ORIGINAL INVESTIGATION

# Prospective Evaluation of Analgesic Use and Risk of Renal Cell Cancer

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**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.

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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-

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

**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

**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)**

| | Regular Use of Analgesics (≥2 times/wk) at Baseline, OR (95% CI) | |
|---|---|---|
| **Analgesic** | **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

**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.

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.

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**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.

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