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Long-term NSAID use and Incident Urothelial Cell Carcinoma in the VITamins and Lifestyle Study

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Abstract

Purpose—Literature on the chemopreventive role of nonsteroidal anti-inflammatory drugs (NSAIDs) in urothelial carcinoma of the bladder (UC) is conflicting. A recent pooled analysis of three cohorts reported regular use of non-aspirin NSAIDs was associated with reduced risk of UC among non-smokers only; however, non-smokers are a group with a low risk of UC. We examine the association between NSAID use and UC risk.

Materials and Methods—Study participants were members of the VITamins and Lifestyle (VITAL) cohort of 77,048 Washington State residents aged 50–76 years who completed a baseline questionnaire in 2000–2002 on NSAID use and cancer risk factors. Ten-year use of aspirin and other NSAIDs was categorized as none, low-use (1–3 days/week or <4 years), or high-use (4 days/week and 4 years). Incident UC cases were prospectively identified via linkage to a local cancer registry. Hazard ratios (HR) were estimated by multivariate Cox regression.

Results—385 incident cases of UC were diagnosed over a mean follow-up of 7 years. There was no association with NSAID use and risk of UC. However, the association of use of non-aspirin NSAIDs with UC risk differed by smoking status (p for interaction = 0.02). Specifically, among long-term former smokers (quit 10 years), non-aspirin NSAID use was associated with a 31% reduction in risk of UC in low-users (HR 0.69, 95% CI 0.46–1.04), and 48% reduction in risk for high-users (HR 0.52, 95% CI 0.24–1.11, p for trend=0.02).

Conclusions—Our results show a risk reduction with non-aspirin NSAID use among long-term quitters, a group with significant risk of UC.

Keywords

Aspirin; cancer prevention; nonsteroidal anti-inflammatory drugs; urothelial carcinoma

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Introduction

Bladder cancer is the fourth most common cancer diagnosed in men [1]. There were over 70,000 new cases diagnosed in the United States in 2010, with 14,680 deaths. More than 90% of bladder cancer cases are urothelial carcinoma (UC). Although approximately 70% of incident UC cases present as non-muscle invasive tumors, as many as 50–70% of those tumors will recur and 10–20% will progress to muscle invasion [2]. The morbidity of UC results not only from progression, but also from the intensive surveillance and treatment of recurrences. Consequently, bladder cancer has the highest lifetime treatment costs per patient of all cancers [3]. This protracted natural history and economic burden make UC an ideal disease for chemoprevention.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have shown promise as chemoprevention in colorectal [4] and breast cancer [5], and there is growing evidence to support its role in UC. *In vitro* and *in vivo* studies have shown that NSAIDs can suppress UC development and growth [6, 7]. NSAIDs may interfere with carcinogenesis by inhibiting cyclooxygenase (COX), the rate-limiting enzyme in arachidonic acid metabolism. COX exists in two isoforms, COX 1 and 2. COX 1 is ubiquitously expressed in both normal and cancerous tissue, but COX 2 expression correlates with both high-grade and advanced-stage UC [8, 9]. COX 2 is produced in response to inflammation and leads to angiogenesis and reduced apoptosis [10].

The literature on NSAIDs as chemoprevention in UC is conflicting. Several case-control studies have reported a protective effect of NSAIDs [11–13]. However, cohort studies, including the Health Professionals Follow-up Study, reported no association between NSAID use and UC [14, 15]. Collectively, these studies were limited by the inability to control for UC risk factors (e.g., smoking), generalizability (e.g. cohort of health care professionals), and by potential recall bias in case-control study. One recent pooled analysis from three large prospective cohorts only found a reduced risk of UC among people who reported regular use (>2 times/week) of non-aspirin NSAIDs who were non-smokers [16]. However, non-smokers are at low risk for UC. Chemoprevention strategies, if effective, would be most beneficial for those at higher baseline risk for UC, such as former smokers.

Given these limitations and conflicting findings, we evaluated the association between long-term NSAID use and UC incidence in the prospective VITamins and Lifestyle (VITAL) cohort.

Materials and Methods

Selection of Study Participants

Details of the VITAL study, approved by the Fred Hutchinson Cancer Research Center institutional review board, have been published previously [17]. Briefly, questionnaires were mailed to 364,418 men and women age 50–76 years living in a 13-county area of western Washington State identified through a purchased commercial mailing list. Between October 2000–December 2002, 79,300 questionnaires were returned, of which 77,719 met eligibility and quality control checks.

We excluded participants who reported a prior diagnosis of UC or had missing data on prior bladder cancer (N=665). Participants (N=4) with incident non-urothelial bladder cancer (e.g., squamous cell carcinoma or adenocarcinoma) were also excluded.

Baseline Data Collection/Exposure Assessment

Participants completed a 24-page self-administered questionnaire on medical history, personal characteristics, cancer risk factors, diet and dietary supplement use. We ascertained information on age, race, education, smoking, and medical conditions associated with NSAID use, including chronic joint pain over the last year, arthritis, frequent headaches (defined as ≥ 2 per week over the last year), and coronary artery disease (defined as heart attack, coronary bypass surgery, angioplasty or angina).

Participants were asked to report their use of the following NSAIDs over the previous 10 years: low-dose “baby” aspirin (81mg), regular or extra-strength aspirin, ibuprofen, naproxen, celecoxib or rofecoxib, and other pain relievers (e.g. piroxicam or indomethacin). A participant was defined as an NSAID user if s/he reported use at least once per week, for at least one year, during the prior 10 years; all other participants were classified as nonusers. Ten-year intake of NSAIDs was categorized as: (1) *no use*, (2) *low-use* (1–3 days/week or for <4 years), or (3) *high-use* (≥ 4 days/week and for ≥ 4 years).

We analyzed NSAID use by type (low-dose aspirin, regular/extra strength aspirin, non-aspirin NSAIDs) and in combinations (use of any type of NSAID and use of any type of NSAID excluding low-dose aspirin).

Follow-Up of Subjects for Urothelial Cancer and Censored Data

Incident cases of UC were identified through December 2008 by linkage to the Seattle-Puget Sound SEER cancer registry. For each subject, the end of follow-up was the earliest date of diagnosis of UC (0.5%), date of withdrawal from the study (0.03%), date of emigration out of the 13 Washington counties covered by SEER (5.4%), date of death (6.8%), or date of last cohort follow-up (December 31, 2008) (87.2%). Deaths were ascertained by linkage to the Washington State death files. US Post Office National Change of Address system and follow-up letters and phone calls to participants were used to identify participants who moved out of the area.

Statistical Analyses

For each NSAID variable, the hazard ratios (HR) for UC comparing each category of users to nonusers, and 95% confidence intervals (95% CI), were determined using Cox proportional hazards regression with age as the time variable. At risk time was defined as the age at completion of the baseline questionnaire through age at last follow-up. The statistical significance of each NSAID variable was tested using a likelihood ratio test for trend with the variable in ordinal form. A base model adjusting for age and gender was performed. Variables to include in the multivariate model were selected *a priori* and included age, gender, race (white, black, other), education, family history of bladder cancer, and smoking status (never; former, quit ≥ 10 yrs prior to baseline questionnaire; former, quit <10 yrs prior to baseline questionnaire; current smoker). We also included as covariates self-reported health conditions that are common indications for aspirin and non-aspirin NSAID use (history of pain/arthritis, frequent headaches, and coronary artery disease). For all NSAIDs examined, we tested for effect modification by smoking status by performing stratified analysis according to smoking status for those who were non-smokers, those who were current smokers, those who quit <10 yrs ago, and those who quit ≥ 10 yrs ago. We also performed stratified analyses for all NSAIDs by gender. Interaction was tested as the significance of the cross product of the ordinal (trend) NSAID variable and the effect modifier, in a model that included the main effects of the NSAID variable and the effect modifier. All analyses were performed in STATA v11 (STATA CORP, College Station, TX USA).

Results

After a median follow-up of 7 years, 385 incident cases of UC were identified among 77,048 eligible participants. Table 1 presents participant demographic variables, smoking status, and health conditions that are indications for chronic NSAID use, by UC status. UC cases were more likely to be male, older, current or former smokers, and to have a history of coronary artery disease, likely due to their increased smoking history.

NSAID use was examined for an association with UC in the entire cohort (Table 2). No significant relationship was identified for aspirin or non-aspirin NSAIDs use by type or in combination. The null association persisted when stratified by gender (data not shown).

Table 3 shows the associations of use of aspirin and non-aspirin NSAIDs with UC risk, stratified by smoking status. There was no interaction of regular aspirin use with smoking status (p for interaction = 0.63). However, there was evidence of effect modification of the non-aspirin NSAID-UC association by smoking status (p for interaction = 0.02). Among current smokers and recent quitters (<10 years before baseline), high use of non-aspirin NSAIDs appeared to increase the risk of UC, while among non-smokers and long-term quitters, high use of non-aspirin NSAIDs appeared to decrease the risk of UC. Within smoking groups, the trend was only statistically significant for the long-term quitters: compared to non-users, a reduction in UC risk was seen for both low (HR 0.69, 95% CI 0.46–1.04) and high (HR 0.52, 95% CI 0.24–1.11) use of non-aspirin NSAIDs (p trend = 0.02).

DISCUSSION

In this large, prospective U.S. cohort study, we observed no association between use of low-dose aspirin, regular aspirin or non-aspirin NSAIDs and UC risk overall. However, we found that smoking status modified the association of use of non-aspirin NSAIDs with UC risk, with a significant dose-dependent reduction in risk of UC associated with non-aspirin NSAID use among those who quit smoking 10 yrs ago.

NSAIDs are thought to exert antitumor effects by their action against the COX enzymes, especially COX2. Low-dose aspirin selectively inhibits COX 1, whereas higher doses systemically inhibit both COX 1 and 2 [18]. It has been shown that non-aspirin NSAIDs, such as ibuprofen, indomethacin, and sulindac, are much more potent than aspirin in inhibiting the activity of both COX 2 [19] and the nuclear factor NF- κ B, a transcription factor that mediates inflammation, suppresses apoptosis, and is commonly overexpressed in cancer [20]. The higher potency of non-aspirin NSAIDs may explain why the association with decreased UC risk is attenuated when aspirin is included in our analysis. It may also explain the discrepancy of results from published epidemiological studies. Several case control studies have reported a reduction in the risk of UC in regular users of aspirin [11, 21], whereas others found no effect on UC risk with aspirin use [22, 23]. Moreover, prospective cohort studies have generally shown no effect of aspirin use on UC risk [24, 25]. A randomized controlled trial looking at the effect of low-dose aspirin (100mg) every other day versus placebo in 39,876 healthy women reported no difference in regards to bladder cancer (RR 1.12, 95% CI 0.65–1.94), but the aspirin dose may have been too low to exert a clinical difference in bladder carcinogenesis [26]. In our study, regular aspirin use was not associated with a decreased risk of UC overall or in any subgroup analysis.

Our findings differ from results in a recently published pooled analysis of over 500,000 individuals from three well-characterized prospective cohort studies [16]. A total of 2,489 incident cases of bladder cancer were identified, and a 40% reduction in risk was found for non-smokers who reported regular use of non-aspirin NSAIDs (HR 0.58, 95% CI 0.41–

0.83). In line with this pooled analysis, we found a similar reduction in risk for non-smokers; however, in our analysis this did not reach statistical significance. With further stratification by time of smoking cessation, the pooled analysis found no reduction in risk for those who quit smoking, even those who quit more than ten years ago (HR 0.96, 95% CI 0.80–1.15). By contrast, our results found a significant reduction in risk of UC in former smokers who quit 10 yrs ago.

Smoking is a well-known risk factor for UC. Many different carcinogens, including polycyclic aromatic hydrocarbons, nitrosamines, and aromatic amines, have been detected in tobacco smoke. Metabolic activation of these carcinogens leads to the accumulation of metabolites that bind covalently to DNA, causing miscoding and other mutations [27]. While smokers have been shown to have increased COX 2 expression and activity in their urothelial tissue [28], it may be that the anti-carcinogenic effects of NSAIDs against COX 2 are overwhelmed by the carcinogenic effects of smoking. Thus, a decrease in UC risk associated with NSAID use has been shown more consistently in non-smokers in a case-control study looking at non-aspirin NSAID exposure (HR 0.57, 95% CI 0.33–0.98) [29] and in the pooled cohort analysis [16] described above. Our study has now shown a decrease in UC risk associated with non-aspirin NSAID use in long-term quitters of tobacco use.

The strong carcinogenic effect of smoking may also explain the surprising trend toward increased risk with non-aspirin NSAID use seen in current smokers. In addition, there may be confounding factors in current smokers that we were not able to account for in this analysis. Although smoking is the strongest UC risk factor, only approximately 50% of bladder cancer risk is attributable to smoking [30]. In our study, more than half of the UC cases were diagnosed in those who quit smoking 10 yrs ago. We believe that this is a reasonable subset to target for chemopreventive therapy with NSAIDs, since they are at a higher baseline risk for UC than non-smokers, and they constitute a significant proportion of UC cases.

The strengths of this study include its prospective design, the large cohort size, and case linkage through the SEER cancer registry. With the availability of baseline information on personal lifestyle and medical history, we were able to adjust for important UC risk factors, including gender, smoking status, and indications for NSAID use. Our measure of NSAID use may have been more accurate than most prior studies. Specifically, the pooled cohort analysis was based on frequency of NSAID use over the last year, while we incorporated years of use as well as frequency in our exposure variables, as associations of NSAID use with cancer likely depend on duration as well as frequency.

In considering NSAIDs for chemoprevention for UC, it is important to consider the toxicity of NSAID therapy. We did not have data on the incidence of adverse effects of NSAIDs in our population, but previous randomized trials looking at low-dose aspirin for prevention of cardiovascular events have shown an increase in gastrointestinal bleeding and other side effects with prophylactic aspirin [31]. Before NSAIDs can be recommended as chemoprevention, the risks of adverse effects will need to be weighed against the benefits.

Another limitation of this study is the possibility of misclassification of medication use in our study due to errors in self-reported use of NSAIDs. However, poor recall should be nondifferential in a prospective study and would lead to an attenuation of the results. Finally, although it is likely that people who returned questionnaires in a vitamin and nutrition study on cancer have fewer cancer risk factors than the general U.S. population, selection bias in the hazard ratios is unlikely because participation would not be influenced jointly by risk factors and future (unknown) bladder cancer risk.

In conclusion, we report results from a large prospective cohort study showing that non-aspirin NSAID use is associated with a reduction in risk of UC in those with a distant history of smoking.

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References

1. Jemal A, et al. Cancer statistics, 2010. *CA Cancer J Clin.* 2010; 60(5):277–300. [PubMed: 20610543]
2. Kaufman DS, Shipley WU, Feldman AS. Bladder cancer. *Lancet.* 2009; 374(9685):239–49. [PubMed: 19520422]
3. Sievert KD, et al. Economic aspects of bladder cancer: what are the benefits and costs? *World journal of urology.* 2009; 27(3):295–300. [PubMed: 19271220]
4. Rostom A, et al. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2007; 146(5):376–89. [PubMed: 17339623]
5. Singh-Ranger G, Mokbel K. The role of cyclooxygenase-2 (COX-2) in breast cancer, and implications of COX-2 inhibition. *Eur J Surg Oncol.* 2002; 28(7):729–37. [PubMed: 12431470]
6. Okamoto A, et al. Etodolac, a selective cyclooxygenase-2 inhibitor, induces upregulation of E-cadherin and has antitumor effect on human bladder cancer cells in vitro and in vivo. *Urology.* 2008; 71(1):156–60. [PubMed: 18242386]
7. Steele VE, et al. Chemopreventive efficacy of naproxen and nitric oxide-naproxen in rodent models of colon, urinary bladder, and mammary cancers. *Cancer Prev Res (Phila).* 2009; 2(11):951–6. [PubMed: 19892664]
8. Komhoff M, et al. Enhanced expression of cyclooxygenase-2 in high grade human transitional cell bladder carcinomas. *Am J Pathol.* 2000; 157(1):29–35. [PubMed: 10880372]
9. Shirahama T. Cyclooxygenase-2 expression is up-regulated in transitional cell carcinoma and its preneoplastic lesions in the human urinary bladder. *Clin Cancer Res.* 2000; 6(6):2424–30. [PubMed: 10873095]
10. Zha S, et al. Cyclooxygenases in cancer: progress and perspective. *Cancer Lett.* 2004; 215(1):1–20. [PubMed: 15374627]
11. Castela JE, et al. Non-steroidal anti-inflammatory drugs and bladder cancer prevention. *Br J Cancer.* 2000; 82(7):1364–9. [PubMed: 10755416]
12. Fortuny J, et al. Use of analgesics and nonsteroidal anti-inflammatory drugs, genetic predisposition, and bladder cancer risk in Spain. *Cancer Epidemiol Biomarkers Prev.* 2006; 15(9):1696–702. [PubMed: 16985032]
13. Fortuny J, et al. Analgesic and anti-inflammatory drug use and risk of bladder cancer: a population based case control study. *BMC Urol.* 2007; 7:13. [PubMed: 17692123]
14. Genkinger JM, et al. Nonsteroidal antiinflammatory drug use and risk of bladder cancer in the health professionals follow-up study. *Int J Cancer.* 2007; 120(10):2221–5. [PubMed: 17290403]
15. Sorensen HT, et al. Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study. *Br J Cancer.* 2003; 88(11):1687–92. [PubMed: 12771981]
16. Daugherty SE, et al. Nonsteroidal antiinflammatory drugs and bladder cancer: a pooled analysis. *Am J Epidemiol.* 2011; 173(7):721–30. [PubMed: 21367875]
17. White E, et al. VITamins And Lifestyle cohort study: study design and characteristics of supplement users. *Am J Epidemiol.* 2004; 159(1):83–93. [PubMed: 14693663]
18. Thun MJ. Beyond willow bark: aspirin in the prevention of chronic disease. *Epidemiology.* 2000; 11(4):371–4. [PubMed: 10874540]
19. Tegeder I, Pfeilschifter J, Geisslinger G. Cyclooxygenase-independent actions of cyclooxygenase inhibitors. *FASEB J.* 2001; 15(12):2057–72. [PubMed: 11641233]

20. Takada Y, et al. Nonsteroidal anti-inflammatory agents differ in their ability to suppress NF-kappaB activation, inhibition of expression of cyclooxygenase-2 and cyclin D1, and abrogation of tumor cell proliferation. *Oncogene*. 2004; 23(57):9247–58. [PubMed: 15489888]
21. Fortuny J, et al. Analgesic and anti-inflammatory drug use and risk of bladder cancer: a population based case control study. *BMC urology*. 2007; 7:13. [PubMed: 17692123]
22. Langman MJ, et al. Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. *BMJ*. 2000; 320(7250):1642–6. [PubMed: 10856067]
23. Pommer W, et al. Urothelial cancer at different tumour sites: role of smoking and habitual intake of analgesics and laxatives. Results of the Berlin Urothelial Cancer Study. *Nephrol Dial Transplant*. 1999; 14(12):2892–7. [PubMed: 10570093]
24. Genkinger JM, et al. Nonsteroidal antiinflammatory drug use and risk of bladder cancer in the health professionals follow-up study. *International journal of cancer Journal international du cancer*. 2007; 120(10):2221–5. [PubMed: 17290403]
25. Sorensen HT, et al. Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study. *British journal of cancer*. 2003; 88(11):1687–92. [PubMed: 12771981]
26. Cook NR, et al. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. *JAMA : the journal of the American Medical Association*. 2005; 294(1):47–55. [PubMed: 15998890]
27. Wogan GN, et al. Environmental and chemical carcinogenesis. *Semin Cancer Biol*. 2004; 14(6):473–86. [PubMed: 15489140]
28. Badawi AF, et al. Influence of cigarette smoking on prostaglandin synthesis and cyclooxygenase-2 gene expression in human urinary bladder cancer. *Cancer Invest*. 2002; 20(5–6):651–6. [PubMed: 12197220]
29. Blumentals WA, et al. Analgesic therapy and the prevention of bladder cancer. *Urol Oncol*. 2004; 22(1):11–5. [PubMed: 14969797]
30. Strobe SA, Montie JE. The causal role of cigarette smoking in bladder cancer initiation and progression, and the role of urologists in smoking cessation. *J Urol*. 2008; 180(1):31–7. discussion 37. [PubMed: 18485400]
31. Ridker PM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med*. 2005; 352(13):1293–304. [PubMed: 15753114]

TABLE 1

Urothelial carcinoma cases and controls by baseline participant characteristics, indications for NSAID use, and smoking status.

	Cases (N= 385)	%	Controls (N= 76,663)	%
<i>Demographic Variables</i>				
Sex				
Male	298	77.4	36,608	47.8
Female	87	22.6	40,055	52.2
Age at baseline (years)				
50 to 54	35	9.1	17,862	23.3
55 to 59	45	11.7	17,449	22.8
60 to 64	51	13.2	13,964	18.2
65 to 69	93	24.2	12,588	16.4
70+	161	41.8	14,800	19.3
Race/ethnicity				
White	360	93.5	70,180	91.5
Black	4	1.0	975	1.3
Other	21	5.5	5,508	7.2
Family history				
No	368	95.6	73,524	95.9
Yes	17	4.4	3,139	4.1
Education				
High school or less	98	25.8	15,194	20.2
Some college/technical	133	35.0	28,891	38.3
College graduate	86	22.6	18,465	24.5
Advanced degree	63	16.6	12,808	17.0
<i>Indications for NSAID use</i>				
Joint pain/arthritis				
No	197	51.2	38,651	50.4
Yes	188	48.8	38,012	49.6
Chronic/migraine headaches				
No	349	90.6	64,751	84.5
Yes	36	9.4	11,912	15.5
Coronary artery disease				
No	303	78.7	69,721	90.9
Yes	82	21.3	6,942	9.1
<i>Smoking status</i>				
Never	101	26.2	37,130	48.4
Current	58	15.1	6,354	8.3
Former, quit < 10 yrs	30	7.8	5,048	6.6
Former, quit 10 yrs	196	50.9	28,131	36.7

TABLE 2

Urothelial carcinoma risk in relation to aspirin and non-aspirin NSAID use

	Number of noncases		Number of UC		Sex and age-adjusted		Multivariate-adjusted ^a	
	No. ^b	%	No. ^b	%	HR	95% CI	HR	95% CI
Low-dose Aspirin								
None	50,771	71	228	66	1.00	Referent	1.00	Referent
Low use ^c	11,623	16	49	14	0.86	0.63 1.17	0.87	0.64 1.18
High use ^d	8,714	12	67	19	1.16	0.88 1.53	1.09	0.82 1.46
P trend						0.50		0.79
Regular Aspirin								
None	54,973	75	255	70	1.00	Referent	1.00	Referent
Low use	9,406	13	45	12	0.97	0.71 1.34	1.00	0.73 1.38
High use	8,503	12	63	17	1.05	0.79 1.39	1.03	0.77 1.38
P trend						0.79		0.84
Nonaspirin NSAIDs								
None	48,808	68	278	77	1.00	Referent	1.00	Referent
Low use	17,617	24	62	17	0.82	0.62 1.08	0.80	0.60 1.07
High use	5,610	8	20	6	0.85	0.54 1.33	0.82	0.52 1.31
P trend						0.17		0.15
Nonaspirin NSAIDs and Regular Aspirin								
None	36,791	52	196	55	1.00	Referent	1.00	Referent
Low use	20,843	29	79	22	0.83	0.64 1.07	0.81	0.62 1.06
High use	13,340	19	79	22	0.95	0.73 1.24	0.85	0.65 1.13
P trend						0.50		0.18
All NSAIDs								
None	25,861	37	117	34	1.00	Referent	1.00	Referent
Low use	24,013	34	90	26	0.81	0.62 1.07	0.80	0.60 1.06
High use	20,098	29	136	40	1.06	0.82 1.36	0.92	0.70 1.21
P trend						0.63		0.58

Abbreviations: CI, confidence interval; HR, hazard ratio

^a Adjusted for the following variables: age, gender, race (white, black, other), education, family history of bladder cancer, smoking status (never; former, quit > 10 yrs ago; former quit <10 yrs ago; current smoker), and indications for NSAID use (joint pain/arthritis, chronic/migraine headaches, coronary artery disease)

^b Missing data excluded from table

^c Low use defined as 1–3 days per week or 1–3 years

^d High use defined as 4 days/week and 4 years

TABLE 3
Urothelial carcinoma risk in relation to NSAID use during the 10 years before baseline, stratified by smoking status

	Number of noncases		Number of UC		Multivariate-adjusted ^a	
	No. ^b	%	No.	%	HR	95% CI
Regular aspirin						
<i>Current smokers</i>						
None	4,431	74	40	71	1.00	Referent
Low use ^c	851	14	6	11	0.70	0.29 1.65
High use ^d	745	12	10	18	0.93	0.44 1.97
P trend						0.67
<i>Former smokers, quit <10 years</i>						
None	3,471	72	15	60	1.00	Referent
Low use	663	14	4	16	1.28	0.42 3.89
High use	667	14	6	24	1.21	0.45 3.24
P trend						0.66
<i>Former smokers, quit ≥10 years</i>						
None	19,489	73	126	67	1.00	Referent
Low use	3,516	13	25	13	1.08	0.70 1.67
High use	3,735	14	37	20	0.95	0.65 1.40
P trend						0.89
<i>Non-smokers</i>						
None	27,582	78	74	79	1.00	Referent
Low use	4,376	12	10	11	0.82	0.41 1.65
High use	3,356	10	10	11	0.79	0.40 1.57
P trend						0.43
P interaction		0.63				
Non-aspirin NSAIDs						
<i>Current smokers</i>						
None	3,967	66	38	69	1.00	Referent
Low use	1,484	25	11	20	1.05	0.51 2.17

Number of noncases		Number of UC		Multivariate-adjusted ^a	
No. ^b	%	No.	%	HR	95% CI
High use	524	9	11	2.07	0.82 5.20
P trend					0.22
<i>Former smokers, quit <10 years</i>					
None	3,135	66	14	58	1.00 Referent
Low use	1,231	26	6	25	1.39 0.51 3.79
High use	399	8	4	17	2.78 0.84 9.18
P trend					0.11
<i>Former smokers, quit 10 years</i>					
None	17,644	67	151	81	1.00 Referent
Low use	6,675	25	29	16	0.69 0.46 1.04
High use	2,182	8	7	4	0.52 0.24 1.11
P trend					0.02
<i>Non-smokers</i>					
None	24,062	69	75	80	1.00 Referent
Low use	8,227	24	16	17	0.80 0.45 1.43
High use	2,505	7	3	3	0.51 0.16 1.65
P trend					0.20
P interaction	0.02				

Abbreviations: CI, confidence interval; HR, hazard ratio

^aAdjusted for the following variables: age, gender, race (white, black, other), education, family history of bladder cancer, and indications for NSAID use (joint pain/arthritis, chronic/migraine headaches, coronary artery disease)

^bMissing data excluded from table

^cLow use defined as 1–3 days per week or 1–3 years

^dHigh use defined as 4 days/week and 4 years