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A large cohort study of nonsteroidal anti-inflammatory drugs and renal cell carcinoma incidence in the National Institutes of Health–AARP Diet and Health Study

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Abstract

Aim—Existing epidemiologic evidence for the association between nonsteroidal anti-inflammatory drugs (NSAIDs) and renal cell carcinoma (RCC) risk is inconsistent.

Methods—We investigated the association between the use of aspirin and nonaspirin NSAIDs and RCC risk in the National Institutes of Health–American Association of Retired Persons (AARP) Diet and Health Study, for which 298,468 AARP members free of cancer, aged 50–71 years, completed a survey on use of NSAIDs (1996–1997). Multivariate Cox proportional hazards models were used to estimate the hazard ratio (HR).

Results—The state cancer registry and mortality index linkage identified 1,084 incident RCC cases through 31 December 2006. No statistically significant associations between the use of aspirin or nonaspirin NSAIDs and RCC risk were found. Compared to nonuse of any NSAIDs, the multivariate-adjusted HRs were 0.95 (95 % CI 0.75–1.21) and 0.93 (95 % CI 0.68–1.26) for monthly use of aspirin and nonaspirin NSAIDs, respectively, 0.92 (95 % CI: 0.69-1.23) and 1.11 (95 % CI: 0.76-1.62) for weekly use, 0.87 (95 % CI: 0.69-1.11) and 1.06 (95 % CI: 0.75-1.48) for daily use; and 0.95 (95 % CI 0.78–1.14) for the use of both aspirin and nonaspirin NSAIDs. We found some suggestions of an increased risk of RCC associated with frequent NSAID use among

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participants who were <63 years and a reduced risk associated with aspirin use among those ≥63 years. No significant associations were found in other stratified analyses by gender, BMI, smoking, history of diabetes, or history of hypertension.

Conclusion—RCC risk was not significantly associated with NSAID use overall. The difference in association by age needs to be explored further.

Keywords

Anti-inflammatory agents/nonsteroidal; Carcinoma/renal cell; NIH–AARP; Cohort studies

Introduction

Though nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used to relieve pain, these drugs have other biological effects. For example, aspirin has been used to prevent cardiovascular disease [1]. Recent meta-analyses also suggest that aspirin may reduce incidence and mortality of several cancer sites [2, 3]. Aspirin and other NSAIDs may exert chemoprotective effects against malignancy through reducing inflammation, inhibiting cyclooxygenase (COX)-1 and/or COX-2 enzymes, inhibiting cell proliferation and angiogenesis, and inducing apoptosis of cancer cells [4]. Quite a number of studies have been conducted to evaluate the association between the use of aspirin or other nonaspirin NSAIDs and risk of renal cell carcinoma (RCC), with conflicting results [5–13]. Nonaspirin NSAID use may increase the risk of RCC, especially among those who used the drug for a long duration (i.e., ≥10 years) [12]. Several previous studies of NSAID use and RCC included only a small number of cases, may be subject to recall or other biases, and often did not adjust for important confounders such as body mass index (BMI). We therefore examined the use of NSAIDs in relation to RCC risk in a large prospective cohort study that followed 298,468 people in the United States for over a decade.

Methods

Study population

The design and methodology of the NIH–AARP Diet and Health Study have been described in detail elsewhere [14]. Briefly, the NIH–AARP Study is a prospective cohort study of diet, other health-related behaviors, and cancer. The study was initiated in 1995 and 1996, when a questionnaire was mailed to 3.5 million members of the AARP (formerly known as the American Association of Retired Persons) aged 50–71 years, who resided in one of six states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) or two metropolitan areas (Atlanta, Georgia; and Detroit, Michigan). The questionnaire captured diet history, demographic characteristics, and various health-related behaviors. Of the 617,119 men and women who returned the baseline questionnaire, 567,169 satisfactorily completed it.

In 1996 and 1997, a second questionnaire (the risk factor questionnaire) was sent to those who did not report history of colon, breast, or prostate cancer at the baseline questionnaire to collect more detailed medical information, including NSAID use, family history of cancer,

and other potential cancer risk factors. A total of 337,074 men and women completed this questionnaire.

Cohort members were followed annually for mailing address changes and vital status. Address changes were identified through linkage to the US Postal Service's National Change of Address database, US Postal Service updates received with undeliverable mail, other address change update services, and participants' notifications. Vital status was updated through linkage to the Social Security Administration Death Master File and was verified by the National Death Index.

Because information regarding NSAID use was collected on the second questionnaire, we limited analyses to the 337,074 men and women who completed the second questionnaire. For these analyses, we excluded individuals for whom either the baseline (n = 6,959) or the risk factor questionnaire (n = 3,424) was completed by proxies, those with prevalent cancer at the return of baseline questionnaire (n = 14,565) or risk factor questionnaire (n = 4,296), those who had a death-only report for any cancer (n = 1,180), those who died or moved out of the cancer ascertainment areas before the second questionnaire was scanned (n = 18), and those with missing data on the use of both aspirin and nonaspirin NSAIDs (n = 6,005). The resulting analytic cohort for our primary analysis included 298,468 participants. The study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute.

Assessment of the use of NSAIDs

The second questionnaire asked whether aspirin products (generic aspirin, Bayer, Bufferin, Anacin, Ecotrin, or Excedrin) or nonaspirin NSAIDs (generic ibuprofen, Advil, Nuprin, Motrin, Naprosyn, etc.) had been used in the past 12 months. As acetaminophen is an analgesic with weak anti-inflammatory activity [15], participants were instructed not to include 'Tylenol, acetaminophen, or any other pain relievers' in nonaspirin NSAIDs. Aspirin or nonaspirin NSAID users were asked to indicate their frequency of usual use: fewer than 2 times per month, 2–3 times per month, 1–2 times per week, 3–4 times per week, 5–6 times per week, 1 time per day, or 2 or more times per day. We collapsed some of the categories into monthly, weekly, and daily. Dose, duration, and indication for use were not collected.

Assessment of other risk factors for RCC

While demographic characteristics, lifestyle, and medical history were largely obtained through the first questionnaire, the second questionnaire ascertained a self-reported history of hypertension and diabetes. History of cancer in a first-degree relative was derived from information collected on both questionnaires.

Self-reported height and weight were collected from the baseline questionnaire. BMI was calculated from weight (kg) divided by height (m) squared.

Cigarette smoking was categorized as never smoker, former smoker (quitting smoking >10 years ago or ≤10 years ago), and current smoker at baseline or quitting for <1 year, and, among current smokers, by dose (≤20 or >20 cigarettes/day). A frequency of physical

activity that lasted 20 min or more and caused either increases in breathing or heart rate or working up a sweat was asked. Self-reported physician-diagnosed history of diabetes and hypertension was dichotomous (yes vs. no).

Identification of cases

Incident RCC cases were identified through original eight state cancer registries and additional three states that participants tended to move during follow-up. RCC was defined as International Classification of Disease for Oncology code, Third Edition (ICD-O-3) 'C649,' and incorporating histology codes (8140, 8141, 8190, 8200, 8211, 8251, 8255, 8260, 8270, 8280, 8310, 8312, 8316, 8317, 8318, 8319, 8320, 8323, 8370, 8440, 8450, 8480, 8481, 8490, 8500, 8504, 8510, 8521, 8550, 8570, 8940, and 8959). We also evaluated clear-cell RCC (histology code 8310, the major histological type) separately.

Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs) for total RCC, or clear-cell RCC associated with NSAID use, with follow-up time as the underlying time metric. Follow-up for each subject began on the date the second questionnaire was received and scanned, and continued through the earliest of the following dates: participant was diagnosed with cancer, moved out of the state cancer registry catchment area, died from any cause, or was censored at 31 December 2006, whichever came first. The proportional hazards assumption was verified through assessment of interaction term for the exposures with follow-up time.

Multivariate models were used to control for age at entry (modeled as a continuous variable), gender, marital status (yes or no), education (<college or postgraduate vs. college or postgraduate), race (non-Hispanic white, non-Hispanic black, other (Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native), tobacco smoking (never, quit >10 years ago, quit ≤10 years ago, currently smoking and smoked ≤20 cigarettes/day, currently smoking and smoked >20 cigarettes/day), first-degree relative diagnosed with any cancer (yes or no), current BMI (in kg/m^2, <18.5, 18.5 to <25 (reference), 25 to <30, 30 to <35, or ≥35), rigorous physical activity (never or rarely, <3 times per month, 1–2 times per week, 3–4 times per week, ≥5 times per week), history of hypertension (yes or no), history of diabetes (yes or no), alcohol consumption (g per day), and total dietary fiber intake. Indicator variables were created for variables with missing values (smoking status and personal history of hypertension). Models examining the frequency of aspirin use and RCC risk also included terms for frequency of nonaspirin NSAID use and vice versa.

We examined whether the relationship between NSAIDs and total RCC, or clear-cell RCC, incidence differed by age (<63, ≥63 years), gender, BMI (<25, ≥25 kg/m^2), smoking status (never smoker, former smoker, current smoker), history of hypertension (yes vs. no), or history of diabetes (yes vs. no). In addition, we conducted lag-time analysis by excluding cases that occurred in the first 2, 4, or 6 years of follow-up. Probability values <0.05 were considered statistically significant. All tests of statistical significance were two-tailed. Analyses were performed using SAS software release 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Among 298,468 participants included in the analysis, a total of 1,084 cases of RCC and 306 clear-cell RCCs were documented over an average of 8.2 years of follow-up. In the 12 months before administration of the risk factor questionnaire (Table 1), 13.5 % of the participants did not use either aspirin or nonaspirin NSAIDs. Of the study population, 30.1 % reported use of aspirin only in the previous 12 months, 13.4 % reported use of nonaspirin NSAIDs only, and 43 % reported use of both aspirin and nonaspirin NSAIDs (Table 1).

Compared with participants who reported no use of either aspirin or nonaspirin NSAIDs in the past 12 months, those who used either aspirin or nonaspirin NSAIDs were more likely to be males, to be white, and to be married (Table 1). They were also more likely to be physically active, to have graduated from college or graduate school, to be former smokers, and to drink more alcohol. They were also less likely to have a history of diabetes. Those who used only aspirin were more likely to be males and married than those who used only nonaspirin NSAIDs.

The HRs and 95 % CIs for the use of aspirin, nonaspirin NSAIDs, and combinations thereof are presented in Table 2. In age- and sex-adjusted analyses, there was no statistically significant association between regular use of aspirin or nonaspirin NSAIDs in the past 12 months and total RCC. Compared with no use of aspirin in the past 12 months, the HR for total RCC was 0.93 (95 % CI 0.81–1.06) for any aspirin use. Compared with no use of nonaspirin NSAIDs, the HR was 1.05 (95 % CI 0.93–1.19) for any nonaspirin NSAID use. The results adjusted for only age and sex were similar to the fully adjusted results. Mutual adjustment of aspirin and nonaspirin NSAIDs did not materially change the results. We found no association when we examined the frequency of aspirin and nonaspirin NSAID use (monthly, weekly, or daily) in relation to total RCC risk (Table 2).

Because a previous epidemiologic study found that nonaspirin NSAIDs, but not aspirin, were associated with an increased risk of RCC [12], we further examined the risk of RCC associated with the use of a combination of aspirin and nonaspirin NSAIDs. Compared with no use of any NSAIDs, the multivariate HRs were 0.91 (95 % CI 0.75–1.11) for aspirin only, 1.01 (95 % CI 0.80–1.27) for nonaspirin only, and 0.95 (95 % CI 0.78–1.14) for use of both aspirin and nonaspirin NSAIDs (Table 2). Frequencies of the use of aspirin only, nonaspirin NSAID only, or both analgesics were not associated with the risk of RCC.

We examined the association between the use of aspirin and nonaspirin NSAIDs and the risk of clear-cell RCC (n = 306), a major histological type of RCC; the results were similar to those for total RCC (data not shown).

We repeated our analyses after excluding individuals who developed RCC during the first 2, 4, or 6 years of follow-up to prevent the possibility of reverse causation, as symptoms of undiagnosed cancer could alter participants' use of NSAIDs; however, no appreciable changes were noted in the associations (data not shown).

We conducted a stratified analysis by age using a median of 63 years as the cutoff (Table 3). Among those <63 years of age and compared with nonusers of any analgesics, use of either

aspirin or nonaspirin NSAIDs was associated with an elevated risk of RCC [multivariate HR 1.38 (95 % CI 0.95-2.02) for aspirin only, 1.63 (95 % CI 1.08-2.45) for nonaspirin NSAIDs only, and 1.43 (95 % CI 0.99–2.04) for use of both aspirin and nonaspirin NSAIDs]. In contrast, among participants who were aged ≥63 years at cohort entry and compared with nonusers of any analgesics, use of aspirin only was associated with a reduced risk of RCC (multivariate HR 0.77, 95 % CI 0.61–0.97), which was largely driven by those who used aspirin daily [multivariate HR 0.68 (95 % CI 0.51-0.90)]. Use of both analgesics was also associated with a reduced risk (multivariate HR 0.79, 95 % CI 0.64–0.99).

Information on dose and indications (i.e., rheumatic disease, cardiovascular disease, or migraine) was not available. However, information on history of heart disease was collected. Low-dose aspirin is typically recommended in the primary prevention of cardiovascular disease. Thus, we conducted a stratified analysis by history of heart disease because those with the history may take low-dose aspirin; the results did not differ by history of heart disease (data not shown). Stratified analyses by gender, BMI, smoking status, history of hypertension, or diabetes revealed no differences in associations across strata (data not shown). Finally, we performed a secondary analysis adding rare users (<2 times per month) to the nonuser group; the results did not change materially (data not shown).

Discussion

In this large prospective cohort study of women and men, we found no overall association between regular NSAID use and risk of RCC. Frequency of use of these NSAIDs was also not associated with RCC risk. We found some differences in association by age. Among younger participants, frequent use of either aspirin or nonaspirin NSAIDs was associated with an elevated risk of RCC. On the other hand, among older participants, there was an inverse association between aspirin use and RCC risk.

Although aspirin use has been associated with an increased risk of RCC in some previous epidemiologic studies [7, 8, 10, 11], other studies reported a null association [6, 7, 9, 12, 13, 16–18]. Previous studies also suggested a tendency toward increased risk with high intake or long duration of aspirin use [8, 11–13]. Consistent with other US studies [6, 12, 13, 18] and one randomized clinical trial [19], we found no overall association between aspirin use and risk of RCC in the NIH–AARP cohort. We were not able to explore the effect of dose or duration of use, because the relevant information was not collected in the study. This potential source of misclassification of exposure would be most likely nondifferential, biasing the results toward the null, and was a limitation of our study. We also do not know the reason for the use of NSAIDs. However, for younger people using nonaspirin NSAIDs, it is most likely due to treatment for chronic pain, whereas a lot of older people may use aspirin for cardioprotection.

As for nonaspirin NSAIDs, our finding of a null association in the total population was in accordance with two case–control studies [6, 20]. However, a positive association with RCC risk was detected in one case–control [8] and three cohort studies [12, 21]. One retrospective cohort study in Denmark using a prescription database found that ibuprofen prescription was associated with kidney cancer mortality [RR 1.72 (95 % CI 1.4–2.1)] [22]. A study found a

positive association between duration of use of nonaspirin NSAIDs and RCC risk; the HR for those who used >10 years was 2.92 (95 % CI 1.71–5.01) [12]. Because we measured the use only at baseline, we were not able to investigate the duration of use.

The differences in association by age are hard to interpret and have not been explored in other studies. They may suggest different etiological pathways how NSAIDs affect RCC risk. NSAIDs in the dose range for the treatment of inflammation and pain have been associated with high blood pressure, a risk factor for RCC [23–25]. In addition, use of NSAIDs is associated with decline in renal function [26, 27] and elevated risk of chronic renal disease [28, 29], which may subsequently contribute to elevated risk of kidney cancer. At the same time, aspirin may be beneficial against RCC, as is the case with cancer at other sites [4]. In younger age, the harmful (and potentially rather acute) effect of NSAIDs may outweigh the beneficial effect of aspirin. In older age, the beneficial (and potentially cumulative) effect of aspirin use may overcome the harmful effect. However, long duration of aspirin use, at least up to 10 years, was not associated with RCC in other studies [12]. Other possible explanations include ‘depletion of the susceptible.’ Elderly people, who are more likely to develop RCC, might have died (i.e., before they reached 63 years). The remaining cohort may be a selected group of individuals who are less likely to develop RCC. Because these results were from secondary analyses, not based on a priori hypothesis, we cannot rule out the possibility of a chance finding. Further studies to specifically test the potential effect modification by age are required to confirm the age effect.

Our study had several strengths. To our knowledge, this is the largest prospective cohort study of NSAID use and risk of RCC. Unlike retrospective studies, recall bias is minimized. Our questionnaire to collect drug use information includes both over-the-counter access to and pharmacy prescriptions for NSAIDs. The study also collected a wide variety of data on potential confounders such as tobacco smoking, physical activity, BMI, family history of cancer, and diet. Despite these strengths, our study is also subject to some limitations. First, this study was limited by lack of information on duration and dose of NSAIDs. One previous study suggested that long duration of NSAID use may be required to alter the risk of RCC [12]. In addition, we ascertained drug exposure only once (at baseline) and lacked information on patterns of NSAID use during follow-up. Individuals could have changed their utilization pattern during follow-up; however, this misclassification of exposure would most likely to be nondifferential, biasing the results toward the null. Second, although we had extensive information on risk factors for RCC and adjusted for them in multivariable analysis, residual confounding due to other unmeasured (i.e., chronic kidney disease) or poorly measured confounders remains a concern. Finally, our cohort consisted of 50–71-year-old men and women in selected areas of the United States. Hence, results from our study may not be applicable to other age-groups.

In summary, our study does not support the hypothesis that regular aspirin and nonaspirin NSAID use increases the risk of RCC. However, the risk of RCC may be increased among frequent aspirin or NSAID users ≤63 years old. Our results provide support for further study of the long-term effects of NSAIDs exposure and the dose–response relationship.

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Table 1

Baseline characteristics of study participants (n = 298,468)

	Total cohort	**Any aspirin users**	**Any nonaspirin NSAID users**	**Neither**	**Aspirin only**	**Nonaspirin NSAIDs only**	**Both aspirin and nonaspirin NSAIDs**	**Either aspirin, nonaspirin NSAIDs, or both**
	***n* = 298,468 %**	***n* = 218,372 %**	***n* = 168,414 %**	***n* = 40,173 %**	***n* = 89,881 %**	***n* = 39,923 %**	***n* = 128,491 %**	***n* = 258,295**
Age, years, mean (SD)	62.8 (5.3)	62.8 (5.3)	62.2 (5.4)	63.6 (5.1)	63.5 (5.1)	62.1 (5.4)	62.3 (5.4)	62.7 (5.3)
Male	58.4	62.6	55.7	53.3	65.8	40.4	60.4	59.2
Race								
White	92.5	93.4	93.0	88.9	93.3	91.4	93.5	93.1
Black	3.3	2.7	3.1	5.4	2.7	4.5	2.7	3.0
Others	4.2	3.9	3.9	5.7	4.0	4.1	3.8	3.9
Married	68.2	70.2	68.6	62.9	69.8	62.4	70.5	69.0
First-degree relative diagnosed with any cancer	49.4	49.2	50.3	48.5	48.2	51.4	50.0	49.6
Rigorous physical activity								
Never or rarely	16.8	15.6	16.3	20.7	16.1	19.7	15.2	16.2
1–3 times per month	13.3	13.3	13.8	12.6	12.6	13.7	13.8	13.4
1–2 times per week	21.4	21.8	21.9	19.7	21.3	21.1	22.1	21.7
3–4 times per week	27.6	28.2	28.0	25.5	27.7	26.3	28.6	27.9
≥5 times per week	20.1	20.3	19.3	20.4	21.5	18.4	19.6	20.0
Unknown	0.8	0.8	0.7	1.1	0.8	0.8	0.7	0.8
College graduate and postgraduate	64.4	66.0	66.1	58.4	63.8	61.4	67.6	65.3
Tobacco smoking								
Never	35.9	35.0	35.5	38.9	35.3	37.9	34.7	35.4
Former	49.8	50.9	50.6	46.3	49.9	47.4	51.7	50.4
Current	11.0	10.8	10.6	11.4	11.5	11.6	10.3	10.9
Unknown	3.3	3.3	3.3	3.4	3.3	3.1	3.3	3.3
Self-reported history of hypertension	39.0	39.6	38.7	38.0	40.2	37.0	39.2	39.2
Self-reported history of diabetes	8.4	8.4	8.1	9.4	8.7	7.8	8.2	8.3
Current body mass index, Kg/m^2 (SD)	26.9 (5.0)	26.9 (4.9)	27.2 (5.1)	26.7 (5.3)	26.6 (4.7)	27.3 (5.6)	27.2 (5.0)	27.0 (5.0)

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	Total cohort	Any aspirin users	Any nonaspirin NSAID users	Neither	Aspirin only	Nonaspirin NSAIDs only	Both aspirin and nonaspirin NSAIDs	Either aspirin, nonaspirin NSAIDs, or both
	n **= 298,468 %**	***n*** **= 218,372 %**	***n*** **= 168,414 %**	***n*** **= 40,173 %**	***n*** **= 89,881 %**	***n*** **= 39,923 %**	***n*** **= 128,491 %**	***n*** **= 258,295**
Alcohol, gram per day, mean (SD)	13.1 (36.0)	13.8 (36.3)	12.8 (34.5)	11.6 (37.6)	14.2 (38.1)	10.8 (32.7)	13.4 (35.0)	13.3 (35.8)
Total dietary fiber, gram, mean (SD)	19.7 (10.6)	19.8 (10.5)	19.5 (10.4)	20.1 (11.7)	19.9 (10.4)	18.8 (10.0)	19.7 (10.5)	19.6 (10.4)

Table 2

Hazard ratios and 95 % CI of association between NSAID use and risk of renal cell carcinoma in the NIH–AARP Diet and Health Study

	No. of cases	Person-years	Age-, sex-adjusted HR (95 % CI)	MV-adjusted HR (95 % CI)[a]
Aspirin				
None	284	692,448	Reference	Reference
Any	800	1,890,436	0.93 (0.81, 1.06)	0.93 (0.81, 1.06)
Frequency of any use				
Monthly	304	818,297	0.86 (0.73, 1.02)	0.92 (0.78, 1.08)
Weekly	175	436,859	0.90 (0.74, 1.09)	0.92 (0.76, 1.11)
Daily	321	635,280	1.02 (0.87, 1.20)	0.95 (0.80, 1.11)
Nonaspirin NSAIDs				
None	477	1,115,326	Reference	Reference
Any	607	1,467,559	1.05 (0.93, 1.19)	1.02 (0.91, 1.15)
Frequency				
Monthly	342	858,961	0.99 (0.86, 1.14)	1.00 (0.86, 1.14)
Weekly	155	346,664	1.18 (0.98, 1.42)	1.13 (0.94, 1.36)
Daily	110	261,933	1.11 (0.90, 1.37)	0.98 (0.79, 1.20)
Type and combination of NSAIDs				
Neither	148	343,069	Reference	Reference
Aspirin only	329	772,257	0.91 (0.75–1.10)	0.91 (0.75–1.11)
Frequency				
Monthly	127	323,602	0.89 (0.70–1.12)	0.95 (0.75–1.21)
Weekly	67	163,672	0.89 (0.67–1.19)	0.92 (0.69–1.23)
Daily	135	284,982	0.94 (0.74–1.19)	0.87 (0.69–1.11)
Nonaspirin NSAIDs only	136	349,379	1.04 (0.82–1.32)	1.01 (0.80–1.27)
Frequency				
Monthly	58	167,560	0.91 (0.67–1.23)	0.93 (0.68–1.26)
Weekly	34	82,500	1.14 (0.78–1.65)	1.11 (0.76–1.62)
Daily	44	99,320	1.20 (0.85–1.68)	1.06 (0.75–1.48)
Both aspirin and nonaspirin NSAIDs	471	1,118,179	0.97 (0.81–1.17)	0.95 (0.78–1.14)
Frequency				
Both monthly	135	358,602	0.90 (0.71–1.14)	0.95 (0.75–1.20)
Aspirin monthly plus nonaspirin NSAIDs weekly or daily	42	136,093	0.79 (0.56–1.11)	0.77 (0.54–1.08)
Nonaspirin monthly plus aspirin weekly or daily	149	332,799	0.96 (0.76–1.20)	0.92 (0.73–1.16)
Both weekly or daily	145	290,685	1.15 (0.91–1.45)	1.04 (0.83–1.31)

[a] Adjusted for age (modeled as a continuous variable), gender, marital status, education (<college or postgraduate vs. college or postgraduate), race (non-Hispanic white, non-Hispanic black, others) (Hispanic, Asian/Pacific Islander, American Indian/Alaskan Native, or unknown), tobacco smoking (never, quit >10 years ago, quit ≤10 years ago, currently smoking and smoked ≤20 cigarettes/day, currently smoking and smoked >20 cigarettes/day), first-degree relative diagnosed with any cancer (yes vs. no), current body mass index (in kg/m^2, <18.5, 18.5 to <25 (reference), 25

to <30, 30 to <35, or ≥35), rigorous physical activity (never or rarely, <3 times per month, 1–2 times per week, 3–4 times per week, ≥5 times per week), history of hypertension (yes vs. no), history of diabetes (yes vs. no), alcohol consumption (g per day), and total dietary fiber

Table 3

Hazard ratios and 95 % CI of association between NSAID use and risk of total renal cell carcinoma (RCC) by age in the NIH–AARP Diet and Health Study, stratified by age-groups

	≤63 years		≥63 years	
	Cases/person-years	**MV-adjusted HR (95 % CI)[a]**	**Cases/person-years**	**MV-adjusted HR (95 % CI)[a]**
Aspirin				
None	103/335,393	Reference	181/357,056	Reference
Any	329/929,131	1.05 (0.84–1.32)	471/961,305	0.86 (0.72–1.03)
Frequency of any use				
Monthly	130/444,791	0.88 (0.68–1.14)	174/373,506	0.86 (0.70–1.06)
Weekly	76/223,900	1.00 (0.75–1.35)	99/212,958	0.84 (0.66–1.07)
Daily	123/260,440	1.29 (0.99–1.69)	198/374,840	0.89 (0.73–1.10)
Nonaspirin NSAIDs				
None	152/477,198	Reference	325/638,128	Reference
Any	280/787,326	1.16 (0.95–1.41)	327/680,232	0.95 (0.81–1.11)
Frequency				
Monthly	154/470,547	1.08 (0.86–1.35)	188/388,415	0.95 (0.80–1.14)
Weekly	76/194,725	1.28 (0.97–1.69)	79/151,939	1.04 (0.81–1.33)
Daily	50/122,054	1.25 (0.90–1.73)	60/139,879	0.83 (0.63–1.10)
Type and combination of NSAIDs				
Neither	35/145,237	Reference	113/197,832	Reference
Aspirin only	117/331,961	1.38 (0.95–2.02)	212/440,296	0.77 (0.61–0.97)
Frequency				
Monthly	42/156,052	1.16 (0.74–1.82)	85/167,550	0.91 (0.69–1.21)
Weekly	27/74,351	1.48 (0.90–2.46)	40/89,321	0.75 (0.52–1.08)
Daily	48/101,558	1.59 (1.03–2.47)	87/183,425	0.68 (0.51–0.90)
Nonaspirin NSAIDs only	68/190,156	1.63 (1.08–2.45)	68/159,224	0.79 (0.58–1.07)
Frequency				
Monthly	30/95,365	1.48 (0.91–2.42)	28/72,196	0.73 (0.48–1.10)
Weekly	17/48,324	1.64 (0.92–2.94)	17/34,176	0.94 (0.57–1.57)
Daily	21/46,467	1.89 (1.09–3.25)	23/52,852	0.78 (0.50–1.22)
Both aspirin and nonaspirin NSAIDs	212/597,170	1.43 (0.99–2.04)	259/521,009	0.79 (0.64–0.99)
Frequency				
Both monthly	65/211,167	1.36 (0.90–2.05)	70/147,435	0.83 (0.62–1.12)
Aspirin monthly plus nonaspirin NSAIDs weekly or daily	23/77,572	1.29 (0.76–2.19)	19/58,521	0.57 (0.35–0.93)
Nonaspirin monthly plus aspirin weekly or daily	59/164,015	1.34 (0.88–2.05)	90/168,784	0.80 (0.60–1.05)
Both weekly or daily	65/144,416	1.67 (1.10–2.52)	80/146,269	0.84 (0.63–1.12)

[*] All *p*'s for interaction >0.05

[a] The models were adjusted for the same covariates as the multivariate model in Table 2