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Nonsteroidal Antiinflammatory Drugs and Bladder Cancer: A Pooled Analysis

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Case-control studies have shown that regular use of nonsteroidal antiinflammatory drugs (NSAIDs) decreases bladder cancer risk, but few cohort studies have evaluated this association. The authors investigated NSAID use and bladder cancer in 3 large prospective studies (NIH-AARP Diet and Health Study; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; and U.S. Radiologic Technologists Study). Frequency of aspirin and nonaspirin NSAID use 1 year prior to baseline was ascertained using self-administered questionnaires. Study-specific hazard ratios and 95% confidence intervals were estimated using Cox regression models and were combined using a fixed-effects meta-analytic model. Data from all studies were aggregated, and aggregated hazard ratios were estimated. The analysis included 508,842 individuals, with 2,489 incident cases of bladder cancer. A reduction in risk was observed for individuals who reported regular use (>2 times/week) of nonaspirin NSAIDs compared with those who reported no use (hazard ratio (HR) = 0.92, 95% confidence interval (CI): 0.81, 1.04). The risk reduction was limited to nonsmokers (HR = 0.58, 95% CI: 0.41, 0.83) (P_{trend} = 0.008) ($P_{\text{interaction}}$ = 0.02). No association was observed between regular aspirin use and bladder cancer risk (HR = 1.04, 95% CI: 0.94, 1.15). Results suggest that nonaspirin NSAIDs, but not aspirin, are associated with a reduction in risk of bladder cancer, particularly for nonsmokers.

anti-inflammatory agents, non-steroidal; aspirin; meta-analysis; urinary bladder neoplasms

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH-AARP, National Institutes of Health (NIH)-AARP [Diet and Health Study]; NSAID, nonsteroidal antiinflammatory drug; PLCO, Prostate, Lung, Colorectal and Ovarian [Cancer Screening Trial]; USRT, U.S. Radiologic Technologists [Study].

Several case-control studies have reported an inverse association with bladder cancer risk for individuals who reported regular use of nonaspirin, nonsteroidal antiinflammatory drugs (NSAIDs) (1–3). The one known prospective cohort study published to date on nonaspirin NSAIDs (4) and a record linkage study in Denmark (5), however, have not supported these findings. Three case-control studies (2, 6, 7) reported a protective association between aspirin and bladder cancer, while other case-control and cohort studies, as well as the Women's Health Study, have found no association with aspirin use (3, 4, 8–12) or an elevated association (13, 14).

NSAIDs inhibit cyclooxygenase-1 and cyclooxygenase-2, a rate-limiting enzyme induced by endogenous (growth factors or cytokines) and exogenous (tobacco carcinogens) stimuli, and are involved in prostaglandin synthesis and the inflammatory response. At high concentrations, NSAIDs have anticarcinogenic properties operating through cyclooxygenase-2-dependent and -independent pathways to inhibit cellular proliferation, inhibit angiogenesis, and induce apoptosis (15, 16). Although not expressed in normal urothelial tissue, cyclooxygenase-2 has been shown to be overexpressed in both transitional cell and squamous cell urothelial tumor tissue (17–20). In vitro and in vivo research suggests that NSAIDs and selective cyclooxygenase-2 inhibitors hinder growth and survival of bladder cancer cells and nitrosamine-induced tumors (21–24).

Because of the limited and conflicting epidemiologic reports, we investigated the association between NSAIDs and bladder cancer risk using 3 large, prospective cohort studies. Our large sample size enabled us to conduct subgroup analyses by gender and smoking status; previous studies have been underpowered to examine potential effect modification by these important bladder cancer risk factors.

MATERIALS AND METHODS

Data sources

We combined data from 3 National Cancer Institute cohorts that met the following criteria: 1) separate assessment of aspirin and nonaspirin NSAID use; 2) assessment of NSAID use over a similar time frame (12 months prior to baseline); and 3) availability of a substantial number of bladder cancer cases (>100), particularly among women because few prospective cohort studies have evaluated the association of NSAIDs with the risk of bladder cancer among women. The cohorts identified for this study were the National Institutes of Health (NIH)-AARP Diet and Health Study; the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial; and the U.S. Radiologic Technologists (USRT) Study. All 3 studies have been approved by institutional review boards at the National Cancer Institute.

NIH-AARP Study. NIH-AARP is a prospective cohort study of diet and lifestyle factors initiated in 1995–1996. A baseline questionnaire was sent to 3.5 million members of AARP (formerly the American Association of Retired Persons), aged 50–71 years, from 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia; and Detroit, Michigan) and was returned by 617,119 individuals (17.6%) (25). A second questionnaire, which contained information on NSAID use, was sent in 1996–1997 to all participants and was completed by 334,908 of them (59% of the 566,402 eligible at baseline).

PLCO Cancer Screening Trial. PLCO is a multicenter, randomized trial designed to evaluate the effectiveness of prostate, lung, colorectal, and ovarian cancer screening modalities on disease-specific mortality (26, 27). The trial enrolled 154,952 subjects (49.5% men) aged 55–74 years at 10 US screening centers (Washington, DC; Detroit, Michigan; Salt Lake City, Utah; Denver, Colorado; Honolulu, Hawaii; Minneapolis, Minnesota; Marshfield, Wisconsin; Pittsburgh, Pennsylvania; St. Louis, Missouri; and Birmingham, Alabama) between October 1993 and July 2001. A questionnaire that included items about NSAID use was administered at the initial screening or soon after enrollment (96.8% of subjects completed the questionnaire).

USRT Study. USRT is a prospective cohort study of radiologic technologists who had been certified for at least 2 years by the American Registry of Radiologic Technologists between 1926 and 1980 (28, 29). The first questionnaire that ascertained NSAID use was sent to all living individuals in the target population in 1994–1998 (N = 126,628) and was returned by 90,972 participants (71.8%).

Bladder cancer case ascertainment

Incident cases of primary carcinoma of the urinary bladder, including carcinoma in situ (*International Classification of Diseases for Oncology*, Third Edition, codes C670–679), were ascertained by annual questionnaires and were subsequently confirmed using medical records (PLCO), by self-report on a subsequent questionnaire with medical record validation (USRT) (29), or by record linkage to state cancer registries (NIH-AARP). Previous validation studies for NIH-AARP have shown a high level of ascertainment of incident cancer cases (≥90%) from cancer registries (16).

Individuals were excluded if they reported a previous cancer at baseline (NIH-AARP: n = 18,881; PLCO: n = 11,730; USRT: n = 3,635); lacked information on both aspirin and nonaspirin NSAID use (NIH-AARP: n = 2,876; PLCO: n = 210; USRT: n = 3,179); had questionnaires filled out by proxies (NIH-AARP: n = 10,383); or died of an unknown cause, had an undetermined case status because of loss to follow-up, were missing date of death (USRT: n = 21,078), or withdrew from the study (PLCO: n = 18). The analytic population consisted of 508,842 individuals, with 2,489 (2,066 men, 423 women) individuals with incident bladder cancer.

Assessment of NSAIDs use

Information on the frequency of NSAID use was obtained by a self-administered questionnaire. Whereas PLCO asked specifically about aspirin and ibuprofen-containing products (e.g., Advil, Nuprin, Motrin), NIH-AARP and USRT asked about aspirin and more generally about nonaspirin NSAIDs (USRT: Ibuprofen, Motrin, Naprosyn, Advil; NIH-AARP: generic ibuprofen, Advil, Nuprin, Motrin, Aleve, Orudis, Ketoprofen, Naprosyn, Anaprox, Feldene, Piroxicam, Clinoril, Sulindac, Indocin, Indomethacin, Relafen, Nalfon, Nambumetone, Fenoprofen). Participants were specifically instructed not to include Tylenol or other pain relievers in their reports. Frequency of acetaminophen use was not ascertained by NIH-AARP and PLCO, and phenacetin was not captured by any of the cohorts, so these drugs were not evaluated.

Covariate information

All studies collected information on gender, race/ethnicity, weight and height, smoking status, and smoking habits (time since quitting and cigarette smoking intensity). PLCO and USRT also obtained information on the duration of cigarette smoking.

Statistical methods

Study-specific hazard ratios and 95% confidence intervals for the association of aspirin and nonaspirin NSAID use with bladder cancer risk were calculated using Cox proportional hazards models, with age as the time metric. Follow-up started at age at baseline (defined as the time when NSAID exposure was ascertained) and ended at age at bladder cancer diagnosis or age at censoring. Censoring events

were diagnosis of any other cancer, death, or end of the study. Three categories for frequency of NSAID use were created based on the literature: no use (referent), nonregular use ($\leq$2 times/week), and regular use (>2 times/week), with regular use subdivided into less than daily use (>2–6 times/week) and daily use ($\geq$7 times/week). NIH-AARP and PLCO assessed frequency of use in similar categories (none, <2/month, 2–3/month, 1–2/week, 3–4/week, 5–6/week (NIH-AARP only), 1/day, $\geq$2/day), with NIH-AARP asking about the number of times and PLCO asking about the number of pills taken per day, per week, and per month. The USRT categories were none, <1 day/month, 1–4 days/month, 5–14 days/month, 15–21 days/month, $\geq$22 days/month. We harmonized USRT as no use, $\leq$14 days/month (nonregular), 15–21 days/month (regular less than daily), and $\geq$22 days/month (daily) by identifying the frequency of use closest to the categories established a priori for the other 2 cohorts.

We checked the assumption of proportional hazards by using a Wald chi-square test with 1 df, and we found a significant interaction between age and reported daily use of nonaspirin NSAIDs in the PLCO ($P_{interaction} = 0.03$) and USRT ($P_{interaction} = 0.03$) cohorts. Although this interaction was not found in NIH-AARP, it was present in the aggregated data set ($P_{interaction} = 0.03$). When a 3-df global test was used, however, no interaction was observed in any of the cohorts or in the combined data set ($P_{global} = 0.10$). Given our findings for daily use of nonaspirin NSAIDs, we present all results for all ages combined and stratified by age $\leq$75 years and age >75 years. For models of regular use that combine daily and moderate categories, no interaction was found in the aggregated data ($P_{global} = 0.45$; $P_{interaction} = 0.21$); thus, all models of regular use are presented with complete follow-up for all cohorts.

Final study-specific models were adjusted for cohort-specific confounding variables. For NIH-AARP, the variables were smoking status and smoking intensity measured as cigarettes per day (never use, former use of 1–20, former use of 21–40, former use of $\geq$41, current use of 1–20, current use of 21–40, current use of $\geq$41), race (white, other), body mass index (18.2–<25 kg/m^2 as the referent, 25–<30 kg/m^2, and $\geq$30 kg/m^2), gender, and mutual adjustment for aspirin and nonaspirin NSAIDs. For PLCO, the relevant variables were pack-years of smoking and smoking status, race, gender, body mass index, and mutual adjustment for aspirin and nonaspirin NSAIDs. Finally, for USRT, the variables were pack-years of smoking and smoking status, birth cohort, number of years working as a radiation technologist, gender, and mutual adjustment for aspirin and nonaspirin NSAIDs.

Tests for linear trend of bladder cancer risk with increasing frequency of NSAID use were evaluated by entering a categorical variable into the model that contained the median value of each exposure category. The coefficient for that variable was evaluated using the Wald test.

Study-specific hazard ratios were combined using fixed-effects and random-effects meta-analytic models. Between-study heterogeneity was tested using the I^2 statistic (30). Because of a lack of evidence of parameter heterogeneity, in this paper we present results from the fixed-effects meta-analytic models.

Because parameter estimates were similar between studies, we aggregated information for all 508,842 individuals into one data set and estimated an aggregated hazard ratio adjusted for smoking status and cigarette dose, study, race, body mass index, and mutual adjustment for aspirin and nonaspirin NSAIDs. A combined smoking variable common to all cohorts was created from smoking status and cigarettes smoked per day (former use of 1–20, former use of 21–40, former use of $\geq$41, current use of 1–20, current use of 20–40, current use of $\geq$41) since NIH-AARP did not ascertain duration of cigarette smoking. Indicator variables were created for missing values, where appropriate. No covariate was missing for more than 5% of the data. Indication for aspirin and nonaspirin NSAID use, including history of hypertension, heart disease, and arthritis (PLCO only), was evaluated but did not change the results substantially and therefore was not included in the final model.

Additional analyses were performed for urothelial carcinomas only ($n = 2,271$, 91.3%, using *International Classification of Diseases for Oncology*, Third Edition, histology codes 8120, 8120/3, 8122, 8130, 8130/2, 8130/3) and by tumor grade and morphology behavior ($n = 2,387$ with grade or morphology data, 882 (37.0%) in situ according to the behavior code). Cases were divided into 3 groups 1) low-grade (grade 1 in situ); 2) intermediate-grade (grade 1 malignant or grade 2); and 3) high-grade (grade 3 or 4 including high-grade in situ) tumors. Stage or pathology information was not available for most cases.

Analyses were stratified by gender, smoking status, and body mass index. Heterogeneity across strata was assessed by the likelihood ratio test comparing models with and without the corresponding interaction term.

Sensitivity analyses were performed to evaluate the possibility of bias introduced by early symptoms of cancer influencing self-reported use of NSAIDs. A lag time of 1 year (2,208 cases) and 2 years (1,853 cases) was introduced such that follow-up time for cohort members and individuals who were diagnosed with bladder cancer within the first year and second year, respectively, after the baseline questionnaire was removed from the analysis.

RESULTS

All 3 cohort studies combined yielded 508,842 individuals (262,680 men and 246,162 women). A total of 3,582,284 person-years were accrued, during which 2,489 incident cases of bladder cancer were identified.

The baseline median age (NIH-AARP: 63.5 years; PLCO: 62.5 years) and prevalence of regular aspirin use (NIH-AARP: 34.8%; PLCO: 34.5%) and nonaspirin NSAID use (NIH-AARP: 16.3%; PLCO: 15.2%) were comparable among PLCO and NIH-AARP participants (Table 1). The prevalence of regular aspirin use among USRT participants was lower (aspirin: 11.2%) compared with the other cohorts, although the prevalence of regular use in USRT for the same age range as PLCO and NIH-AARP (55–75 years) was similar (data not shown).

Regular aspirin users were more likely to be older, be male, be white, and have a higher body mass index than

Table 1. Characteristics of the Cohort Studies Included in the Multicohort Analysis of Aspirin and Nonaspirin NSAID Use and Risk of Bladder Cancer Among Men and Women, NIH-AARP, PLCO, USRT

Study	Follow-up Period	No. of Subjects in the Baseline Cohorts	No. of Cases	Baseline Median Age, Years (IQR)	Prevalence of Aspirin Use, %				Prevalence of Nonaspirin NSAID Use,[a] %			
					No Use	≤2/Week	>2–6/Week	≥7/Week	No Use	≤2/Week	>2–6/Week	≥7/Week
Overall	1993–2005	508,842	2,489	62.1 (56.9–66.8)	36.0	32.0	8.5	23.5	49.7	34.6	5.9	9.9
Men		262,680	2,066	63.0 (58.2–67.3)	29.0	31.8	9.5	29.7	54.1	33.3	4.8	7.9
Women		246,162	423	60.9 (55.5–66.2)	43.6	32.2	7.4	16.9	44.9	36.1	7.0	12.1
NIH-AARP	1996–2003	302,768	1,681	63.5 (58.7–67.3)	26.9	38.2	9.6	25.2	43.7	40.0	6.1	10.2
Men		176,650	1,431	63.7 (58.9–67.4)	21.6	37.6	10.3	30.5	46.4	40.5	5.1	8.0
Women		126,118	250	63.1 (58.3–67.1)	34.4	39.2	8.7	17.7	40.0	39.2	7.6	13.3
PLCO	1993–2005	142,994	706	62.5 (58.5–67.2)	50.9	14.6	8.3	26.2	70.5	14.2	5.5	9.7
Men		72,130	580	62.7 (58.6–67.2)	46.4	15.1	8.8	30.3	75.0	13.0	4.4	7.6
Women		70,864	126	62.3 (58.3–67.1)	56.0	14.2	7.9	22.0	66.0	15.5	6.7	11.8
USRT[b]	1994–2004	63,080	102	46.4 (41.5–52.9)	46.7	42.1	2.9	8.3	29.9	56.1	5.4	8.7
Men		13,900	55	48.5 (43.5–56.4)	35.7	46.0	3.6	14.7	42.2	47.6	3.5	6.7
Women		49,180	47	45.5 (40.8–52.3)	49.9	41.0	2.7	6.4	26.5	58.4	5.9	9.3

Abbreviations: IQR, interquartile range; NIH-AARP, National Institutes of Health (NIH)-AARP Diet and Health Study; NSAID, nonsteroidal antiinflammatory drug; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; USRT, U.S. Radiologic Technologists Study.

[a] Nonaspirin NSAIDs defined for PLCO: Advil, Nuprin, Motrin; for USRT: Ibuprofen, Motrin, Naprosyn, Advil; and for NIH-AARP: generic Ibuprofen, Advil, Nuprin, Motrin, Aleve, Orudis, Ketoprofen, Naprosyn, Anaprox, Feldene, Piroxicam, Clinoril, Sulindac, Indocin, Indomethacin, Relafen, Nalfon, Nambumetone, or Fenoprofen.

[b] USRT categories differed slightly because of definitions provided on the questionnaire: no use, ≤14/month; 15–21/month, ≥22 days/month.

individuals who reported no use of aspirin (Table 2). Former smokers were more likely to be regular aspirin users compared with never and current smokers. Regular nonaspirin NSAID users were more likely to be female, be white, and have a higher body mass index than individuals who reported no use of nonaspirin NSAIDs.

A reduction in risk was observed for regular use of nonaspirin NSAIDs in the fixed-effects meta-analysis (hazard ratio (HR) = 0.90, 95% confidence interval (CI): 0.80, 1.02; $P = 0.10$) (Table 3). No significant heterogeneity was observed between the study-specific hazard ratios for nonaspirin NSAID use overall ($\chi^2 = 1.41$, $P_{\text{heterogeneity}} = 0.50$) or when stratified by age (≤75 years: $\chi^2 = 2.16$, $P_{\text{heterogeneity}} = 0.34$; >75 years: $\chi^2 = 2.57$, $P_{\text{heterogeneity}} = 0.28$). When we stratified by age 75 years, a significant inverse association was observed for regular nonaspirin NSAID users compared with nonusers in the age ≤75 years group (HR = 0.87, 95% CI: 0.77, 0.99), but no association was observed in the age >75 years group (HR = 1.13, 95% CI: 0.80, 1.59; $P_{\text{interaction}} = 0.21$) (Table 3). Results from the aggregated analysis were similar to those from the meta-analysis (Table 3). We observed no significant trend in risk with increasing frequency of nonaspirin NSAID use ($P = 0.30$). The protective association between regular nonaspirin NSAID use and bladder cancer was stronger for women (HR = 0.78, 95% CI: 0.59, 1.03) than for men (HR = 0.96, 95% CI: 0.84, 1.10), although this difference was not significant ($P_{\text{interaction}} = 0.14$) (Table 4). Adjustment for history of cardiovascular disease as a proxy for low-dose aspirin use had no impact on our results.

No association was observed between aspirin use and risk of bladder cancer in the fixed-effects meta-analytic model (HR = 1.04, 95% CI: 0.94, 1.14) or the aggregate data (HR = 1.04, 95% CI: 0.94, 1.15) (Table 4). In addition, no significant differences were found by gender or smoking status.

Since smoking is an important risk factor for bladder cancer and constituents of tobacco smoke increase cyclooxygenase-2 expression (31, 32), we stratified our pooled data by smoking status. A significant 40% reduction in risk of bladder cancer was found for nonsmokers who reported regular use of nonaspirin NSAIDs (HR = 0.58, 95% CI: 0.41, 0.83; $P_{\text{trend}} = 0.008$); no association was observed for former smokers (HR = 0.98, 95% CI: 0.85, 1.14) or current smokers (HR = 0.98, 95% CI: 0.74, 1.29) ($P_{\text{interaction}} = 0.02$) (Table 5). Similar inverse associations for nonsmokers were found for regular nonaspirin NSAID users by gender (HR for males = 0.58, 95% CI: 0.38, 0.89; HR for females = 0.61, 95% CI: 0.33, 1.15). Former smokers were further stratified by recency of quitting smoking. No reduction in risk was observed for individuals who reported regular use of nonaspirin NSAIDs and quit smoking more than 10 years ago (HR = 0.96, 95% CI: 0.80, 1.15) or quit in the last 10 years (HR = 1.01, 95% CI: 0.78, 1.32).

Because use of aspirin and nonaspirin NSAIDs was positively correlated in our data set ($\rho = 0.028$), we compared those individuals who exclusively reported use of nonaspirin NSAIDs with those who had not used either aspirin or nonaspirin NSAIDs. No significant association was observed for exclusive users (HR = 0.98, 95% CI: 0.79, 1.21), but

Table 2. Selected Characteristics of Participants by Aspirin and Nonaspirin NSAID Use in a Pooled Analysis, NIH-AARP, PLCO, USRT

	Aspirin								Nonaspirin NSAID							
	No Use		≤2/Week		>2–6/Week		≥7/Week		No Use		≤2/Week		>2/–6/Week		≥7/Week	
	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%	Median (IQR)	%
Baseline age, years	61.6 (56.4–66.5)		61.0 (55.7–66.0)		62.8 (58.2–67.1)		64.2 (59.5–67.9)		63.3 (58.4–67.5)		60.3 (54.7–65.6)		60.9 (56.2–65.8)		62.5 (57.5–67.0)	
Sex: male		41.9		51.7		58.4		65.6		56.4		49.7		42.5		41.1
Race: white		89.6		92.3		93.6		93.2		90.4		93.1		92.9		92.2
Body mass index, kg/m²	25.9 (23.4–29.3)		25.9 (23.5–28.9)		26.2 (23.8–29.2)		26.7 (24.3–29.9)		25.9 (23.6–29.1)		25.9 (23.4–29.0)		26.6 (24.0–30.1)		27.4 (24.4–31.2)	
Smoking status																
Never		40.2		32.5		8.0		19.2		50.2		34.9		5.6		9.3
Former		32.5		31.4		8.9		27.3		48.7		34.9		6.1		10.4
Current		36.4		32.8		8.3		22.5		50.3		33.6		6.0		10.2

Abbreviations: IQR, interquartile range; NIH-AARP, National Institutes of Health (NIH)-AARP Diet and Health Study; NSAID, nonsteroidal antiinflammatory drug; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; USRT, U.S. Radiologic Technologists Study.

power was low because of the smaller number of cases who were exclusive users (*n* = 106). Exclusive regular aspirin users had a higher risk (HR = 1.12, 95% CI: 0.99, 1.27), but there was no association for users of both aspirin and nonaspirin NSAIDs (HR = 1.03, 95% CI: 0.91, 1.16).

The magnitude of the association between regular nonaspirin NSAID use and bladder cancer did not change when we excluded the first year of follow-up (HR = 0.91, 95% CI: 0.80, 1.04), although, for the second year of follow-up, it was closer to the null (HR = 0.96, 95% CI: 0.84, 1.11) compared with the nonlagged analysis (HR = 0.92, 95% CI: 0.81, 1.04). The null associations between regular aspirin use and risk of bladder cancer were unaffected by the lagged time analysis (data not shown).

When we restricted the analysis to urothelial carcinoma, we observed associations similar to the overall findings (HR = 0.92, 95% CI: 0.81, 1.04). Although no association between regular use of nonaspirin NSAIDs and low-grade in situ tumors was observed (HR = 1.03, 95% CI: 0.73, 1.45), suggestive inverse associations were observed with intermediate (HR = 0.83, 95% CI: 0.68, 1.01) and high-grade (HR = 0.92, 95% CI: 0.75, 1.13) bladder cancers.

DISCUSSION

To our knowledge, this multicohort analysis is the largest prospective evaluation of NSAIDs and bladder cancer risk to date. It included 3 well-characterized prospective cohort studies with similar assessments of the frequency of NSAID use. We observed a reduction in risk of bladder cancer for men and women who reported regular use of nonaspirin NSAIDs compared with those who reported no use. We found a significant risk reduction associated with nonaspirin NSAIDs for nonsmokers but saw no effect for smokers. Since the baseline risk of bladder cancer is lower for nonsmokers, the modest reduction in risk conferred by NSAIDs may be more evident.

In several case-control studies, nonaspirin NSAID use has been shown to reduce risk of bladder cancer (1–3). Inverse associations with nonaspirin NSAID use have been reported with increasing cumulative lifetime exposure to nonaspirin NSAIDs (2), longer duration of nonaspirin NSAID use (3), and nonsmoking status (1). One record linkage study from Denmark reported elevated standardized incidence ratios for bladder cancer for individuals prescribed nonaspirin NSAIDs (5). Although these results may suggest an elevation in risk due to nonaspirin NSAIDs, other noncausative explanations such as surveillance bias, potential misclassification due to lack of accounting for over-the-counter medication use, and failure to control for smoking status cannot be ruled out. Another cohort study reported null results for regular ibuprofen use and bladder cancer in men (4), although the number of case events was small.

In contrast to previous studies, we found a significant interaction of reported daily use of nonaspirin NSAIDs and age in the PLCO and USRT cohorts, with an inverse association in the age ≤75 years group and an elevated association in those aged >75 years. This interaction was not found in NIH-AARP, however. We investigated the distribution of key confounders (body mass index, smoking

Table 3. Bladder Cancer Risk and Use of Nonaspirin NSAIDs Stratified by Age 75 Years in a Pooled Analysis, NIH-AARP, PLCO, USRT

Study and Use	Overall			Censored at Age 75 Years			Entry at Age 75 Years		
	No. of Cases	HR[a]	95% CI	No. of Cases	HR[a]	95% CI	No. of Cases	HR[a]	95% CI
PLCO									
No use	525	1.00	Ref	417	1.00	Ref	108	1.00	Ref
Nonregular[b]	89	0.97	0.77, 1.22	76	1.00	0.77, 1.28	13	0.82	0.45, 1.49
Regular[b]	90	0.94	0.75, 1.18	66	0.83	0.64, 1.08	24	1.39	0.89, 2.17
>2–6/week	28	0.83	0.56, 1.21	23	0.78	0.51, 1.20	5	1.05	0.43, 2.60
Daily	62	0.99	0.76, 1.30	43	0.86	0.63, 1.18	19	1.52	0.93, 2.48
P_{global}								0.16	
$P_{interaction}$								0.03	
NIH-AARP									
No use	804	1.00	Ref	730	1.00	Ref	74	1.00	Ref
Nonregular[b]	632	0.99	0.89, 1.10	586	0.99	0.89, 1.10	46	1.01	0.70, 1.47
Regular[b]	224	0.89	0.77, 1.03	209	0.89	0.76, 1.03	15	0.77	0.44, 1.35
>2–6/week	75	0.85	0.67, 1.08	74	0.85	0.67, 1.08	1	0.17	0.02, 1.21
Daily	149	0.91	0.76, 1.09	135	0.91	0.76, 1.09	14	1.04	0.59, 1.85
P_{global}								0.38	
$P_{interaction}$								0.74	
USRT									
No use	44	1.00	Ref	40	1.00	Ref	4	1.00	Ref
Nonregular[b]	37	0.81	0.51, 1.30	35	0.77	0.48, 1.26	2	1.35	0.22, 8.18
Regular[b]	16	0.92	0.50, 1.69	13	0.80	0.41, 1.54	3	2.03	0.33, 12.50
>2–6/week	6	1.25	0.52, 3.01	6	1.27	0.53, 3.07	0	0.0	
Daily	10	0.79	0.39, 1.63	7	0.60	0.26, 1.39	3	3.03	0.53, 17.20
P_{global}								0.17	
$P_{interaction}$								0.03	
Meta-analytic									
No use	1,373	1.00	Ref	1,187	1.00	Ref	186	1.00	Ref
Nonregular[b]	758	0.98	0.89, 1.07	697	0.98	0.89, 1.08	61	0.96	0.71, 1.32
Regular[b]	330	0.90	0.80, 1.02	288	0.87	0.77, 0.99	42	1.13	0.80, 1.59
>2–6/week	109	0.86	0.71, 1.05	103	0.85	0.70, 1.04	6	0.77	0.34, 1.74
Daily	221	0.93	0.81, 1.07	185	0.89	0.76, 1.03	36	1.35	0.93, 1.94
$P_{heterogeneity}$		0.50			0.34			0.28	
Pooled									
No use	1,373	1.00	Ref	1,187	1.00	Ref	186	1.00	Ref
Nonregular[b]	758	0.99	0.91, 1.09	697	0.99	0.90, 1.09	61	1.02	0.75, 1.38
Regular[b]	330	0.92	0.81, 1.04	288	0.89	0.78, 1.01	42	1.14	0.81, 1.60
>2–6/week	109	0.87	0.71, 1.06	103	0.89	0.73, 1.09	6	0.57	0.25, 1.29
Daily	221	0.94	0.82, 1.09	185	0.89	0.76, 1.04	36	1.37	0.96, 1.97
P_{global}								0.10	
$P_{interaction}$								0.03	

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH-AARP, National Institutes of Health (NIH)-AARP Diet and Health Study; NSAID, nonsteroidal antiinflammatory drug; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; Ref, reference; USRT, U.S. Radiologic Technologists Study.

[a] Adjusted for aspirin or nonaspirin NSAIDs as appropriate, smoking status, cigarette dose, study, white race, and body mass index.

[b] Nonregular use was defined as ≤2/week, and regular use was defined as >2/week.

status, race, history of heart disease and hypertension) associated with regular nonaspirin NSAID use for differences by age in the 2 larger cohorts. No differential behavior in the patterns was observed by age in either cohort. This interaction could thus be due to residual confounding or be a chance finding.

Table 4. Bladder Cancer Risk and Use of Nonaspirin NSAIDs or Aspirin Among Men and Women in a Pooled Analysis, NIH-AARP, PLCO, USRT

	Overall			Male			Female		
	No. of Cases	HR[a]	95% CI	No. of Cases	HR[a]	95% CI	No. of Cases	HR[a]	95% CI
Nonaspirin NSAIDS[b]									
No use	1,373	1.00	Ref	1,161	1.00	Ref	212	1.00	Ref
Nonregular[c]	758	0.99	0.90, 1.09	618	0.97	0.88, 1.08	140	1.07	0.85, 1.34
Regular[c]	330	0.92	0.81, 1.04	264	0.96	0.84, 1.10	66	0.78	0.59,1.03
>2–6/week	109	0.87	0.71, 1.06	89	0.92	0.74, 1.14	20	0.69	0.44, 1.10
7/week	221	0.94	0.82, 1.09	175	0.98	0.84, 1.15	46	0.82	0.59, 1.13
Aspirin									
No use	733	1.00	Ref	560	1.00	Ref	173	1.00	Ref
Nonregular[c]	717	1.03	0.92, 1.15	584	1.02	0.91, 1.15	133	1.06	0.84, 1.34
Regular[c]	1,004	1.04	0.94, 1.15	895	1.06	0.95, 1.18	109	0.92	0.73, 1.18
>2–6/week	229	1.00	0.86, 1.16	197	1.01	0.86, 1.19	32	0.96	0.66, 1.41
≥7/week	775	1.05	0.95, 1.17	698	1.08	0.96, 1.20	77	0.91	0.70, 1.20

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH-AARP, National Institutes of Health (NIH)-AARP Diet and Health Study; NSAID, nonsteroidal inflammatory drug; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; Ref, reference; USRT, U.S. Radiologic Technologists Study.

[a] Adjusted for aspirin or nonaspirin NSAIDs as appropriate, smoking status, cigarette dose, study, white race, and body mass index.

[b] Nonaspirin NSAIDs defined for PLCO: Advil, Nuprin, Motrin; for USRT: Ibuprofen, Motrin, Naprosyn, Advil; and for NIH-AARP: generic Ibuprofen, Advil, Nuprin, Motrin, Aleve, Orudis, Ketoprofen, Naprosyn, Anaprox, Feldene, Piroxicam, Clinoril, Sulindac, Indocin, Indomethacin, Relafen, Nalfon, Nambumetone, or Fenoprofen.

[c] Nonregular use was defined as ≤2/week, and regular use was defined as >2/week.

We observed no association with bladder cancer risk for regular aspirin users. Three case-control studies have reported a reduction in risk of bladder cancer for regular (6, 7) and heavy (2) users of aspirin, although this inverse association has not been replicated by other case-control (9, 10) or cohort (4, 8, 11, 14) studies. A nonsignificant inverse association was found in the Cancer Prevention Study II Nutrition Cohort for current daily users of adult-strength aspirin (325 mg) reporting a duration of ≥5 years, while no association was found for those less-frequent or lower-dose users (33). The inconsistency in aspirin associations with bladder cancer may in part be due to lack of information on aspirin dose (4) or evaluation of aspirin at concentrations too low to have a significant impact on development of bladder carcinogenesis (8). With the exception of the Cancer Prevention Study II Nutrition Cohort, most cohort studies to date evaluating the association with aspirin, including those in this pooled analysis, did not ascertain aspirin dose. Aspirin, in particular, requires high concentrations to inhibit cyclooxygenase-2, and NSAIDs in general require higher concentrations to exhibit antitumorigenic and proapoptotic associations (15). Dose information may be particularly important in the evaluation of aspirin because it is commonly prescribed at low doses (80 mg) for cardioprotective purposes.

Aspirin and nonaspirin NSAIDs inhibit cyclooxygenase-1- and cyclooxygenase-2-dependent and -independent mechanisms to varying degrees depending on dose and formulation. Nonaspirin NSAIDs, including ibuprofen, indomethacin, and sulindac, have been found to be more potent than aspirin in inducing antiproliferative and proapoptotic mechanisms, such as the suppression of NF-κB, a transcription factor involved in mediating the inflammatory response and regulating expression of cyclooxygenase-2 and cyclin D1 (34, 35). Although aspirin has been found to reduce risk of cancers at other sites, the potency of nonaspirin NSAIDs may be tissue specific. Urogenital tumor cells (compared with those of the lung or breast) have been shown to be particularly sensitive to ibuprofen-induced expression of the p75[NTR] tumor suppressor gene that may trigger downstream cyclooxygenase-2-independent mechanisms (34).

When we stratified our data by smoking status, a significant reduction in risk with nonaspirin NSAIDs was observed for both men and women nonsmokers. A similar reduction in risk of bladder cancer for nonsmokers has been reported previously (1), and a nonsignificant reduction in risk with total NSAID use (ibuprofen and aspirin combined) for nonsmokers was found in the Health Professionals Follow-up Study (4). While many reports found no differences in NSAID use by smoking status for other smoking-related cancers, a few reports on lung cancer (36) and all cancer incidence (8, 37) have shown differences in NSAID associations (total NSAID use and aspirin only, respectively) by smoking status, with the strongest inverse relations observed for former smokers or nonsmokers.

We did not account for occupation as a potential confounder because occupational information was not available for any of the cohorts. Another large bladder case-control study conducted in Spain, however, found that adjusting for occupational status made little difference in the NSAID parameter estimates (3), suggesting that occupation

Table 5.   Bladder Cancer Risk and Use of Nonaspirin NSAIDs or Aspirin Among Men and Women by Smoking Status in a Pooled Analysis, NIH-AARP, PLCO, USRT

	Nonsmokers			Former Smokers			Current Smokers		
	No. of Cases	HR[a]	95% CI	No. of Cases	HR[a]	95% CI	No. of Cases	HR[a]	95% CI
Nonaspirin NSAIDs[b]									
No use	269	1.00	Ref	803	1.00	Ref	256	1.00	Ref
Nonregular[c]	124	0.91	0.72, 1.14	469	1.00	0.89, 1.13	145	1.08	0.88, 1.34
Regular[c]	35	0.58	0.41, 0.83	220	0.98	0.85, 1.14	64	0.98	0.74, 1.29
>2–6/week	11	0.52	0.29, 0.96	78	1.00	0.79, 1.26	18	0.80	0.49, 1.29
≥7/week	24	0.61	0.40, 0.94	142	0.97	0.81, 1.17	46	1.08	0.79, 1.48
P_{trend}		0.008			0.90			0.97	
$P_{interaction}$									0.02
Aspirin									
No use	155	1.00	Ref	403	1.00	Ref	152	1.00	Ref
Nonregular[c]	126	0.96	0.75, 1.23	425	1.08	0.94, 1.24	142	0.94	0.74, 1.19
Regular[c]	144	0.93	0.74, 1.18	663	1.09	0.96, 1.24	169	0.99	0.79, 1.23
>2–6/week	31	0.75	0.51, 1.11	159	1.17	0.97, 1.41	33	0.75	0.52, 1.10
≥7/week	113	1.00	0.78, 1.28	504	1.07	0.94, 1.22	136	1.07	0.85, 1.35
P_{trend}		0.85			0.57			0.51	
$P_{interaction}$									0.84

Abbreviations: CI, confidence interval; HR, hazard ratio; NIH-AARP, National Institutes of Health (NIH)-AARP Diet and Health Study; NSAID, nonsteroidal antiinflammatory drug; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; Ref, reference; USRT, U.S. Radiologic Technologists Study.

[a] Adjusted for aspirin or nonaspirin NSAIDs as appropriate, cigarette dose for former and current smokers, study, white race, and body mass index.

[b] Nonaspirin NSAIDs defined for PLCO: Advil, Nuprin, Motrin; for USRT: Ibuprofen, Motrin, Naprosyn, Advil; and for NIH-AARP: generic Ibuprofen, Advil, Nuprin, Motrin, Aleve, Orudis, Ketoprofen, Naprosyn, Anaprox, Feldene, Piroxicam, Clinoril, Sulindac, Indocin, Indomethacin, Relafen, Nalfon, Nambumetone, or Fenoprofen.

[c] Nonregular use was defined as ≤2/week, and regular use was defined as >2/week.

would not likely be a large source of confounding in our data set.

Some misclassification of NSAID use likely occurred because the assessments relied solely on self-reports at baseline. While some underreporting of NSAID use has been noted, specificity tends to be high; reporting accuracy improves with more frequent and regular use (38, 39). In addition, any misclassification would be nondifferential and would therefore attenuate our results. Harmonizing the USRT frequency of NSAID use with the NSAID assessments from NIH-AARP and PLCO may have also caused some misclassification because some regular users (as defined in this analysis) were placed in the nonregular use category. However, the impact of this misclassification was negligible because of the small number of cases in USRT.

Further studies need to determine the optimal dose, duration, and critical time window within which nonaspirin NSAIDs are most effective at altering the natural history of bladder cancer. The stronger protective association with advanced tumors in our study suggests that nonaspirin NSAIDs may act later in the carcinogenic process by reducing the progression or promotion of bladder cancer. Additional epidemiologic studies on nonselective cyclooxygenase-2 inhibitors and bladder cancer progression are necessary because, for a large number of individuals diagnosed with bladder cancer, the cancer recurs.

To our knowledge, we conducted the largest prospective evaluation of NSAIDs and bladder cancer risk to date using 3 well-characterized cohort studies. Important risk factors for bladder cancer, including gender, smoking status, cigarette dose, and indications for NSAID use, were accounted for in the analysis. Our cohort-specific results support the hypothesis that regular use of nonaspirin NSAIDs, but not aspirin, is associated with a reduction in risk of bladder cancer, particularly for nonsmokers.

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