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Prospective evaluation of analgesic use and risk of renal cell cancer

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Abstract

Background—Epidemiologic data suggest that analgesic use increases the risk of renal cell cancer (RCC), but few prospective studies exist. We investigated the association between analgesic use and RCC in two large prospective studies.

Methods—We examined the relation between analgesic use and RCC risk in the Nurses’ Health Study and the Health Professionals Follow-up Study. Use of aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen was ascertained in 1990 in the NHS and 1986 in the HPFS 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 non-aspirin NSAIDs was associated with an increased RCC risk; the pooled multivariable relative risk (RR) was 1.51 (95% confidence interval [CI] 1.12–2.04) for the use at baseline. The absolute risk differences for the users vs. non-users of non-aspirin NSAIDs were 9.16/100,000 person-years in women and 10.92/100,000 person-years in men. There was a dose-response relation between duration of non-aspirin NSAIDs use and RCC risk; compared with non-regular users, the pooled multivariable RRs were 0.81 (95% CI 0.59–1.11) for use under 4 years, 1.36 (95% CI 0.98–1.89) for use 4–10 years, and 2.92 (95% CI 1.71–5.01) for use 10+ years (P for trend <0.001).

Conclusions—Our prospective data suggest that longer duration of use of non-aspirin NSAIDs may increase the risk of RCC.

INTRODUCTION

Kidney cancer is the 7th leading cancer among men and the 9th among women in the U.S. 1. Renal cell cancer (RCC) is the most common type of kidney cancer, accounting for 85% of all cases. Incidence of RCC has been rising in the U.S. and worldwide 2. Smoking, obesity, hypertension are established modifiable risk factors.

Analgesics are among the most commonly used group of drugs in the U.S. In one survey, acetaminophen, ibuprofen, and aspirin were the three most commonly used prescription and
over-the-counter drugs; those drugs are considered by the World Health Organization as “essential medicines.” A national survey in the U.S. found that aspirin and acetaminophen were used by 28% and 8% of participants aged 57–85, respectively. These drugs have effects beyond analgesia. For example, aspirin has a well-established protective effect against cardiovascular disease and colorectal cancer. Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) may exert their protective effect against malignancy by reducing inflammation, inhibiting cyclooxygenase (COX)-2, inhibiting cell proliferation, and inducing apoptosis of cancer cells. However, some epidemiologic data, mainly from case-control studies, suggest an association between analgesic use and an increased RCC risk. Most prospective studies of analgesics and kidney cancer have been small (<100 cases) and had a short follow-up. We therefore examined use of analgesics in relation to RCC risk in two prospective studies.

MATERIALS AND METHODS

Study population

The Nurses’ Health Study (NHS) enrolled 121,700 female nurses aged 30–55 years in 1976. The Health Professionals Follow-up Study (HPFS) included 51,529 male health professionals aged 40–75 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 1980 for aspirin and starting 1990 for non-aspirin analgesics) and to ascertain 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 ascertained through these sources.

In the NHS, we started follow-up for the current analysis in 1990 when the use of non-aspirin analgesics was first ascertained. In the HPFS, we started follow-up in 1986, the start of the study. We excluded those 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 those participants with baseline information on analgesic use were 97% in the NHS and 91% 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 questionnaire assessed regular use of aspirin, other non-aspirin NSAIDs, and acetaminophen in 1990 and every 2 years thereafter. In the HPFS, similar questions on use of analgesics were asked since 1986. We collected information on dose (number of tablets/wk; 4 baby aspirin=1 tablet) of aspirin since 1994 in the NHS and 1992 in the HPFS. Information on dose of other analgesics was ascertained since 1998 in the NHS and since 2000 in the HPFS.

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

In 1999, we also sent a supplementary questionnaire to 4,238 of the NHS participants who were either frequent user or non-users of analgesic in previous follow-up questionnaires and provided a blood sample in 1989, to ascertain detailed information on analgesic use. Among non-aspirin NSAID users, 73% used ibuprofen, 14% used naproxen, and 13% used other types. The major reasons for use among ibuprofen and acetaminophen users were...
muscle/joint pain (84% and 65%, respectively); headache (5% and 24%); backache (5% and 4%); and other reasons (6% and 8%)\textsuperscript{17}.

To maintain consistency across the cohorts and with prior studies \textsuperscript{9}, we defined regular users as those who used individual analgesic medication $\geq$ 2 times/week, when information on frequency of use was available. Whenever dose of use was available, we also took into consideration the dose and defined $\geq$ 2 tablets/week as regular use.

**Assessment of other risk factors for RCC**

Information on body weight, smoking, recreational physical activity, and history of hypertension was collected biennially in the two cohorts. The diagnosis of hypertension has been shown to be reliably reported \textsuperscript{18}. Pack-years of smoking were calculated by multiplying the duration and dose of smoking; one pack-year is equivalent to having smoked one pack/day for one year. Body mass index (BMI; kg/m$^2$) was calculated using the height and weight. Dietary information was collected using validated food frequency questionnaires in 1990 in the NHS and in 1986 in the HPFS and every four 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 participant’s questionnaire information reviewed medical records. Based on the WHO classification \textsuperscript{19}, we included clear cell, papillary, chromophobe, collecting duct RCC, and RCC not otherwise classified as RCC. We evaluated RCC as the primary disease endpoint; in secondary analyses, we also evaluated clear cell RCC, the major histological subtype of RCC.

**Statistical analysis**

To take advantage of long follow-up time and repeated assessment of use of analgesics, 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 into consideration of intermittent use. Duration of analgesic use was calculated based on 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 two consecutive biennial questionnaires, then two years of use were assigned. If a person reported being a regular user on one questionnaire but not the other questionnaire, then one year of use was assigned. If a person missed a questionnaire, we carried forward information on use of the analgesic class from previous questionnaire. If a person missed two or more consecutive questionnaires, no use (0 year) was assigned for the time period(s) and the person-time for the participant was censored in the analysis for that time period(s). For each person, total number of year of use up to each follow-up cycle was summed up 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 employed Cox proportional hazards regression to adjust for other risk factors for RCC \textsuperscript{20}. To control as finely as
possible for confounding by age, calendar time, and any possible two-way interactions between these two time scales, we stratified the analysis jointly by age in months at start of follow-up and calendar year of the current questionnaire cycle. In multivariable models, we also adjusted for BMI, smoking, history of hypertension, physical activity, and intakes of fruit intake, vegetable, and alcohol and parity in women. SAS PROC PHREG 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 multivariable models. The P value for the test for interaction was obtained from a Wald test. All P values are two-sided.

We conducted separate analyses for each cohort, tested for heterogeneity between studies, and used meta-analytic methods using 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 most frequently used in both women and men. Among aspirin users in women, 12% used non-aspirin NSAIDs, 10% used acetaminophen, and 4% used both medications. Among aspirin users in men, the corresponding percentages were 6%, 8%, and 1%, respectively. Women and men who were regular users of 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 non-aspirin NSAIDs use at baseline was associated with an increased RCC risk; the pooled multivariable RRs was 1.51 (95% CI 1.12–2.04), compared with non-regular users. The results did not differ by gender (P=0.60 for heterogeneity). In women, we had more detailed information on frequency of non-aspirin NSAID use at baseline and there was a linear increase in RCC risk by increasing frequency of use; compared with non-users, the RR were 1.08 (95% CI 0.67–1.74), 1.30 (95% CI 0.71–2.39) and 1.86 (95% CI 1.19–2.90) for use of 1–4 days/m, 5–14 days/m, and more than 15 times/m, respectively. Because some participants used multiple analgesic medications, we evaluated the associations among individuals who used one medication exclusively by excluding those who also used the other analgesics. The results were essentially similar. The pooled multivariable RR was 1.57 (95% CI 1.07–2.33) for exclusive use of non-aspirin NSAIDs compared with those who did not use any of the analgesics. The absolute risk differences for the users vs. non-users of non-aspirin NSAIDs were 9.16/100,000 person-years in women and 10.92/100,000 person-years in men. Assuming a causal relation, use of non-aspirin NSAIDs by each of 10,917 women or 9,158 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 doseresponse relation between duration of regular use of non-aspirin NSAIDs and RCC risk; compared with non-regular users, the pooled multivariable RRs were 0.81 (95% CI 0.59–1.11) for use under 4 years, 1.36 (95% CI 0.98–1.89) for use 4–10
years, and 2.92 (95% CI 1.71–5.01) for use of 10-years or longer (P for trend <0.001). The positive association did not differ by gender (P=0.33 for heterogeneity). Duration of use of aspirin or acetaminophen was not associated with RCC risk. When we mutually adjusted for the three analgesics in a multivariable model, the positive association between non-aspirin NSAIDs and RCC risk remained essentially unchanged; the pooled multivariable RR was 3.00 (95% CI 1.74–5.18) for use of 10+ years. For those who used non-aspirin NSAIDs 10+ years, we also examined non-consecutive vs consecutive use. In women, the RRs for non-consecutive and consecutive use were 4.01(95% CI 1.98–8.29; n=11) and 2.40 (95% CI 0.72–7.95; n=3), respectively. In men, all of the cases with use of 10 years or longer were non-consecutive users. When we excluded prevalent users of non-aspirin NSAIDs at baseline, few cases remained among those with 4+ years of use. The pooled RR combining 4-<10 years and 10+ years of non-aspirin NSAIDs use was 1.18 (95% CI 0.78–1.77).

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

The association between duration of regular use of non-aspirin NSAIDs and RCC risk did not differ by levels of other RCC risk factors including smoking, BMI, and history of hypertension (data not shown; P >0.30 for all interactions).

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

**DISCUSSION**

In these large prospective studies of women and men, we found that use of non-aspirin NSAIDs was associated with an elevated risk of RCC, especially among those who used them for a long duration. Use of aspirin or acetaminophen was not associated with RCC risk.

Although aspirin has been associated with a reduced risk of several types of cancer, previous epidemiologic data pointed toward an increased risk of RCC in aspirin users. A meta-analysis 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 (95% CI 0.87–2.40) for small cohort studies.

However, we found no association for aspirin with risk of RCC in our two independent populations. Evaluation of dose and duration of use of aspirin also did not reveal any association with RCC risk.

One prospective study and seven case-control studies have evaluated acetaminophen in relation to RCC risk; three of the studies found a positive association. Acetaminophen is a metabolite of phenacetin, which was banned in 1970s-early 1980s worldwide due to its carcinogenic effect especially in renal pelvis tumors. 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.

The potential explanation for the discrepancy in findings for aspirin and acetaminophen in our studies vs. previous studies may include that most of the previous studies were retrospective, which might be susceptible to biased recall of use of analgesics and reverse causation (i.e., cases might have used analgesics due to symptoms related to RCC).

In terms of non-aspirin NSAIDs, there have been few studies with RCC risk. Although one case-control study found a positive association with RCC risk, the study reported a similar positive association with other analgesics including aspirin, acetaminophen, and phenacetin. A retrospective cohort study in Denmark using prescription database found that...
prescription of non-aspirin NSAIDs was associated with incidence (RR=1.4 [95% CI 0.9–2.1])\textsuperscript{29} and mortality (RR=1.72 [95% CI 1.4–2.1])\textsuperscript{29} of kidney cancer. In our study, we found a positive association only with non-aspirin NSAIDs, with a strong dose-response relation for duration of use. Because we observed the associations in two 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 we found with non-aspirin NSAIDs.

Contrary to our findings on RCC, meta-analyses reported that use of non-aspirin NSAIDs was associated with reduced risk of breast\textsuperscript{30}, prostate\textsuperscript{31}, and colorectal cancers\textsuperscript{7} with the magnitude of association similar to that of aspirin. Analgesics in general have been associated with elevated risk of high blood pressure\textsuperscript{32}, a risk factor for RCC. However, our results did not differ by presence of hypertension. NSAIDs are also associated with elevated risks of both acute and chronic renal diseases by inhibiting the synthesis of renal prostaglandins\textsuperscript{33, 34}, which can result in chronic subacute renal injuries, such as tubular necrosis, papillary necrosis and interstitial nephritis\textsuperscript{35, 36}. This has the potential for an injury-related DNA damage and subsequent uncontrolled cell proliferation, leading to carcinogenesis\textsuperscript{37}. The mechanism may be mediated by the inhibition of COX-1-derived renal prostaglandins which are important for renal homeostasis\textsuperscript{38} and NSAIDs are known to inhibit both COX-1 and 2. Selective COX-2 inhibitors, another NSAIDs class, were recently added to the cohorts’ questionnaires, so we were not able to study their relation to RCC risk due to a short follow up time. Still, this does not provide an explanation why non-aspirin NSAIDs, but not aspirin was positively associated with RCC, since both are considered NSAIDs and the renal injuries aforementioned have been described with both classes\textsuperscript{35, 39}.

Since the actual doses of aspirin and non-aspirin NSAIDs are different, the delivered target renal tissue dose could also be different between these 2 classes and may lead to a different threshold for neoplastic transformation.

These analgesics are frequently and often heavily used by individuals with rheumatoid arthritis (RA). Studies among RA patients which evaluated cancer incidence have not found increased risk for RCC, although the analgesic exposure history in the study was somewhat limited\textsuperscript{40}.

Our study carries limitations. First, although we had extensive information on risk factors for RCC and adjusted for them in multivariable analysis, residual confounding can remain a concern. The results on non-aspirin 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 (e.g., RCC patients started to use analgesics due to symptoms before diagnosis) may have been an issue for these widely used analgesics. However, the strongest association we found among those who used the longest duration argues against the possibility. Third, because phenacetin was still available in the U.S. up to the mid-1980s, our results with follow-up started in 1986 and 1990 might have been still confounded by past use of phenacetin. However, differential association between non-aspirin NSAIDs and other analgesics and strong duration effect for non-aspirin NSAIDs are not explained by the possibility. Fourth, we have only recently started to collect more detailed information on dose of use 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 non-aspirin NSAIDs and RCC risk in the future.

This study has strengths. To our knowledge, it is the first prospective study of non-aspirin 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 usage, a much stronger predictor of RCC risk for non-aspirin NSAIDs than usage 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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REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009 Jul-Aug;59(4):225–249. [PubMed: 19474385]
2. Mathew A, Devesa SS, Fraumeni JF Jr, Chow WH. Global increases in kidney cancer incidence, 1973–1992. Eur J Cancer Prev. 2002 Apr; 11(2):171–178. [PubMed: 11984136]
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 Jan 16; 287(3):337–344. [PubMed: 11790213]
4. World Health Organization. Model List of Essential Medicines. 16th edition. [http://www.who.int/selection_medicines/committees/expert/17/sixteenth_adult_list_en.pdf]
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 Dec 24; 300(24):2867–2878. [PubMed: 19109115]
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 Jan 18; 295(3):306–313. [PubMed: 16418466]
7. Rostom A, Dube C, Lewin G, et al. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S Preventive Services Task Force. Ann Intern Med. 2007 Mar 6; 146(5):376–389. [PubMed: 17339623]
8. Bosetti C, Gallus S, La Vecchia C. Aspirin and cancer risk: an updated quantitative review to 2005. Cancer Causes Control. 2006 Sep; 17(7):871–888. [PubMed: 16841255]
9. Gago-Dominguez M, Yuan JM, Castelao JE, Ross RK, Yu MC. Regular use of analgesics as a risk factor for renal cell carcinoma. Br J Cancer. 1999 Oct; 81(3):542–548. [PubMed: 10507783]
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 Jan 27; 60(3):350–354. [PubMed: 7829243]
11. Derby LE, Jick H. Acetaminophen and renal and bladder cancer. Epidemiology. 1996 Jul; 7(4):358–362. [PubMed: 8793360]
12. Sorensen HT, Friis S, Norgard B, et al. Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study. Br J Cancer. 2003 Jun 2; 88(11):1687–1692. [PubMed: 12771981]
13. Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. Nat Rev Cancer. 2005 May; 5(5):388–396. [PubMed: 15864280]
14. AStampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. Am J Epidemiol. 1984; 119(5):837–839. [PubMed: 6720679]
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. [PubMed: 2061978]
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 Jul 26; 164(14):1519–1524. [PubMed: 15277282]

17. Chan AT, Manson JE, Albert CM, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. Circulation. 2006 Mar 28; 113(12):1578–1587. [PubMed: 16534006]

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. 5:894–900.

19. Storkel S, Eble JN, Adlakha K, et al. Classification of renal cell carcinoma: Workgroup No. 1 Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer. 1997 Sep 1; 80(5):987–989. [PubMed: 9307203]

20. Prentice RL. The analysis of failure times in the presence of competing risks. Biometrics. 1978; 34:541–554. [PubMed: 373811]

21. Therneau, TM. Extending the Cox Model. In: Lin, DY.; Fleming, TR., editors. Proceedings of the First Seattle Symposium in Biostatistics: Survival Analysis. New York: Springer Verlag; 1997. p. 51–84.

22. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7:177–188. [PubMed: 3802833]

23. Chow WH, McLaughlin JK, Linet MS, Niwa S, Mandel JS. Use of analgesics and risk of renal cell cancer. Int J Cancer. 1994 Nov 15; 59(4):467–470. [PubMed: 7960214]

24. Friis S, Nielsen GL, Møllemkjær L, et al. Cancer risk in persons receiving prescriptions for paracetamol: a Danish cohort study. Int J Cancer. 2002 Jan 1; 97(1):96–101. [PubMed: 11774249]

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 Dec 69:217–222. [PubMed: 3834336]

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 Jan 21; 53(2):245–249. [PubMed: 8425761]

27. McCredie M, Pommer W, McLaughlin JK, et al. International renal-cell cancer study. I. Analgesics. Int J Cancer. 1995 Jan 27; 60(3):345–349. [PubMed: 7829242]

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 Jan; 9(1): 83–88. [PubMed: 9486467]

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 May-Jun;11(3):156–163. [PubMed: 15133529]

30. Takkouche B, Requeira-Mendez C, Etminan M. Breast cancer and use of nonsteroidal anti-inflammatory drugs: a meta-analysis. J Natl Cancer Inst. 2008 Oct 15; 100(20):1439–1447. [PubMed: 18840819]

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 Aug 3;3(4):233–330. [PubMed: 19672448]

32. Forman JP, Rimm EB, Curhan GC. Frequency of analgesic use and risk of hypertension among men. Arch Intern Med. 2007 Feb 26; 167(4):394–399. [PubMed: 17325302]

33. Sandler DP, Burr FR, Weinberg CR. Nonsteroidal anti-inflammatory drugs and the risk for chronic renal disease. Ann Intern Med. 1991 Aug 1; 115(3):165–172. [PubMed: 2058870]

34. Griffin MR, Yared A, Ray WA. Nonsteroidal antiinflammatory drugs and acute renal failure in elderly persons. Am J Epidemiol. 2000 Mar 1; 151(5):488–496. [PubMed: 10707917]

35. Segasothy M, Samad SA, Zulficar 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 Jul; 24(1):17–24. [PubMed: 8023820]

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 Mar 13; 380(3):531–536. [PubMed: 19250643]

37. Henderson BE, Ross RK, Pike MC. Toward the primary prevention of cancer. Science. 1991; 254:1131–1138. [PubMed: 1957166]
38. Ruffin, MT; Krishnan, K.; Rock, CL., et al. Suppression of human colorectal mucosal prostaglandins: determining the lowest effective aspirin dose. J Natl Cancer Inst. 1997 Aug 6; 89(15):1152–1160. [PubMed: 9262254]

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 Apr; 23(2):107–114. [PubMed: 1745559]

40. Yamada T, Nakajima A, Inoue E, et al. Incidence of malignancy in Japanese patients with rheumatoid arthritis. Rheumatol Int. 2010 May 16.
| Characteristics | Regular Use of Analgesics (≥2/wk) |  |
|-----------------|----------------------------------|---|
|                 | Aspirin                          | Non-aspirin NSAIDs | Acetaminophen |
|                 | No  | Yes | No  | Yes | No  | Yes |
| **Women**       |     |     |     |     |     |     |
| Number          | 58934 | 18591 | 62947 | 14578 | 65547 | 11978 |
| % users         | 24  | 19  | 15  | 17  | 17  | 15  |
| Past smoker, %  | 39  | 40  | 38  | 42  | 39  | 41  |
| Current smoker, %| 17  | 17  | 17  | 16  | 17  | 17  |
| Hypertension, % | 29  | 36  | 29  | 37  | 30  | 37  |
| **Mean**        |     |     |     |     |     |     |
| Age, years      | 56  | 58  | 57  | 56  | 57  | 57  |
| Body mass index, kg/m² | 26  | 26  | 25  | 27  | 26  | 26  |
| 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**         |     |     |     |     |     |     |
| Number          | 34858 | 14545 | 46691 | 2712 | 46573 | 2830 |
| % users         | 29  | 5   | 6   | 9   | 10  | 9   |
| Past smoker, %  | 39  | 48  | 41  | 51  | 41  | 49  |
| Current smoker, %| 9   | 10  | 9   | 10  | 9   | 12  |
| Hypertension, % | 20  | 27  | 22  | 27  | 22  | 27  |
| **Mean**        |     |     |     |     |     |     |
| Age, years      | 54  | 56  | 54  | 56  | 55  | 54  |
| Body mass index, kg/m² | 25  | 26  | 26  | 26  | 26  | 26  |
| 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 |

*Except for the data on mean age and % users, all data shown are standardized to the age distributions of each cohort
### Table 2

Age-adjusted and multivariate relative risk and 95% confidence intervals (CIs) of renal cell cancer according to analgesic use at baseline (1990 in women and 1986 in men)

| Analgesics       | Regular Use of Analgesics (≥2/wk) at Baseline |   |   |   |   |   |   |   |   |
|------------------|----------------------------------------------|---|---|---|---|---|---|---|---|
|                  |                                              | No |   | Yes |   |   |   |   |   |
| **Aspirin**      |                                              |    |   |     |   |   |   |   |   |
| Women            |                                              |    |   |     |   |   |   |   |   |
| Person-years     | 844,006                                      | 262,677 |   |     |   |   |   |   |   |
| Number of cases  | 116                                          | 37  |   |     |   |   |   |   |   |
| Age-adjusted     | 1.00                                         | 0.96 (0.66–1.40) |   |     |   |   |   |   |   |
| Multivariate     | 1.00                                         | 0.93 (0.64–1.35) |   |     |   |   |   |   |   |
| Men              |                                              |    |   |     |   |   |   |   |   |
| Person-years     | 578,491                                      | 228,526 |   |     |   |   |   |   |   |
| Number of cases  | 123                                          | 57  |   |     |   |   |   |   |   |
| Age-adjusted     | 1.00                                         | 1.08 (0.78–1.48) |   |     |   |   |   |   |   |
| Multivariate     | 1.00                                         | 0.99 (0.71–1.37) |   |     |   |   |   |   |   |
| **Pooled Multivariate** |                                      | 0.96 (0.75–1.23) |   |     |   |   |   |   |   |
| **Non-aspirin NSAIDs** |                                      |    |   |     |   |   |   |   |   |
| Women            |                                              |    |   |     |   |   |   |   |   |
| Person-years     | 899,796                                      | 206,887 |   |     |   |   |   |   |   |
| Number of cases  | 109                                          | 44  |   |     |   |   |   |   |   |
| Age-adjusted     | 1.00                                         | 1.74 (1.22–2.47) |   |     |   |   |   |   |   |
| Multivariate     | 1.00                                         | 1.59 (1.11–2.27) |   |     |   |   |   |   |   |
| **Pooled Multivariate** |                                      | 1.51 (1.12–2.04) |   |     |   |   |   |   |   |
| **Acetaminophen** |                                              |    |   |     |   |   |   |   |   |
| Women            |                                              |    |   |     |   |   |   |   |   |
| Person-years     | 937,641                                      | 169,042 |   |     |   |   |   |   |   |
| Number of cases  | 123                                          | 30  |   |     |   |   |   |   |   |
| Age-adjusted     | 1.00                                         | 1.34 (0.90–2.01) |   |     |   |   |   |   |   |
| Multivariate     | 1.00                                         | 1.26 (0.84–1.88) |   |     |   |   |   |   |   |
| Men              |                                              |    |   |     |   |   |   |   |   |
| Person-years     | 761,515                                      | 45,502 |   |     |   |   |   |   |   |
| Number of cases  | 166                                          | 14  |   |     |   |   |   |   |   |
| Age-adjusted     | 1.00                                         | 1.60 (0.92–2.78) |   |     |   |   |   |   |   |
| Multivariate     | 1.00                                         | 1.47 (0.84–2.56) |   |     |   |   |   |   |   |
| **Pooled Multivariate** |                                      | 1.32 (0.96–1.84) |   |     |   |   |   |   |   |
* 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, ≥40 pack-years)), body mass index (<25, 25–26.9, 27–29.9, ≥30 kg/m2), history of hypertension (yes/no), physical activity (quintiles), fruit intake (continuous), vegetable intake (continuous), alcohol intake (continuous), and parity (nulliparous, 1–2, 3, 4, ≥5 children) in women.
Table 3

Age-adjusted and multivariate relative risk and 95% confidence intervals (CIs) of renal cell cancer according to cumulative updated duration of regular use of analgesics *.

| Analgesics | Cumulative Updated Duration of Regular Use of Analgesics (≥2/wk) | P for trend |
|------------|---------------------------------------------------------------|------------|
|            | No | >0-< 4 years | 4-<10 years | ≥10 years |
| **Aspirin** |     |               |             |            |
| Women      |     |               |             |            |
| Person-years | 523,069 | 280,760 | 209,270 | 49,151 |
| Number of cases | 69 | 42 | 27 | 13 |
| Age-adjusted | 1.00 | 1.03 (0.70–1.51) | 0.73 (0.45–1.16) | 1.34 (0.70–2.59) |
| Multivariate | 1.00 | 0.98 (0.66–1.44) | 0.67 (0.42–1.07) | 1.24 (0.64–2.40) |
| **Men**     |     |               |             |            |
| Person-years | 286,738 | 201,852 | 156,421 | 62,802 |
| Number of cases | 57 | 43 | 45 | 22 |
| Age-adjusted | 1.00 | 0.94 (0.63–1.40) | 1.09 (0.70–1.68) | 1.22 (0.68–2.16) |
| Multivariate | 1.00 | 0.86 (0.57–1.29) | 0.98 (0.63–1.52) | 1.05 (0.58–1.87) |
| **Pooled Multivariate** | 1.00 | 0.92 (0.69–1.22) | 0.82 (0.56–1.19) | 1.13 (0.73–1.74) |
| **Non-aspirin NSAIDs** |     |               |             |            |
| Women      |     |               |             |            |
| Person-years | 616,037 | 242,914 | 182,120 | 21,178 |
| Number of cases | 76 | 24 | 37 | 14 |
| Age-adjusted | 1.00 | 0.77 (0.48–1.23) | 1.51 (1.00–2.28) | 4.13 (2.16–7.87) |
| Multivariate | 1.00 | 0.71 (0.44–1.14) | 1.35 (0.89–2.06) | 3.51 (1.83–6.74) |
| **Men**     |     |               |             |            |
| Person-years | 535,347 | 111,908 | 51,345 | 9,212 |
| Number of cases | 117 | 26 | 19 | 5 |
| Age-adjusted | 1.00 | 0.96 (0.62–1.48) | 1.46 (0.87–2.45) | 2.16 (0.84–5.55) |
| Multivariate | 1.00 | 0.90 (0.58–1.40) | 1.38 (0.82–2.31) | 1.98 (0.76–5.12) |
| **Pooled Multivariate** | 1.00 | 0.81 (0.59–1.11) | 1.36 (0.98–1.89) | 2.92 (1.71–5.01) |
| **Acetaminophen** |     |               |             |            |
| Women      |     |               |             |            |
| Person-years | 702,283 | 217,404 | 65,379 | 77,184 |

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| Analgesics | Cumulative Updated Duration of Regular Use of Analgesics (≥2/wk) | P for trend |
|------------|-------------------------------------------------------------|-------------|
|            | Number of cases | 93 | 31 | 10 | 17 |
|            | Age-adjusted   | 1.00 | 1.02 (0.68–1.54) | 0.97 (0.50–1.89) | 1.28 (0.74–2.20) | 0.46 |
|            | Multivariate   | 1.00 | 0.93 (0.62–1.41) | 0.86 (0.44–1.68) | 1.12 (0.65–1.93) | 0.87 |
| Men        | Person-years   | 601,975 | 75,144 | 15,265 | 15,427 |
|            | Number of cases| 138 | 19 | 6 | 4 |
|            | Age-adjusted   | 1.00 | 1.02 (0.63–1.66) | 1.49 (0.64–3.45) | 0.94 (0.34–2.59) | 0.74 |
|            | Multivariate   | 1.00 | 0.97 (0.59–1.57) | 1.37 (0.59–3.17) | 0.83 (0.30–2.29) | 0.98 |
| Pooled Multivariate | 1.00 | 0.94 (0.69–1.30) | 1.03 (0.61–1.74) | 1.05 (0.65–1.69) | 0.90 |

*The models were adjusted for the same covariates as the multivariate model in Table 2. Total number of cases in this Table is slightly different (2 less women and 13 less men) from Table 2 because this Table is based on updated analgesic use and those who missed follow-up questionnaire(s) were censored for the time period(s).