.7)	7,230 (25.1)	1.29 (1.17-1.43)	730 (22.0)	6,646 (24.3)	1.00 (0.90-1.10)
P-trend			<0.001			0.98
10-y physical activity (MET hours/week)						
0	415 (16.6)	4,421 (14.6)	1.00 (referent)	527 (15.7)	4,085 (14.7)	1.00 (referent)
0-4.38	873 (35.0)	10,284 (33.9)	0.91 (0.81-1.02)	6,481 (23.3)	6,481 (23.3)	0.90 (0.80-1.00)
4.39-13.59	706 (28.3)	8,707 (28.7)	0.85 (0.75-0.96)	7,645 (27.5)	7,645 (27.5)	0.88 (0.79-0.98)
>13.59	503 (20.1)	6,948 (22.9)	0.76 (0.67-0.87)	9,552 (34.4)	9,552 (34.4)	0.90 (0.81-1.00)
P-trend			<0.0001			0.10
Smoking history (pack-years)						
Never smoker	1,252 (50.0)	17,499 (57.2)	1.00 (referent)	1,087 (32.5)	11,143 (40.3)	1.00 (referent)
0-12.5	414 (16.5)	5,888 (19.3)	1.00 (0.89-1.12)	546 (16.3)	5,204 (18.8)	1.03 (0.93-1.14)
12.6-35.0	441 (17.6)	4,549 (14.9)	1.36 (1.22-1.51)	818 (24.4)	6,445 (23.3)	1.19 (1.09-1.30)
>35.0	398 (15.9)	2,652 (8.7)	1.90 (1.70-2.13)	897 (26.8)	4,877 (17.6)	1.55 (1.42-1.69)
P-trend			<0.0001			<0.0001
Alcohol at 45 years (drinks/d)						
None	535 (22.2)	7,015 (23.8)	1.00 (referent)	493 (15.0)	4,551 (16.6)	1.00 (referent)
<1	1,454 (60.3)	18,387 (62.3)	1.04 (0.94-1.15)	1,554 (47.4)	13,650 (49.9)	1.00 (0.90-1.10)
1-2	258 (10.7)	2,506 (8.5)	1.34 (1.16-1.56)	555 (16.9)	4,461 (16.3)	1.02 (0.90-1.15)
≥2	165 (6.8)	1,590 (5.4)	1.43 (1.20-1.70)	678 (20.7)	4,695 (17.2)	1.23 (1.09-1.38)
P-trend			<0.0001			<0.0001
Fruit + vegetable consumption (servings/d)						
0-2.4	634 (28.2)	7,175 (26.0)	1.00 (referent)	1,251 (39.7)	10,674 (40.9)	1.00 (referent)
2.4-4.1	703 (31.3)	8,851 (32.0)	0.86 (0.77-0.96)	1,174 (37.2)	8,988 (34.4)	1.04 (0.96-1.13)
>4.1	912 (40.6)	11,628 (42.1)	0.85 (0.77-0.94)	728 (23.1)	6,458 (24.7)	0.91 (0.83-1.00)
P-trend			<0.01			0.08
Red or processed meats (servings/d)						

Characteristic	Women (*n*=33,299)			Men (*n*=31,548)		
	Cancer Cases (*n*=2,534), *n* (%)	Non-cases (*n*=30,765), *n* (%)	Cancer HR (95% CI)[a]	Cancer Cases (*n*=3,412), *n* (%)	Non-cases (*n*=28,136), *n* (%)	Cancer HR (95% CI)[a]
0-2.7	897 (39.9)	11,435 (41.4)	1.00 (referent)	753 (23.9)	6,663 (25.5)	1.00 (referent)
2.7-5.8	775 (34.5)	9,235 (33.4)	1.08 (0.98-1.18)	1,061 (33.7)	9,387 (32.1)	1.12 (1.02-1.23)
>5.8	577 (25.7)	6,984 (25.3)	1.08 (0.98-1.21)	1,339 (42.5)	11,070 (42.4)	1.15 (1.05-1.26)
P-trend			0.09			<0.01
Multivitamin use						
Never	750 (29.6)	9,051 (29.4)	1.00 (referent)	1,344 (39.39)	11,351 (40.4)	1.00 (referent)
Former	215 (8.5)	2,647 (8.6)	1.03 (0.88-1.19)	210 (6.2)	1,887 (6.7)	1.01 (0.87-1.16)
Current	1,569 (61.9)	19,067 (62.0)	0.95 (0.87-1.03)	1,858 (54.5)	14,890 (52.9)	1.00 (0.94-1.08)
Self-rated health						
Excellent	262 (10.5)	4,714 (15.6)	1.00 (referent)	483 (14.4)	4,615 (16.6)	1.00 (referent)
Very good	959 (38.4)	11,943 (39.4)	1.34 (1.17-1.54)	1,294 (38.5)	10,994 (39.7)	1.07 (0.96-1.19)
Good	912 (36.6)	10,232 (33.8)	1.43 (1.24-1.64)	1,157 (34.4)	9,083 (32.8)	1.13 (1.01-1.25)
Fair	304 (12.2)	2,935 (9.7)	1.69 (1.43-2.00)	365 (10.9)	2,612 (9.4)	1.21 (1.06-1.39)
Poor	58 (2.3)	473 (1.6)	2.23 (1.68-2.96)	62 (1.8)	425 (1.5)	1.44 (1.11-1.88)
P-trend			<0.0001			<0.001

[a]Adjusted for age

Table 2

Associations between NSAID use and total cancer incidence, stratified by sex.

NSAID	10-year Use			
	Non-user	Low (<4d/wk or <4y)	High (≥4d/wk and ≥4y)	*P* trend
Low-dose aspirin				
Men				
Cases / Non-cases	2,178 / 18,727	513 / 4,178	527 / 3,734	
HR (95% CI)[a]	1.00 (reference)	0.98 (0.88-1.09)	0.98 (0.88-1.09)	0.67
Women				
Cases / Non-cases	1,693 / 21,495	454 / 4,838	259 /2,841	
HR (95% CI)[a]	1.00 (reference)	1.09 (0.97-1.22)	0.89 (0.77-1.03)	0.44
			P interaction = 0.83	
Regular-strength aspirin				
Men				
Cases / Non-cases	2,304 / 19,179	433 / 3,816	557 / 4,272	
HR (95% CI)[a]	1.00 (reference)	1.00 (0.89-1.12)	0.90 (0.80-1.00)	0.07
Women				
Cases / Non-cases	1,937 / 24,011	295 / 3,628	246 / 2,279	
HR (95% CI)[a]	1.00 (reference)	0.98 (0.86-1.13)	1.13 (0.97-1.31)	0.23
			P interaction = 0.01	
Ibuprofen				
Men				
Cases / Non-cases	2,738 / 21,582	464 / 4,704	128 / 1,199	
HR (95% CI)[a]	1.00 (reference)	0.89 (0.79-0.99)	0.85 (0.69-1.03)	0.01
Women				
Cases / Non-cases	1,763 / 21,228	515 / 6,416	161 / 1,961	
HR (95% CI)[a]	1.00 (reference)	1.05 (0.94-1.18)	1.05 (0.88-1.27)	0.37
			P interaction < 0.01	
Naproxen				
Men				
Cases / Non-cases	3,175 / 26,235	166 / 1,416	44 / 300	
HR (95% CI)[a]	1.00 (reference)	0.98 (0.82-1.18)	1.11 (0.80-1.54)	0.76
Women				
Cases / Non-cases	2,245 / 27,063	198 / 2,662	52 / 572	
HR (95% CI)[a]	1.00 (reference)	0.96 (0.81-1.13)	1.05 (0.77-1.44)	0.90
			P interaction = 0.88	
Non-aspirin NSAIDs [b]				
Men				
Cases / Non-cases	2,534 / 20,200	602 / 5,661	181 / 1,501	

NSAID	10-year Use			
	Non-user	Low (<4d/wk or <4y)	High (≥4d/wk and ≥4y)	*P* trend
HR (95% CI)[a]	1.00 (reference)	0.92 (0.83-1.01)	0.98 (0.83-1.15)	0.24
Women				
Cases / Non-cases	1,537 / 18,577	640 / 8,039	204 / 2,514	
HR (95% CI)[a]	1.00 (reference)	1.04 (0.93-1.15)	1.00 (0.85-1.18)	0.75
			P interaction = 0.17	
Regular-strength NSAIDs [c]				
Men				
Cases / Non-cases	1,749 / 14,226	788 / 7,136	695 / 5,476	
HR (95% CI)[a]	1.00 (reference)	0.94 (0.86-1.04)	0.88 (0.79-0.97)	0.01
Women				
Cases / Non-cases	1,202 / 15,090	717 / 8,994	417 / 4,441	
HR (95% CI)[a]	1.00 (reference)	1.04 (0.94-1.15)	1.10 (0.96-1.25)	0.16
			P interaction < 0.01	

[a]Adjusted for age, education, race, marital status, height, body mass index, physical activity, pack-years of smoking, alcohol intake at 45y, fruit and vegetable intake, red meat intake, multivitamin use, self-rated health, family history of colon, lung, and hematological cancers (as separate terms), sigmoidoscopy in the past 10y, diabetes, use of cholesterol-lowering medications, use of blood pressure medications, coronary heart disease, osteoarthritis/chronic joint pain, migraine/chronic headaches, ulcers, and use of other NSAIDs. Additionally adjusted for family history of breast cancer, mammogram in the past 2y, age at menarche, age at menopause, age at first birth, years of estrogen therapy, years of combined hormone therapy, and hysterectomy (among women); and family history of prostate cancer and PSA test in the past 2y (among men).

[b]Includes ibuprofen, naproxen, and COX-2 inhibitors

[c]Includes regular-strength aspirin, ibuprofen, naproxen, and COX-2 inhibitors

Table 3

Associations between NSAID use and cancer incidence, stratified by cancer site and sex.

NSAID	10-year Use			
	Non-user	Low (<4d/wk or <4y)	High (≥4d/wk and ≥4y)	*P* trend
Colorectal (n=451)				
Low-dose aspirin				
Men				
Cases / Non-cases	165 / 20,740	29 / 4,662	20 / 4,241	
HR (95% CI)[a]	1.00 (reference)	0.74 (0.48-1.15)	0.55 (0.33-0.92)	0.01
Women				
Cases / Non-cases	158 / 23,030	37 / 5,255	18 / 3,082	
HR (95% CI)[a]	1.00 (reference)	0.89 (0.59-1.36)	0.55 (0.31-0.97)	0.05
			P interaction = 0.44	
Regular-strength aspirin				
Men				
Cases / Non-cases	159 / 21,324	29 / 4,220	26 / 4,803	
HR (95% CI)[a]	1.00 (reference)	0.97 (0.63-1.50)	0.55 (0.33-0.91)	0.03
Women				
Cases / Non-cases	181 / 25,767	15 / 3,908	20 / 2,505	
HR (95% CI)[a]	1.00 (reference)	0.53 (0.29-0.96)	0.84 (0.49-1.07)	0.16
			P interaction = 0.32	
Non-aspirin NSAIDs[b]				
Men				
Cases / Non-cases	173 / 22,561	30 / 6,233	12 / 1,670	
HR (95% CI)[a]	1.00 (reference)	0.65 (0.42-1.02)	1.01 (0.54-1.91)	0.30
Women				
Cases / Non-cases	153 / 19,961	47 / 8,632	13 / 2,705	
HR (95% CI)[a]	1.00 (reference)	0.73 (0.49-1.07)	0.48 (0.23-1.00)	0.02
			P interaction = 0.35	
Regular-strength NSAIDs[c]				
Men				
Cases / Non-cases	125 / 15,850	48 / 7,876	36 / 6,135	
HR (95% CI)[a]	1.00 (reference)	0.78 (0.54-1.13)	0.60 (0.38-0.92)	0.02
Women				
Cases / Non-cases	126 / 16,166	48 / 9,663	31 / 4,827	
HR (95% CI)[a]	1.00 (reference)	0.60 (0.41-0.88)	0.60 (0.37-0.96)	<0.01
			P interaction = 0.89	
Other shared sites (n=2,551)[d]				
Low-dose aspirin				

NSAID	10-year Use			
	Non-user	Low (<4d/wk or <4y)	High (≥4d/wk and ≥4y)	*P* trend
Men				
Cases / Non-cases	960 / 19,1945	218 / 4,473	248 / 4,013	
HR (95% CI)[a]	1.00 (reference)	0.95 (0.81-1.11)	1.01 (0.86-1.19)	0.99
Women				
Cases / Non-cases	661 / 22,527	188 / 5,104	130 / 2,970	
HR (95% CI)[a]	1.00 (reference)	1.11 (0.92-1.33)	1.07 (0.86-1.33)	0.39
			P interaction = 0.37	
Regular-strength aspirin				
Men				
Cases / Non-cases	1,031 / 20,452	186 / 4,063	257 / 4,572	
HR (95% CI)[a]	1.00 (reference)	0.94 (0.79-1.11)	0.84 (0.72-0.99)	0.04
Women				
Cases / Non-cases	776 / 25,172	127 / 3,796	111 / 2,414	
HR (95% CI)[a]	1.00 (reference)	1.07 (0.87-1.32)	1.18 (0.93-1.49)	0.15
			P interaction <0.01	
Non-aspirin NSAIDs[b]				
Men				
Cases / Non-cases	1,136 / 21,598	267 / 5,996	79 / 1,603	
HR (95% CI)[a]	1.00 (reference)	0.91 (0.78-1.06)	0.91 (0.71-1.18)	0.23
Women				
Cases / Non-cases	612 / 19,502	259 / 8,420	84 / 2,634	
HR (95% CI)[a]	1.00 (reference)	1.04 (0.88-1.23)	1.04 (0.80-1.36)	0.63
			P interaction = 0.29	
Regular-strength NSAIDs[c]				
Men				
Cases / Non-cases	783 / 15,192	345 / 7,579	318 / 5,853	
HR (95% CI)[a]	1.00 (reference)	0.91 (0.79-1.05)	0.84 (0.72-0.97)	0.02
Women				
Cases / Non-cases	469 / 15,823	292 / 9,419	182 / 4,676	
HR (95% CI)[a]	1.00 (reference)	1.08 (0.91-1.27)	1.18 (0.97-1.44)	0.09
			P interaction <0.01	
Female cancers (n=1,269)[e]				
Low-dose aspirin				
Cases / Non-cases	861 / 22,327	227 / 5,065	110 / 2,990	
HR (95% CI)[a]	1.00 (reference)	1.12 (0.95-1.32)	0.81 (0.65-1.02)	0.34
Regular-strength aspirin				
Cases / Non-cases	964 / 24,984	151 / 3,772	115 / 2,410	

NSAID	10-year Use			
	Non-user	Low (<4d/wk or <4y)	High (≥4d/wk and ≥4y)	*P* trend
HR (95% CI)[a]	1.00 (reference)	1.01 (0.84-1.22)	1.16 (0.93-1.44)	0.26
Non-aspirin NSAIDs[b]				
Cases / Non-cases	761 / 19,353	331 / 8,348	104 / 2,614	
HR (95% CI)[a]	1.00 (reference)	1.08 (0.93-1.25)	1.04 (0.82-1.31)	0.45
Regular-strength NSAIDs[c]				
Cases / Non-cases	598 / 15,694	372 / 9,339	201 / 4,657	
HR (95% CI)[a]	1.00 (reference)	1.11 (0.96-1.28)	1.13 (0.94-1.36)	0.13
Male cancers (n=1,636)[f]				
Low-dose aspirin				
Cases / Non-cases	1,034 / 19,871	263/ 4,428	255 / 4,006	
HR (95% CI)[a]	1.00 (reference)	1.06 (0.91-1.23)	1.02 (0.87-1.19)	0.68
Regular-strength aspirin				
Cases / Non-cases	1,097 / 20,386	210 / 4,039	272 / 4,557	
HR (95% CI)[a]	1.00 (reference)	1.04 (0.89-1.22)	1.01 (0.86-1.17)	0.86
Non-aspirin NSAIDs[b]				
Cases / Non-cases	1,204 / 21,530	300 / 5,963	90 / 1,592	
HR (95% CI)[a]	1.00 (reference)	0.95 (0.83-1.10)	1.05 (0.83-1.33)	0.91
Regular-strength NSAIDs[c]				
Cases / Non-cases	828 / 15,147	383 / 7,541	339 / 5,832	
HR (95% CI)[a]	1.00 (reference)	0.98 (0.86-1.12)	0.97 (0.84-1.13)	0.70

[a]Adjusted for age, education, race, marital status, height, body mass index, physical activity, pack-years of smoking, alcohol intake at 45y, fruit and vegetable intake, red meat intake, multivitamin use, self-rated health, family history of colon, lung, and hematological cancers (as separate terms), sigmoidoscopy in the past 10y, diabetes, use of cholesterol-lowering medications, use of blood pressure medications, coronary heart disease, osteoarthritis/chronic joint pain, migraine/chronic headaches, ulcers, and use of other NSAIDs. Additionally adjusted for family history of breast cancer, mammogram in the past 2y, age at menarche, age at menopause, age at first birth, years of estrogen therapy, years of combined hormone therapy, and hysterectomy (among women); and family history of prostate cancer and PSA test in the past 2y (among men).

[b]Includes ibuprofen, naproxen, and COX-2 inhibitors

[c]Includes regular-strength aspirin, ibuprofen, naproxen, and COX-2 inhibitors

[d]Includes cancers of the lung, head and neck, pancreas, skin, kidney, bladder, brain, hematologic malignancies, and other sites shared between the sexes (except colorectal and breast)

[e]Includes cancers of the female breast and reproductive system

[f]Includes cancers of the male reproductive system