ORIGINAL INVESTIGATION

Prospective Evaluation of Analgesic Use and Risk of Renal Cell Cancer

Eunyoung Cho, ScD; Gary Curhan, MD, ScD; Susan E. Hankinson, ScD; Philip Kantoff, MD; Michael B. Atkins, MD; Meir Stampfer, MD, DrPH; Toni K. Choueiri, MD

Background: Epidemiologic data suggest that analgesic use increases the risk of renal cell cancer (RCC), but few prospective studies have been published. We investigated the association between analgesic use and RCC in 2 large prospective studies.

Methods: We examined the relationship between analgesic use and RCC risk in the Nurses' Health Study and the Health Professionals Follow-up Study. Use of aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen was ascertained in 1990 in the Nurses' Health Study and in 1986 in the Health Professionals Follow-up Study, and every 2 years thereafter. We evaluated baseline and duration of use of analgesics.

Results: During follow-up of 16 years among 77 525 women and 20 years among 49 403 men, we documented 333 RCC cases. Aspirin and acetaminophen use were not associated with RCC risk. However, regular use of nonaspirin NSAIDs was associated with an increased RCC risk; the pooled multivariate relative risk was 1.51 (95% confidence interval, 1.12-2.04) at baseline. The absolute risk differences for users vs nonusers of nonaspirin NSAIDs were 9.15 per 100 000 person-years in women and 10.92 per 100 000 person-years in men. There was a dose-response relationship between duration of nonaspirin NSAID use and RCC risk; compared with nonregular use, the pooled multivariate relative risks were 0.81 (95% confidence interval, 0.59-1.11) for use less than 4 years, 1.36 (0.98-1.89) for 4 to less than 10 years, and 2.92 (1.71-5.01) for use for 10 or more years ($P<.001$ for trend).

Conclusion: Our prospective data suggest that longer duration of use of nonaspirin NSAIDs may increase the risk of RCC.

Arch Intern Med. 2011;171(16):1487-1493

Author Affiliations: Channing Laboratory, Department of Medicine (Drs Cho, Curhan, Hankinson, and Stampfer), and Dana-Farber Cancer Institute (Drs Kantoff and Choueiri), Harvard Medical School and Brigham and Women's Hospital, Departments of Nutrition (Drs Cho and Stampfer) and Epidemiology (Drs Curhan, Hankinson, and Stampfer), Harvard School of Public Health, and Department of Medicine, Harvard Medical School and Beth Israel Deaconess Medical Center (Dr Atkins), Boston, Massachusetts.

KIDNEY CANCER IS THE SEVenth leading type of cancer among men and the ninth among women in the United States.[1] Renal cell cancer (RCC) is the most common type of kidney cancer, accounting for 85% of all cases. The incidence of RCC has been rising in the United States and worldwide.[2] Smoking, obesity, and hypertension are established modifiable risk factors.

See Editor's Note at end of article

Analgesics are among the most commonly used groups of drugs in the United States. In one survey, acetaminophen, ibuprofen, and aspirin were the 3 most commonly used prescription and over-the-counter drugs[3]; those drugs are considered by the World Health Organization as "essential medicines."[4] A US national survey found that aspirin and acetaminophen were taken by 28% and 8% of participants aged 57 to 85 years, respectively.[5] These drugs have more effects than just analgesia. For example, aspirin has a well-established protective effect against cardiovascular disease[6] and colorectal cancer.[7] Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) may exert their protective effect against cancer by reducing inflammation, inhibiting cyclooxygenase 2, inhibiting cell proliferation, and inducing apoptosis of cancer cells.[8] However, some epidemiologic data, mainly from case-control studies, suggest an association between analgesic use and an increased risk of RCC.[8-12] Most prospective studies of analgesics and kidney cancer have been small (<100 cases)[8] and had a short follow-up period. We therefore examined the use of analgesics in relation to RCC risk in 2 prospective studies.

METHODS

STUDY POPULATION

The Nurses' Health Study (NHS)[13] enrolled 121 700 female nurses aged 30 to 55 years in 1976. The Health Professionals Follow-up Study (HPFS) included 51 529 male health pro-

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 02/14/2016

fessionals aged 40 to 75 years in 1986. Follow-up questionnaires to both cohorts were sent biennially to update information regarding lifestyle factors, including use of analgesics (for NHS, starting in 1980 for aspirin and in 1990 for nonaspirin analgesics), and to identify new diagnoses of major illnesses, including RCC. Deaths in the cohorts were ascertained by reports from family members, the postal service, and a search of the National Death Index; more than 98% of deaths were identified through these sources.[14]

In the NHS, we started follow-up for the current analysis in 1990 when the use of nonaspirin analgesics was first documented. In the HPFS, we started follow-up in 1986—the start of the study. We excluded individuals who did not answer the baseline questionnaire and those with a history of cancer other than nonmelanoma skin cancer at baseline and during follow-up. The follow-up rates among participants with baseline information on analgesic use were 97.0% in the NHS and 91.0% in the HPFS.

The studies were approved by the institutional review boards of the Brigham and Women's Hospital and Harvard School of Public Health.

ASSESSMENT OF USE OF ANALGESICS

In the NHS, biennial follow-up questionnaires assessed regular use of aspirin, nonaspirin NSAIDs, and acetaminophen in 1990 and every 2 years thereafter. In the HPFS, similar questions on the use of analgesics have been asked since 1986. We collected information on dosage (number of tablets per week; 4 baby aspirin = 1 tablet) of aspirin since 1994 in the NHS and 1992 in the HPFS. Information on dosages of other analgesics has been determined since 1998 in the NHS and since 2000 in the HPFS.

In 1990, we inquired as to the reasons for aspirin use in a random subsample of 200 women in the NHS. The major reasons for women taking 7 or more tablets per week were headache (19%), arthritis or other musculoskeletal pain (50%), a combination of these symptoms (15%), cardiovascular disease prevention (8%), and other reasons (9%).[15]

In 1999, we sent a supplementary questionnaire to 4238 of the NHS participants who had reported either frequent use or nonuse of analgesics in previous follow-up questionnaires and had provided a blood sample in 1989, to ascertain detailed information on analgesic use.[16] The nonaspirin NSAIDs taken by these participants included ibuprofen (73%) and naproxen (14%); 13% used other types of these medications. The major reasons for use of ibuprofen and acetaminophen were muscle/joint pain (84% and 65%, respectively), headache (5% and 24%), backache (5% and 4%), and other reasons (6% and 8%).[17]

To maintain consistency across the cohorts and with previous studies,[9] we defined regular users as those who took 1 type of analgesic medication 2 or more times per week when information on frequency of use was available. Whenever information on dose was available, we also took into consideration the dose and defined regular use as 2 or more tablets per week.

ASSESSMENT OF OTHER RISK FACTORS FOR RCC

Information on body weight, smoking, recreational physical activity, and history of hypertension was collected biennially in the 2 cohorts. The diagnosis of hypertension has been shown[18] to be reliably reported. Pack-years of smoking were calculated by multiplying the duration and dose of smoking; 1 pack-year is equivalent to having smoked 1 pack per day for 1 year. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Dietary information was collected using validated food frequency questionnaires in 1990 in the NHS, in 1986 in the HPFS, and every 4 years thereafter. Women were asked about parity.

IDENTIFICATION OF CASES

We inquired about the occurrence of cancer on each questionnaire and asked participants (or next-of-kin for those who died) who reported a diagnosis of kidney cancer for permission to access the medical records. Physicians blinded to the participants' questionnaire information reviewed the medical records. Based on the World Health Organization classification,[19] we included, as RCC, clear cell, papillary, chromophobe, collecting duct RCC, and RCC not otherwise classified. We evaluated RCC as the primary disease end point; in secondary analyses, we evaluated clear cell RCC, the major histologic subtype of RCC.

STATISTICAL ANALYSIS

To take advantage of long follow-up time and repeated assessment of analgesic use, we evaluated baseline and duration of use of analgesics. Baseline use was ascertained in 1990 in the NHS and in 1986 in the HPFS. To evaluate the cumulative impact of use of analgesics on RCC risk, we calculated cumulative duration of use, which took intermittent use into consideration. Duration of analgesic use was calculated from information from subsequent follow-up biennial questionnaires and was a time-varying exposure variable. For example, if a person reported being a regular user of a specific analgesic class on 2 consecutive biennial questionnaires, then 2 years of use were assigned. If a person reported being a regular user on 1 questionnaire but not the other questionnaire, then 1 year of use was assigned. If a person missed a questionnaire, we carried forward information on use of the analgesic class from the previous questionnaire. If a person missed 2 or more consecutive questionnaires, no use (0 year) was assigned for the period and the person-time for the participant was censored in the analysis for that period. For each person, total number of years of use up to each follow-up cycle was summed as the duration of use of the analgesic class.

Participants contributed person-time from the date of return of the baseline questionnaire until the date of RCC diagnosis, report of other cancer other than nonmelanoma skin cancer, death, or end of follow-up (June 2006 for NHS and January 2006 for HPFS), whichever came first. Participants were divided into categories according to their use of analgesics and duration of use. Relative risks (RRs) of RCC were calculated as the incidence rate for a given category divided by the rate for reference category. We used Cox proportional hazards regression to adjust for other risk factors for RCC.[20] To control as finely as possible for confounding by age, calendar time, and any possible 2-way interactions between these 2 time scales, we stratified the analysis jointly by age in months at the start of follow-up and calendar year of the current questionnaire cycle. In multivariate models, we also adjusted for BMI; smoking; history of hypertension; physical activity; intake of fruits, vegetables, and alcohol; and parity in women. Commercial software (SAS PROC PHREG; SAS Institute, Inc, Cary, North Carolina) was used, and the Anderson-Gill data structure[21] was used to handle time-varying covariates efficiently. For all RRs, 95% confidence intervals (CIs) were calculated. To test whether the association between analgesics and RCC risk was modified by smoking, BMI, or history of hypertension, cross-product terms for the level of an interaction variable and analgesic use were included in multivariate models. The *P* value

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 02/14/2016

Table 1. Baseline Characteristics of the Cohorts According to Use of Analgesics in the Nurses' Health Study and Health Professionals Follow-up (1990 in Women and 1986 in Men)[a]

	Regular Use of Analgesics (≥2 times/wk)					
	Aspirin		Nonaspirin NSAIDs		Acetaminophen	
Characteristic	No	Yes	No	Yes	No	Yes
Women						
No.	58 934	18 591	62 947	14 578	65 547	11 978
Users, %		24.0		18.8		15.5
Past smoker, %	38.5	40.0	38.2	42.2	38.7	40.1
Current smoker, %	16.9	17.3	17.2	15.9	16.9	16.9
Hypertension, %	29.1	35.9	29.3	37.1	29.5	37.2
Mean						
Age, y	56.2	58.2	56.8	56.4	56.7	56.6
BMI	25.7	26.0	25.5	26.9	25.6	26.3
Alcohol, g/d	4.5	5.1	4.7	4.6	4.7	4.4
Fruit, servings/d	1.9	2.0	1.9	1.9	1.9	1.9
Vegetable, servings/d	2.4	2.5	2.4	2.4	2.4	2.4
Men						
No.	34 858	14 545	46 691	2712	46 573	2830
Users, %		29.4		5.5		5.7
Past smoker, %	39.5	47.6	41.3	51.0	41.4	49.0
Current smoker, %	9.3	10.4	9.6	10.1	9.5	11.6
Hypertension, %	20.3	26.6	21.9	27.0	21.9	26.6
Mean						
Age, y	53.7	56.4	54.4	55.9	54.6	53.6
BMI	25.5	25.7	25.5	26.2	25.5	25.6
Alcohol, g/d	10.5	12.3	10.9	12.3	11.0	10.6
Fruit, servings/d	2.3	2.3	2.3	2.2	2.3	2.2
Vegetable, servings/d	3.0	3.0	3.0	3.0	3.0	2.9

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NSAIDs, nonsteroidal anti-inflammatory drugs.
[a] Except for the data on mean age and the percentage who were users, all data shown are standardized to the age distributions of each cohort.

for the test for interaction was obtained from a Wald test. All *P* values are 2-sided.

We conducted separate analyses for each cohort, tested for heterogeneity between studies, and applied meta-analytic methods with a random-effects model to pool the RRs from the cohorts.[22]

RESULTS

During follow-up of 16 years among 77 525 women (1 106 683 person-years) and 20 years among 49 403 men (807 017 person-years), we documented 333 cases of RCC (153 women and 180 men).

The distribution of risk factors for RCC by use of analgesics at baseline in each cohort is presented in **Table 1**. Among analgesic classes, aspirin was taken most frequently by both women and men. Other drugs used by the women who took aspirin were nonaspirin NSAIDs (12%), acetaminophen (10%), and both medications (4%). The corresponding percentages in men were 6%, 8%, and 1%. Women and men who regularly took analgesics were more likely to be past smokers and to have a history of hypertension.

Table 2 presents the results for baseline use of analgesics and RCC risk. Use of aspirin or acetaminophen was not associated with RCC risk, although there was some suggestion of positive association for acetaminophen. However, regular use of nonaspirin NSAIDs at baseline was associated with an increased RCC risk; the pooled multivariate RR was 1.51 (95% CI, 1.12-2.04), compared with nonregular use. The results did not differ by sex ($P = .60$ for heterogeneity). In women, we had more detailed information on frequency of nonaspirin NSAID use at baseline and there was a linear increase in RCC risk by increasing frequency of use; compared with nonuse, the RRs were 1.08 (95% CI, 0.67-1.74), 1.30 (0.71-2.39), and 1.86 (1.19-2.90) for use of 1 to 4 days per month, 5 to 14 days per month, and more than 15 times per month, respectively. Because some participants used multiple analgesic medications, we evaluated the associations among individuals who used 1 medication exclusively by excluding those who also took other analgesics. The results were essentially similar. The pooled multivariate RR was 1.57 (95% CI, 1.07-2.33) for participants with exclusive use of nonaspirin NSAIDs compared with those who did not use any of the analgesics. The absolute risk differences for the users vs nonusers of nonaspirin NSAIDs were 9.15 per 100 000 person-years in women and 10.92 per 100 000 person-years in men. Assuming a causal relation, use of nonaspirin NSAIDs by each of 10 929 women or 9158 men would lead to 1 RCC case (the numbers needed to harm).

Table 3 presents the results for cumulative updated duration of use of analgesics and RCC risk. There was a dose-response relationship between duration of regular use of nonaspirin NSAIDs and RCC risk; compared with nonregular use, the pooled multivariate RRs were 0.81

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 02/14/2016

Table 2. Age-Adjusted and Multivariate[a] Analysis of Renal Cell Cancer According to Analgesic Use at Baseline (1990 in Women and 1986 in Men)

Analgesic	Regular Use of Analgesics (≥2 times/wk) at Baseline, OR (95% CI)	
	No	Yes
Aspirin		
Women		
Person-years	844 006	262 677
No. of cases	116	37
Age-adjusted	1 [Reference]	0.96 (0.66-1.40)
Multivariate	1 [Reference]	0.93 (0.64-1.35)
Men		
Person-years	578 491	228 526
No. of cases	123	57
Age-adjusted	1 [Reference]	1.08 (0.78-1.48)
Multivariate	1 [Reference]	0.99 (0.71-1.37)
Pooled multivariate	1 [Reference]	0.96 (0.75-1.23)
Nonaspirin NSAIDs		
Women		
Person-years	899 796	206 887
No. of cases	109	44
Age-adjusted	1 [Reference]	1.74 (1.22-2.47)
Multivariate	1 [Reference]	1.59 (1.11-2.27)
Men		
Person-years	764 127	42 890
No. of cases	166	14
Age-adjusted	1 [Reference]	1.47 (0.85-2.56)
Multivariate	1 [Reference]	1.33 (0.76-2.32)
Pooled multivariate	1 [Reference]	1.51 (1.12-2.04)
Acetaminophen		
Women		
Person-years	937 641	169 042
No. of cases	123	30
Age-adjusted	1 [Reference]	1.34 (0.90-2.01)
Multivariate	1 [Reference]	1.26 (0.84-1.88)
Men		
Person-years	761 515	45 502
No. of cases	166	14
Age-adjusted	1 [Reference]	1.60 (0.92-2.78)
Multivariate	1 [Reference]	1.47 (0.84-2.56)
Pooled multivariate	1 [Reference]	1.32 (0.96-1.84)

Abbreviations: CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio.

[a] Multivariate was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for smoking status (never, 1-19, 20-39, or ≥40 pack-years), body mass index (<25, 25-26.9, 27-29.9, or ≥30 [calculated as weight in kilograms divided by height in meters squared]), history of hypertension (yes/no), physical activity (quintiles), fruit intake (continuous), vegetable intake (continuous), alcohol intake (continuous), and parity in women (0, 1-2, 3, 4, or ≥5 children).

(95% CI, 0.59-1.11) for use less than 4 years, 1.36 (0.98-1.89) for 4 to 10 years, and 2.92 (1.71-5.01) for 10 years or longer ($P<.001$ for trend). The positive association did not differ by sex ($P=.33$ for heterogeneity). Duration of use of aspirin or acetaminophen was not associated with RCC risk. When we mutually adjusted for the 3 analgesics in a multivariate model, the positive association between nonaspirin NSAIDs and RCC risk remained essentially unchanged; the pooled multivariate RR was 3.00 (95% CI, 1.74-5.18) for use of 10 or more years. For participants who used nonaspirin NSAIDs for 10 or more years, we also examined nonconsecutive vs consecutive use. In women, the RRs for nonconsecutive and consecutive use were 4.01 (95% CI, 1.98-8.29; 11 cases) and 2.40 (0.72-7.95; 3 cases), respectively. All men with use of 10 or more years were nonconsecutive users. When we excluded prevalent users of nonaspirin NSAIDs at baseline, few cases remained among those with 4 or more years of use. The pooled RR combining 4 to less than 10 years and 10 or more years of nonaspirin NSAID use was 1.18 (95% CI, 0.78-1.77).

In the NHS, use of aspirin was first determined in 1980. When we evaluated the use since 1980 instead of 1990, we did not find any association with RCC risk (data not shown).

The association between duration of regular use of nonaspirin NSAIDs and RCC risk did not differ significantly by levels of other RCC risk factors including smoking, BMI, and history of hypertension (data not shown; $P>.30$ for all interactions).

We evaluated the use of analgesics in relation to clear cell RCC (101 cases women and 117 men), the major histologic subtype of RCC. The results were similar to those for all histologic types of RCC (data not shown).

COMMENT

In these large prospective studies of women and men, we found that use of nonaspirin NSAIDs was associated with an elevated risk of RCC, especially among those who took them for a long duration. Aspirin and acetaminophen were not associated with RCC risk.

Although aspirin has been associated with a reduced risk of several types of cancer, previous epidemiologic data[8,23] pointed toward an increased risk of RCC with this drug. A meta-analysis[8] of 5 case-control studies and 3 cohort studies of RCC reported RRs of 1.21 (95% CI, 1.07-1.36) for case-control studies and 1.45 (0.87-2.40) for small cohort studies. However, we found no association between aspirin and risk of RCC in our 2 independent populations. Evaluation of dose and duration also did not reveal any association with RCC risk.

One prospective study[24] and 7 case-control studies[9-11,23,25-28] have evaluated acetaminophen in relation to RCC risk; 3 of the studies[9-11] found a positive association. Acetaminophen is a metabolite of phenacetin, which was banned in the 1970s to early 1980s worldwide because of its carcinogenic effect, especially in renal pelvis tumors.[9,26] However, we found little evidence that use of acetaminophen was associated with RCC risk, although a small elevated risk related to remote use cannot be excluded.

A potential explanation for the discrepancy in findings for aspirin and acetaminophen in our studies vs previous studies may be that most of the previous studies were retrospective, which might be susceptible to biased recall of use of analgesics and reverse causation (ie, individuals might have taken analgesics to treat symptoms related to RCC).

In terms of nonaspirin NSAIDs, there have been few studies on RCC risk. Although one case-control study[9] found a positive association with RCC risk, the investigators reported a similar finding with other analgesics, including aspirin, acetaminophen, and phenacetin. A retrospective cohort study in Denmark using a prescription database found that prescription of nonaspirin

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 02/14/2016

Table 3. Age-Adjusted and Multivariate Analysis of Renal Cell Cancer According to Cumulative Updated Duration of Regular Use of Analgesics[a]

Analgesics	Cumulative Updated Duration of Regular Use of Analgesics (≥2 times/wk), OR (95% CI)				*P* for Trend
Aspirin	No	>0 to <4 y	4 to <10 y	≥10 y	
Women					
Person-years	523 069	280 760	209 270	49 151	
No. of cases	69	42	27	13	
Age-adjusted	1 [Reference]	1.03 (0.70 to 1.51)	0.73 (0.45 to 1.16)	1.34 (0.70 to 2.59)	.87
Multivariate	1 [Reference]	0.98 (0.66 to 1.44)	0.67 (0.42 to 1.07)	1.24 (0.64 to 2.40)	.61
Men					
Person-years	286 738	201 852	156 421	62 802	
No. of cases	57	43	45	22	
Age-adjusted	1 [Reference]	0.94 (0.63 to 1.40)	1.09 (0.70 to 1.68)	1.22 (0.68 to 2.16)	.44
Multivariate	1 [Reference]	0.86 (0.57 to 1.29)	0.98 (0.63 to 1.52)	1.05 (0.58 to 1.87)	.78
Pooled multivariate	1 [Reference]	0.92 (0.69 to 1.22)	0.82 (0.56 to 1.19)	1.13 (0.73 to 1.74)	.93
Nonaspirin NSAIDs	No	>0 to <4 y	4 to <10 y	≥10 y	
Women					
Person-years	616 037	242 914	182 120	21 178	
No. of cases	76	24	37	14	
Age-adjusted	1 [Reference]	0.77 (0.48 to 1.23)	1.51 (1.00 to 2.28)	4.13 (2.16 to 7.87)	<.001
Multivariate	1 [Reference]	0.71 (0.44 to 1.14)	1.35 (0.89 to 2.06)	3.51 (1.83 to 6.74)	<.001
Men					
Person-years	535 347	111 908	51 345	9212	
No. of cases	117	26	19	5	
Age-adjusted	1 [Reference]	0.96 (0.62 to 1.48)	1.46 (0.87 to 2.45)	2.16 (0.84 to 5.55)	.06
Multivariate	1 [Reference]	0.90 (0.58 to 1.40)	1.38 (0.82 to 2.31)	1.98 (0.76 to 5.12)	.11
Pooled multivariate	1 [Reference]	0.81 (0.59 to 1.11)	1.36 (0.98 to 1.89)	2.92 (1.71 to 5.01)	<.001
Acetaminophen	No	>0 to <4 y	4 to <6 y	≥6 y	
Women					
Person-years	702 283	217 404	65 379	77 184	
No. of cases	93	31	10	17	
Age-adjusted	1 [Reference]	1.02 (0.68 to 1.54)	0.97 (0.50 to 1.89)	1.28 (0.74 to 2.20)	.46
Multivariate	1 [Reference]	0.93 (0.62 to 1.41)	0.86 (0.44 to 1.68)	1.12 (0.65 to 1.93)	.87
Men					
Person-years	601 975	75 144	15 265	15 427	
No. of cases	138	19	6	4	
Age-adjusted	1 [Reference]	1.02 (0.63 to 1.66)	1.49 (0.64 to 3.45)	0.94 (0.34 to 2.59)	.74
Multivariate	1 [Reference]	0.97 (0.59 to 1.57)	1.37 (0.59 to 3.17)	0.83 (0.30 to 2.29)	.98
Pooled multivariate	1 [Reference]	0.94 (0.69 to 1.30)	1.03 (0.61 to 1.74)	1.05 (0.65 to 1.69)	.90

Abbreviations: CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio.

[a]The models were adjusted for the same covariates as the multivariate model in Table 2. The total number of cases in this table is slightly different (2 fewer women and 13 fewer men) from Table 2 because this Table is based on updated analgesic use and those who missed follow-up questionnaires were censored for the periods.

NSAIDs was associated with incidence of (RR,1.4; 95% CI, 0.9-2.1)[12] and mortality from (1.72; 1.4-2.1)[29] kidney cancer. In our study, we found a positive association only with nonaspirin NSAIDs, with a strong dose-response relation for duration of use. Because we observed the association in 2 independent populations, it is unlikely to be a chance finding. Also, because we found no association with other analgesics and the study period was until 2006, residual confounding by phenacetin may not explain the positive association that we found with nonaspirin NSAIDs. Contrary to our findings on RCC, meta-analyses reported that use of nonaspirin NSAIDs was associated with reduced risk of breast,[30] prostate,[31] and colorectal cancers,[7] with the magnitude of association similar to that of aspirin. Analgesics in general have been associated with elevated risk of hypertension,[32] a risk factor for RCC. However, our results did not differ by presence of hypertension. The NSAIDs are also associated with elevated risks of both acute and chronic renal diseases by inhibiting the synthesis of renal prostaglandins,[33,34] which can result in chronic subacute renal injuries such as tubular necrosis, papillary necrosis, and interstitial nephritis.[35,36] This has the potential for injury-related DNA damage and subsequent uncontrolled cell proliferation, leading to carcinogenesis.[37] The mechanism may be mediated by the inhibition of cyclooxygenase 1–derived renal prostaglandins, which are important for renal homeostasis[38] and NSAIDs are known to inhibit cyclooxygenase 1 and 2. Selective cyclooxygenase 2 inhibitors, another NSAID class, were recently added to the cohorts' questionnaires; the short follow-up time did not allow us to evaluate their relationship to RCC risk. Still, this does not provide an explanation why nonaspirin NSAIDs, but not aspirin, were associated with RCC, since both are considered NSAIDs and the renal injuries described herein have been reported[35,39] with both classes. Because the dosages of aspirin and nonaspirin NSAIDs are different, the delivered target renal tissue dose could also differ between these 2 classes and may lead to a different threshold for neoplastic transformation.

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 02/14/2016

The analgesics discussed herein are frequently used by individuals with rheumatoid arthritis, often at high dosages. A study[40] that evaluated cancer incidence in this population did not find an increased risk for RCC, although the analgesic exposure history in the study was somewhat limited.

Our study has limitations. First, although we gathered extensive information on risk factors for RCC and adjusted for them in multivariate analysis, residual confounding can remain a concern. The results on nonaspirin NSAIDs were somewhat attenuated after adjustment for multiple covariates. However, given the strength of the association, especially for long duration of use, residual confounding may not entirely explain the association. Second, confounding by indication (eg, patients with RCC started to take analgesics before diagnosis to treat the symptoms) may have been an issue for these widely used drugs. However, the strongest association that we found among individuals who used analgesics for the longest duration argues against the possibility. Third, because phenacetin was available in the United States up to the mid-1980s, our results with follow-up started in 1986 and 1990 might have been confounded by past use of phenacetin. However, differential association between nonaspirin NSAIDs and other analgesics and strong duration effect for nonaspirin NSAIDs are not explained by the possibility. Fourth, we have only recently started to collect more detailed information on the dose of NSAIDs, with inadequate follow-up to evaluate this issue. With longer follow-up, we will be able to evaluate more detailed dose-response relation between nonaspirin NSAIDs and RCC risk.

This study has strengths. To our knowledge, it is the first prospective study of nonaspirin NSAIDs and the largest prospective study of analgesics in relation to RCC risk. The prospective design minimizes biases that can affect case-control studies. Our study was unique to have information on use of analgesics ascertained multiple times during follow-up, which enabled us to calculate duration of use, a much stronger predictor of RCC risk for nonaspirin NSAIDs than use at baseline.

Risks and benefits should be considered in deciding whether to use analgesics; if our findings are confirmed, an increased risk of RCC should also be considered.

Accepted for Publication: May 20, 2011.
Correspondence: Eunyoung Cho, ScD, Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Ave, Boston, MA 02115 (eunyoung.cho@channing.harvard.edu).
Author Contributions: Dr Cho had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Cho and Choueiri. *Acquisition of data:* Curhan and Hankinson. *Analysis and interpretation of data:* Cho, Curhan, Hankinson, Kantoff, Atkins, Stampfer, and Choueiri. *Drafting of the manuscript:* Cho and Choueiri. *Critical revision of the manuscript for important intellectual content:* Curhan, Hankinson, Kantoff, Atkins, Stampfer, and Choueiri. *Statistical analysis:* Cho. *Obtained funding:* Cho, Atkins, and Choueiri. *Administrative, technical, and material support:* Curhan, Atkins, Stampfer, and Choueiri. *Study supervision:* Kantoff, Atkins, and Choueiri.
Financial Disclosure: None reported.
Funding/Support: This study was supported by research grants CA137764, CA87969, and CA55075 from the National Institutes of Health; the Kidney Cancer Association; and grant NIH P50CA101942 from the Dana-Farber/Harvard Cancer Center Kidney Cancer Specialized Programs of Research Excellence.
Additional Contributions: Rong Tilney, MA (Brigham and Women's Hospital, Boston, Massachusetts), provided valuable computer support.

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin.* 2009;59(4):225-249.
2. Mathew A, Devesa SS, Fraumeni JF Jr, Chow WH. Global increases in kidney cancer incidence, 1973-1992. *Eur J Cancer Prev.* 2002;11(2):171-178.
3. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone Survey. *JAMA.* 2002;287(3):337-344.
4. *WHO Model List of Essential Medicines*, 16th ed. Geneva, Switzerland: World Health Organization; March 2009. http://www.who.int/selection_medicines/committees/expert/17/sixteenth_adult_list_en.pdf. Accessed January 5, 2011.
5. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA.* 2008;300(24):2867-2878.
6. Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. *JAMA.* 2006;295(3):306-313.
7. Rostom A, Dubé C, Lewin G, et al; U.S. Preventive Services Task Force. 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):376-389.
8. Bosetti C, Gallus S, La Vecchia C. Aspirin and cancer risk: an updated quantitative review to 2005. *Cancer Causes Control.* 2006;17(7):871-888.
9. Gago-Dominguez M, Yuan JM, Castelao JE, Ross RK, Yu MC. Regular use of analgesics is a risk factor for renal cell carcinoma. *Br J Cancer.* 1999;81(3):542-548.
10. Mellemgaard A, Lindblad P, Schlehofer B, et al. International renal-cell cancer study, III: role of weight, height, physical activity, and use of amphetamines. *Int J Cancer.* 1995;60(3):350-354.
11. Derby LE, Jick H. Acetaminophen and renal and bladder cancer. *Epidemiology.* 1996;7(4):358-362.
12. Sørensen HT, Friis S, Nørgård B, et al. Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study. *Br J Cancer.* 2003;88(11):1687-1692.
13. Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. *Nat Rev Cancer.* 2005;5(5):388-396.
14. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. *Am J Epidemiol.* 1984;119(5):837-839.
15. Manson JE, Stampfer MJ, Colditz GA, et al. A prospective study of aspirin use and primary prevention of cardiovascular disease in women. *JAMA.* 1991;266(4):521-527.
16. Curhan GC, Knight EL, Rosner B, Hankinson SE, Stampfer MJ. Lifetime nonnarcotic analgesic use and decline in renal function in women. *Arch Intern Med.* 2004;164(14):1519-1524.
17. Chan AT, Manson JE, Albert CM, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. *Circulation.* 2006;113(12):1578-1587.
18. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol.* 1986;123(5):894-900.
19. Störkel S, Eble JN, Adlakha K, et al; Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Classification of renal cell carcinoma: Workgroup No. 1. *Cancer.* 1997;80(5):987-989.
20. Prentice RL, Kalbfleisch JD, Peterson AV Jr, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics.* 1978;34(4):541-554.
21. Therneau TM. Extending the Cox model. In: Lin DY, Fleming TR, eds. *Proceed-*

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 02/14/2016

ings of the First Seattle Symposium in Biostatistics: Survival Analysis. New York, NY: Springer Verlag; 1997:51-84.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986; 7(3):177-188.
23. Chow WH, McLaughlin JK, Linet MS, Niwa S, Mandel JS. Use of analgesics and risk of renal cell cancer. *Int J Cancer.* 1994;59(4):467-470.
24. Friis S, Nielsen GL, Mellemkjaer L, et al. Cancer risk in persons receiving prescriptions for paracetamol: a Danish cohort study. *Int J Cancer.* 2002;97(1):96-101.
25. McLaughlin JK, Blot WJ, Mehl ES, Fraumeni JF Jr. Relation of analgesic use to renal cancer: population-based findings. *Natl Cancer Inst Monogr.* 1985;69: 217-222.
26. McCredie M, Stewart JH, Day NE. Different roles for phenacetin and paracetamol in cancer of the kidney and renal pelvis. *Int J Cancer.* 1993;53(2):245-249.
27. McCredie M, Pommer W, McLaughlin JK, et al. International renal-cell cancer study, II: analgesics. *Int J Cancer.* 1995;60(3):345-349.
28. Rosenberg L, Rao RS, Palmer JR, et al. Transitional cell cancer of the urinary tract and renal cell cancer in relation to acetaminophen use (United States). *Cancer Causes Control.* 1998;9(1):83-88.
29. Lipworth L, Friis S, Blot WJ, et al. A population-based cohort study of mortality among users of ibuprofen in Denmark. *Am J Ther.* 2004;11(3):156-163.
30. Takkouche B, Regueira-Méndez C, Etminan M. Breast cancer and use of nonsteroidal anti-inflammatory drugs: a meta-analysis. *J Natl Cancer Inst.* 2008; 100(20):1439-1447.
31. Jafari S, Etminan M, Afshar K. Nonsteroidal anti-inflammatory drugs and prostate cancer: a systematic review of the literature and meta-analysis. *Can Urol Assoc J.* 2009;3(4):323-330.
32. Forman JP, Rimm EB, Curhan GC. Frequency of analgesic use and risk of hypertension among men. *Arch Intern Med.* 2007;167(4):394-399.
33. Sandler DP, Burr FR, Weinberg CR. Nonsteroidal anti-inflammatory drugs and the risk for chronic renal disease. *Ann Intern Med.* 1991;115(3):165-172.
34. Griffin MR, Yared A, Ray WA. Nonsteroidal antiinflammatory drugs and acute renal failure in elderly persons. *Am J Epidemiol.* 2000;151(5):488-496.
35. Segasothy M, Samad SA, Zulfigar A, Bennett WM. Chronic renal disease and papillary necrosis associated with the long-term use of nonsteroidal anti-inflammatory drugs as the sole or predominant analgesic. *Am J Kidney Dis.* 1994; 24(1):17-24.
36. Ou YC, Yang CR, Cheng CL, et al. Indomethacin causes renal epithelial cell injury involving Mcl-1 down-regulation. *Biochem Biophys Res Commun.* 2009; 380(3):531-536.
37. Henderson BE, Ross RK, Pike MC. Toward the primary prevention of cancer. *Science.* 1991;254(5035):1131-1138.
38. Ruffin MT IV, Krishnan K, Rock CL, et al. Suppression of human colorectal mucosal prostaglandins: determining the lowest effective aspirin dose. *J Natl Cancer Inst.* 1997;89(15):1152-1160.
39. Burrell JH, Yong JL, Macdonald GJ. Analgesic nephropathy in Fischer 344 rats: comparative effects of chronic treatment with either aspirin or paracetamol. *Pathology.* 1991;23(2):107-114.
40. Yamada T, Nakajima A, Inoue E, et al. Incidence of malignancy in Japanese patients with rheumatoid arthritis [published online May 16, 2010]. *Rheumatol Int.* doi:10.1007/s00296-010-1524-0.

EDITOR'S NOTE

Renal Cell Carcinoma and the Widespread Use of NSAIDs

An estimated 60 million Americans use nonsteroidal anti-inflammatory drugs (NSAIDs) regularly. The study by Cho et al uses prospective data from 2 different cohorts to estimate the risk of renal cell carcinoma related to NSAID use and reports a pooled multivariate relative risk of 1.51 (95% confidence interval, 1.12-2.04) for nonaspirin NSAID use, with a dose-response relationship based on duration of use. Although the absolute risk differences between users and nonusers of NSAIDS were quite low, we find the results compelling in light of the widespread use of these drugs.

Kirsten L. Johansen, MD

©2011 American Medical Association. All rights reserved.

Downloaded From: http://archinte.jamanetwork.com/ on 02/14/2016