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# Analgesic use and the risk of kidney cancer: a meta-analysis of epidemiologic studies

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## Abstract

Analgesics are the most commonly used over-the-counter drugs worldwide with certain analgesics having cancer prevention effect. The evidence for an increased risk of developing kidney cancer with analgesic use is mixed. Using a meta-analysis design of available observational epidemiologic studies, we investigated the association between analgesic use and kidney cancer risk. We searched the MEDLINE and EMBASE databases to identify eligible case-control or cohort studies published in English until June 2012 for 3 categories of analgesics: acetaminophen, aspirin or other Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Study-specific effect estimates were pooled to compute an overall relative risk (RR) and its 95% confidence interval (CI) using a random effects model for each category of the analgesics. We identified 20 studies (14 with acetaminophen, 13 with aspirin, and 5 with other NSAIDs) that were performed in 6 countries, including 8,420 cases of kidney cancer. Use of acetaminophen and non-aspirin NSAIDs were associated with an increased risk of kidney cancer (pooled RR, 1.28; 95% CI, 1.15 to 1.44 and 1.25; 95% CI, 1.06 to 1.46, respectively). For aspirin use, we found no overall increased risk (pooled RR, 1.10; 95% CI, 0.95 to 1.28), except for non-US studies (5 studies, pooled RR=1.17, 95% CI, 1.04 to 1.33). Similar increases in risks were seen with higher analgesic intake. In this largest meta-analysis to date, we found that acetaminophen and non-aspirin NSAIDs are associated with a significant risk of developing kidney cancer. Further work is needed to elucidate biologic mechanisms behind these findings.

### Keywords

analgesics; aspirin; non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs); acetaminophen; kidney cancer

## Introduction

The incidence of kidney cancer and its most common form, renal cell carcinoma (RCC), has been rising in the U.S. and worldwide [12]. This cancer is primarily treated with surgery; however, a significant number of patients, 20-30%, continue to present with incurable

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metastatic disease.[3] Furthermore, depending on tumor grade or stage, up to 50% of patients who present with "localized" disease can recur in distant sites.[4] Adjuvant therapies for high risk localized disease are lacking and in the metastatic setting, systemic therapies seldom present long-term remissions. Therefore, preventive measures and modifications of life-style risk factors may hold a crucial key to fighting this disease. It is well established that smoking, obesity, and hypertension are modifiable risk factors for RCC. [5]

Use of certain analgesics including aspirin and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with reduced risk of breast, prostate, and colorectal cancers. [6] The effect of these analgesics on RCC is less clear. [7] Analgesic abuse nephropathy among patients taking compounds containing phenacetin, a currently banned substance in the US since 1983, can lead to chronic renal failure. Such patients, however, are at increased risk for renal pelvic or urothelial tumors, rather than RCC. [89]. There have been few meta-analysis of use of analgesics and cancer risk in general, which included some studies of kidney cancer and did not exclusively focus on this disease. [101112] These studies have shown inconsistent results. We therefore embarked on an up-to-date, and comprehensive meta-analysis of studies exclusively dedicated to the relationship between the 3 most commonly used analgesics and kidney cancer risk.

## Materials and Methods

### Selection of Studies

We searched the electronic databases MEDLINE and EMBASE to identify eligible studies published in English through June 2012. The following keywords were used for computer searches: "(analgesics or acetaminophen or aspirin or nonsteroidal anti-inflammatory agents or NSAID) in combination with (neoplasms or kidney neoplasms or renal cell carcinoma)". We also manually searched the reference lists of every article retrieved and review papers to identify additional studies. Studies were eligible for inclusion if they fulfilled the following criteria: 1) presented original data from case-control or cohort studies. 2) the outcome of interest was clearly defined as renal cell cancer or kidney cancer incidence, 3) the exposure of interest was use of aspirin, NSAIDs or acetaminophen, and 4) provided relative risk (RR) estimates and their confidence intervals (CIs) or sufficient data to calculate them (e.g., number of cases and controls in exposure categories). Odds Ratios (ORs) were considered as estimates of the RR for case-control studies since kidney cancer is rare.

### Data Extraction

Data abstraction was conducted independently by 3 investigators (T.C, Y.J. and E.C.) according to the meta-analysis of observation studies in epidemiology (MOOSE) guidelines [13] and discrepancies were adjudicated. For each study, the following information was extracted: first author's last name; year of publication; country of the population studied; study design; type of controls; number of cases and controls/subjects; RRs and 95% CIs of kidney cancer risk that compared exposed subjects with unexposed subjects; definitions of acetaminophen, aspirin or NSAIDs exposure; and control of confounding factors by matching or adjustment. In studies where more than one estimate of effect was presented, we chose the 'most adjusted' estimate.

### Statistical Analysis

Separate analyses were performed according to use of acetaminophen, aspirin, and non-aspirin NSAIDs. We pooled study-specific log RRs to compute an overall RR and its 95% CI for regular/any use versus reference group from each study in both sexes combined if there is no evidence of significant heterogeneity among men and women. Otherwise, we included all estimates according to sex in the analysis as if obtained from different studies.

For reference group, it was defined as "subjects who never took analgesics, who were not regular takers, or who took a lifetime total of <0.1kg of analgesics". Where data for different intake levels or different duration of use were available, we subsequently restricted the analyses to the highest intake or the longest duration given by each study. Summary measures were calculated using random-effects models that consider both within-study and between-study variations.[14] Statistical heterogeneity among studies included in the meta-analysis was assessed using the Cochrane's Q statistic[15], and inconsistency was quantified with the $I^2$ statistic [100% X (Q-df)/Q] that estimates the percentage of total variation across studies due to heterogeneity rather than chance. [16] The assumption of homogeneity was considered invalid for p value< 0.05.

To explore sources of heterogeneity (e.g., gender, male or female; study design, cohort or case-control studies; type of controls, population-based or hospital-based controls; study outcome, kidney cancer or renal cell cancer; countries, US or non-US), we used a random-effects meta-regression, weighted linear regression model relating the risk of kidney cancer to the study-level covariates. In addition, we conducted sensitivity analyses for the study quality assessment by limiting the analysis to studies that had adjusted for at least smoking and body mass index(BMI), which are two important risk factors of RCC.

Finally, publication bias was evaluated through funnel plots (i.e., plots of study results against precision) and with the Begg's and Egger's tests.[1718] A two-tailed p value of less than 0.05 was considered statistically significant. All statistical analyses were performed by using Stata/SE version 12.0 software (Stata Corporation, College Station, Texas).

## Results

The detailed steps of our literature search are shown in Supplemental Figure 1. Briefly, we identified a total of 20 observational studies that were performed in six countries including 8,420 incident cases of kidney cancer that were eligible for inclusion in the meta-analysis. These included 12 case-control studies including 7,075 cases/579,285 controls[19-30] and 8 cohort studies including 1,165 cases among 579,285 subjects.[9, 31-37] Fourteen studies including 6,852 cases were used for analysis of acetaminophen use[9, 19-29, 33, 37](Table 1), 13 studies including 6,655 cases for aspirin use[9, 19-21, 23-25, 28, 30-32, 34, 36] (Table 2) and 5 studies including 2,230 cases for non-aspirin NSAIDs use.[9, 23, 28, 29, 3523] (Table 3) The characteristics of the included studies for the 3 most commonly used analgesics are summarized in Tables 1-3. All of the included studies used self-reported data except for five studies which used data from pharmacy registries.[26, 29, 33-35].

### Acetaminophen

Regular/any use of acetaminophen was associated with an increased risk of kidney cancer (pooled RR=1.28, 95% CI: 1.15 to 1.44)[9, 19-29, 33, 37] (Figure 1). The increased risk of kidney cancer was stronger with high intake of acetaminophen (pooled RR=1.68, 95% CI: 1.22 to 2.30),[21, 23-26, 28, 29, 33, 37] while the association was not significant with long duration of acetaminophen use among limited number of studies with that available information (pooled RR=1.16, 95% CI: 0.84 to 1.59).[9, 19, 21, 27, 37] There was no statistically significant heterogeneity among studies of acetaminophen use (P value for heterogeneity =. 41, $I^2$=4.0%). Overall, no significant difference was found by study design (p=.58), type of controls (p=.82), study outcome (p=.89), gender (p=.11), or countries (p=.16).

### Aspirin

Overall, regular/any use of aspirin was not significantly associated with an increased risk of kidney cancer (pooled RR=1.10, 95% CI: 0.95 to 1.28)[9, 19-21, 23-25, 28, 30-32, 34, 36] (Figure

2).There was a tendency of increasing risk with high intake (pooled RR=1.31, 95% CI: 0.93 to 1.83)[23, 25, 28, 30, 34] or long duration of aspirin use (pooled RR=1.28, 95% CI: 0.91 to 1.81),[9, 19, 28, 30, 34, 36] but it did not reach statistical significance (. There was evidence of heterogeneity among studies of aspirin use (P value for heterogeneity = <.001, $I^2$=65.5%). Overall, no significant difference was found by study design (p=.94), type of controls (p=. 71), study outcome (p=.94), or gender (p=.92). When we stratified by countries, non-US studies showed a significant increased risk of kidney cancer with regular/any use of aspirin (pooled RR=1.17, 95% CI: 1.04 to 1.33)[20, 21, 24, 25, 30, 34] with no significant heterogeneity(P value for heterogeneity = .35, $I^2$=9.6%),while US studies showed no increased risk of kidney cancer (pooled RR=1.05, 95% CI: 0.81 to 1.36; P value for heterogeneity < .001, $I^2$=77.5%).[9, 19, 23, 28, 31, 32, 36] No significant difference, however, was found by countries (p=.53).

### Non-aspirin NSAIDs

Regular/any use of non-aspirin NSAIDs was associated with an increased risk of kidney cancer (pooled RR=1.25, 95% CI: 1.06 to 1.46)[9, 23, 28, 29, 35] (Figure 3). The increased risk of kidney cancer was stronger with high intake of non-aspirin NSAIDs (pooled RR=1.56, 95% CI: 1.11 to 2.19).[28, 35] Only one cohort study[9] provided RR of long duration of non-aspirin NSAIDs (≥ 10 years) compared to no use, which showed an increased risk of kidney cancer (RR=2.92, 95% CI: 1.71 to 5.01), especially among females (RR=3.51, 95% CI: 1.83 to 6.74). There was no statistically significant heterogeneity among studies of non-aspirin NSAIDs use (P value for heterogeneity =.24, $I^2$=27.3%). Overall, no significant difference was found by study design (p=.54), study outcome (p=.25), gender (p=.51), or countries (p=0.88).

### Sensitivity Analysis

When limited to studies that had adjusted for at least BMI and smoking, the pooled RRs for the use of acetaminophen use[9, 21-26, 28, 29, 37] or non-aspirin NSAIDs[9, 23, 28] were even stronger (pooled RR, 1.32; 95% CI, 1.15 to 1.51; pooled RR, 1.38; 95% CI, 1.16 to 1.65) than pooled estimates from all studies. For aspirin use, the corresponding pooled RR was similar (pooled RR, 1.10; 95% CI, 0.95 to 1.28) [9, 21, 23-25, 28, 36] to the pooled RR from all studies.

### Publication Bias

There was no indication of publication bias from either visualization of the funnel plots (Supplemental Figures 2-4), Begg's test or Egger's test for use of acetaminophen (Begg's P=.55, Egger's P=.21), aspirin (Begg's P=.78, Egger's P=.86), or non-aspirin NSAIDs (Begg's P=.81, Egger's P=.41).

## Discussion

In this meta-analysis of the 3 most commonly used analgesics and RCC risk, we found that use of acetaminophen and non-aspirin NSAIDs are each associated with an increased risk of kidney cancer. There was a greater risk with high intake of the corresponding analgesics. We included 20 studies from North America, Europe, and Australia (more than 8000 RCC patients) and explored several sources of heterogeneity. The results were not different by study for use of acetaminophen and non-aspirin NSAIDs. The results were not significantly different by gender, study design, study outcome, and countries, as well as when limited to studies adjusting for major RCC risk factors such as smoking and obesity. However, the results were different by study for aspirin use.

This finding may have some public health consequences since these analgesics are the most commonly used group of over-the-counter drugs [19] and some of them have been associated with reduced risk of several major cancer sites. Although kidney cancer is relatively rare, risks and benefits should be considered in making decisions of using these analgesics.

We found that acetaminophen use was associated with the risk of kidney cancer with a pooled RR=1.21 from 14 studies, with no differences in risk according to several subgroup analyses. The risk was higher with higher intake (RR: 1.66), suggesting a potential dose-response relationship. Three prior case-control studies found a positive association [20-22] with acetaminophen and kidney cancer with 2 specifically investigating RCC, rather than kidney cancer. The biologic explanation could be that acetaminophen is a metabolite of phenacetin, a well known banned carcinogen which has been more so linked to renal pelvic tumors rather than RCC.[8] However, mice models clearly show that acetaminophen itself can induce tumors in the kidney.[2324] McCredie et al [25] postulate that phenacetin compounds are weakly carcinogenic in the renal parenchyma through the metabolic conversion of phenacetin to acetaminophen, and potently carcinogenic in the renal pelvis by different or additional pathways involving renal papillary necrosis.

We found from 13 studies that aspirin use was not associated with the risk of kidney cancer in general. Nevertheless, there was significant heterogeneity by study. When the analysis was restricted to non-US countries, a significant risk was found. While the reason for this discrepancy is not completely clear, it is possible that some of the labeling or dosage of “aspirin” in non-US countries may have been different or that the product contains other analgesics substances beside aspirin such as acetaminophen and other NSAIDs, both shown in our study to increase the overall risk of kidney cancer. A likely explanation could be a simple chance and general misclassification that can occur when individuals report non-salient exposures such as common, over-the-counter medication usage. It is unclear why aspirin can have established protective effect against colorectal cancer for example but not in kidney cancer. After all, the proposed mechanisms of aspirin on cancer prevention through reducing inflammation, inhibiting cycloxygenase (COX)-2, and inducing apoptosis of cancer cells [10], are not considered to be tissue-specific. However, it is possible the mechanisms that induce colon carcinogenesis are quite different from renal carcinogenesis. In fact, NSAIDs reduce the risk of colorectal adenomas which are known precursors to colorectal cancer, but there are no known precursor lesions for kidney cancer to investigate.

We also found that non-aspirin NSAIDs are associated with an increase in the risk of kidney cancer. Despite that only five studies were included in the meta-analysis; the results were consistent in all subgroup analyses.[2226] Since both aspirin and non-aspirin NSAIDs can lead to acute and chronic subacute renal injuries [27] that can theoretically lead to carcinogenesis, we postulated that the delivered dose on the kidney tissue could also be variable between these 2 classes of agents and may lead to a different threshold for neoplastic transformation. In many instances, aspirin is used for cardioprotection with typically lower doses than for analgesic purposes. The fact that there is clear trend for both NSAIDs of a higher risk for a higher dosage is supportive of this theory. However, the information regarding level of intake and duration of use were limited, especially for non-aspirin NSAID. Further studies exploring the risk pattern for renal cell carcinoma according to these measures of analgesic use are warranted. On the other hand, use of non-aspirin NSAIDs have been associated with reduced risk of breast, prostate, and colorectal cancers with the magnitude of association similar to that of aspirin. [72829]

Our study has several strengths: it is the most up-to-date comprehensive review of analgesics on one specific type of cancer, kidney cancer. It includes the 3 mostly used contemporary drugs and does provide several subgroup analyses including study design,

outcome, gender, and countries. We have carefully followed the MOOSE guidelines checklist for meta-analyses reporting. Furthermore and when available, our meta-analyses examined studies adjusted for at least BMI and smoking, known established kidney cancer risk factors in the sensitivity analysis. In a meta-analysis of published studies, publication bias could be of concern since small studies with null results tend not to be published. In this meta-analysis, however, we found little evidence of publication bias.

Nevertheless, several limitations are worth mentioning: First, residual confounding remain a concern since not all of the studies adjusted for important risk factors for RCC. However, when we restricted the analysis to those studies which adjusted for BMI and smoking, major risk factors for RCC, the associations were even stronger. It suggests that residual confounding may not completely explain the positive associations we found. Second, some of the studies did not specifically evaluate RCC and collapsed all cancers of the kidneys which might have included renal pelvis or ureter cancers. Nevertheless, the majority of the studies did specifically mention RCC rather than kidney cancer, and the fact that RCC is by far the most common type of kidney cancer makes an association with only non-RCC kidney cancers very unlikely. Third, studies used different definition of analgesic use, which might have limited comparability of the results across the studies. However, test for heterogeneities by study for acetaminophen and non-aspirin NSAIDs were not statistically significant, supporting robustness of our positive findings. Fourth, long-term analgesic users may switch the type of analgesics they use over time. Because almost all of the studies had baseline information only, we were not able to address the impact of change of use of analgesics. The study does not clearly distinguish between multiple exposures to analgesics. The possibility of confounding would be especially relevant for long duration users of acetaminophen and non-aspirin-NSAIDS, as those patients could have used phenacetin many years previously.

In conclusion, the results of this meta-analysis of 20 observational studies provide quantitative evidence that acetaminophen and non-aspirin NSAIDs may increase the risk of kidney cancer.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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## Abbreviations used in this paper

| | |
|---|---|
| **NSAIDs** | Non-Steroidal Anti-Inflammatory Drugs |
| **BMI** | body mass index |
| **RR** | relative risk |
| **OR** | odds ratio |
| **CI** | confidence interval |
| **COX-2** | cyclooxygenase-2 |
| **NHS** | Nurses' Health Study |

| | |
|---|---|
| **HPFS** | Health Professionals Follow-up Study |
| **RCC** | renal cell carcinoma |

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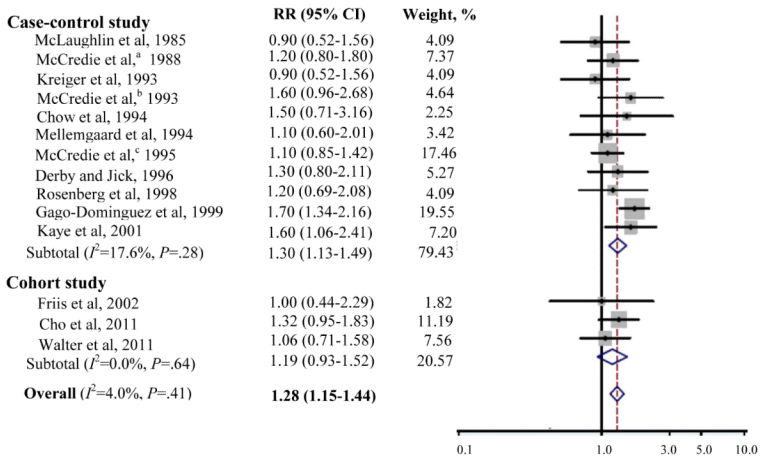
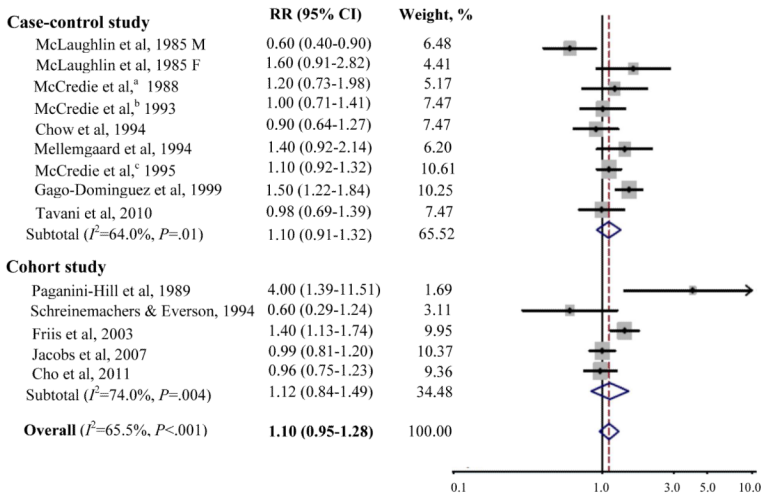
## Novelty & Impact Statements

We did not find a beneficial role of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) in kidney cancer as in other cancers such as breast, prostate, and colorectal cancers. In addition, we found acetaminophen to increase the risk of kidney cancer. Our findings may have some public health implications since these analgesics are the most commonly used group of over-the-counter drugs. Although kidney cancer is relatively rare, risks and benefits should be considered in making decisions of using these analgesics.



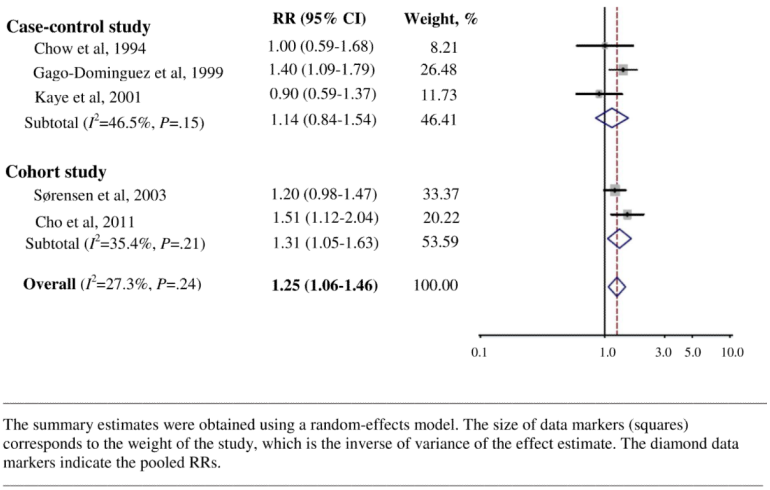

The summary estimates were obtained using a random-effects model. The size of data markers (squares) corresponds to the weight of the study, which is the inverse of variance of the effect estimate. The diamond data markers indicate the pooled RRs.

**Figure 1.**
Adjusted Relative Risks (RRs) of Kidney Cancer Associated with Acetaminophen Use




The summary estimates were obtained using a random-effects model. The size of data markers (squares) corresponds to the weight of the study, which is the inverse of variance of the effect estimate. The diamond data markers indicate the pooled RRs.

**Figure 2.**
Adjusted Relative Risks (RRs) of Kidney Cancer Associated with Aspirin Use




The summary estimates were obtained using a random-effects model. The size of data markers (squares) corresponds to the weight of the study, which is the inverse of variance of the effect estimate. The diamond data markers indicate the pooled RRs.

**Figure 3.**
Adjusted Relative Risks (RRs) of Kidney Cancer Associated with Non-Aspirin NSAIDs Use

## Table 1

Characteristics of studies included in the meta-analysis of acetaminophen and risk of kidney cancer

| Study (year) | Country | Design | Outcome | No. of cases/controls or subjects | Exposure definition | RR (95% CI) | Adjustment factors |
|---|---|---|---|---|---|---|---|
| Mclaughlin et al. (1985)[19] | USA | Population-based case-control | RCC | 495/697 | Any use vs. no use<br>Long duration (>3 yr) vs. no use | 0.9 (0.5-1.5)<br>0.7 (0.5-1.0) M<br>1.2 (0.8-1.9) F<br>1.0 (0.3-2.9)<br>0.7 (0.1-3.4) M<br>1.2 (0.3-4.6) F | Age, smoking |
| McCredie et al.[a] (1988)[20] | Austrailia | Population-based case-control | Kidney cancer | 360/985 | Regular use (≥0.1kg) vs. no use | 1.2 (0.8-1.8) | Age, sex, smoking, phenacetin, aspirin, antihypertensive drugs, urological disease |
| Kreiger et al. (1993)[22] | Canada | Population-based case-control | RCC | 518/1,381 | Regular use (at least every other day for one month or more) vs. no use | 0.9 (0.5-1.5)<br>0.8 (0.3-1.7) M<br>0.9 (0.5-2.0) F | Age, smoking, BMI, |
| McCredie et al.[b] (1993)[21] | Austrailia | Population-based case-control | RCC | 489/523 | Regular use as a single drug (taken at least 20 times during lifetime) vs. no use<br>High intake (>1.94 kg) vs. no use<br>Long duration (> 7yr) of any use vs. no use | 1.6 (1.0-2.8)<br>2.1 (0.8-5.2)<br>2.3 (1.0-5.4) | Age, sex, smoking, obesity, method of interview (in subjects who had never taken phenacetin/aspirin compounds) |
| Chow et al. (1994)[23] | USA | Population-based case-control | RCC | 440/691 | Any use vs. no use<br>High intake (>5 kg) vs. no use | 1.5 (0.7-3.1)<br>1.2 (0.5-3.2) M<br>2.1 (0.6-6.9) F<br>0.7 (0.2-2.5)<br>0.4 (0.0-4.2) M<br>0.9 (0.2-4.6) F | Age, smoking, BMI |
| Mellemgaard et al. (1994)[24] | Denmark | Population-based case-control | RCC | 368/396 | Any use vs. no use<br>High intake (>1kg) vs. no use | 1.1 (0.6-2.0)<br>1.1 (0.5-3.0) M<br>1.0 (0.4-2.5) F<br>0.7 (0.2-1.9)<br>0.9 (0.2-4.0) M<br>0.5 (0.1-1.8) F | Age, smoking (male), BMI (female), history of hypertension, socioeconomic status |
| McCredie et al.[c] (1995)[25] | Austrailia, Denmark, Germany, Sweden, USA | Population-based case-control | RCC | 1,732/2,309 | Regular use (≥0.1kg) vs. no use<br>High intake (>5kg) vs. no use | 1.1 (0.9-1.5)<br>1.0 (0.7-1.4) M<br>1.3 (0.9-2.0) F<br>1.9 (0.9-3.9)<br>1.1 (0.3-4.0) M<br>2.5 (1.0-6.2) F | Age, sex, BMI, smoking, study center |
| Derby and Jick (1996)[26] | USA | Population-based case-control | Kidney cancer | 222/885 | Any use vs. no use<br>High intake (>1kg) vs. non-use | 1.3 (0.8-2.1)<br>4.5 (0.7-29.9) | Age, sex, duration of GHC membership, smoking, BMI, history of urinary tract infection |
| Rosenberg et al. (1998)[27] | USA | Hospital-based case-control | RCC | 383/8,149 | Regular use (>2/wk for at least a month) | 1.2 (0.7-2.1)<br>1.1 (0.5-2.6) | Age, sex, interview year, geographic area |

| Study (year) | Country | Design | Outcome | No. of cases/controls or subjects | Exposure definition | RR (95% CI) | Adjustment factors |
|---|---|---|---|---|---|---|---|
| | | | | | Long duration (>5 yr) of regular use vs. no use | | |
| Gago-Dominguez et al. (1999)[28] | USA | Population-based case-control | RCC | 1,204/1,204 | Regular use (>2/wk for at least a month) vs. no use<br>High intake (>8g/wk) vs. no use | 1.7 (1.3-2.1)<br>2.1 (1.3-3.3) | Age, sex, race, smoking, BMI, education, history of hypertension, regular use of amphetamines |
| Kaye et al. (2001)[29] | USA | Population-based case-control | Kidney cancer | 109/434 | Any use vs. no use<br>High intake (>20 prescriptions) vs. no use | 1.6 (1.1-2.5)<br>2.3 (1.0-5.3) | Age, sex, general practice, duration of prescription history in the database, index date, smoking, BMI, history of hypertension, diuretic use |
| Friis et al. (2002)[33] | Denmark | Cohort (1989-1997) | Kidney cancer | 38/13,482 | Any use vs. no use (in general population)<br>High intake (>10 prescriptions) vs. no use (in general population) | 1.0 (0.4-2.1)<br>2.5 (0.7-6.4) | Age, sex<br>*excluding persons with a prescription for aspirin/NSAIDs prior to or within 1 year after first prescription for acetaminophen |
| Cho et al. (2011)[9] | USA | Cohort (1990-2006, NHS; 1986-2006, HPFS) | RCC | 333/126,928 | Regular use (>2/wk) vs. no use<br>Long duration (>10 yr) of regular use vs. no use | 1.32 (0.96-1.84)<br>1.47 (0.84-2.56) M<br>1.26 (0.84-1.88) F<br>1.05 (0.65-1.69)<br>0.83 (0.30-2.29) M<br>1.12 (0.65-1.93) F | Age, calendar year, smoking, BMI, history of hypertension, physical activity, fruit, vegetable, alcohol intakes, parity (female) |
| Walter et al. (2011)[37] | USA | Cohort (2000-2008, VITAL study) | Kidney cancer | 161/62,841 | Any use vs. no use<br>High intake (>4d/wk and >4 years) vs. no use | 1.06 (0.71-1.58)<br>0.96 (0.46-1.98) | Age, education, race, marital status, height, BMI, physical activity, pack-years of smoking, alcohol intake at 45 years, fruit, vegetable, red meat, multivitamin, self-rated health, family history of colon and hematologic cancers, sigmoidoscopy in the past 10 years, diabetes, osteoarthritis/chronic joint pain, migraine/chronic headaches, and use of NSAIDs. For women, additionally adjusted for |

| Study (year) | Country | Design | Outcome | No. of cases/controls or subjects | Exposure definition | RR (95% CI) | Adjustment factors |
|---|---|---|---|---|---|---|---|
| | | | | | | | family history of breast cancer, mammogram in the past 2 years, age at menarche, age at menopause, age at first birth, years of estrogen therapy, year of combined hormone therapy, and hysterectomy. For men, additionally adjusted for family history of prostate cancer and prostate-specific antigen test in the past 2 years. |

M: Male, F: Female, RCC: Renal Cell Carcinoma, wk: week,BMI: Body Mass Index, NHS: Nurses' Health Study, HPFS: Health Professionals Follow-Up Study, NSAIDs: Non-steroidal-anti-inflammatory drugs

## Table 2

Characteristics of studies included in the meta-analysis of aspirin and risk of kidney cancer

| Study (year) | Country | Design | Outcome | No. of cases/controls or subjects | Exposure definition | RR (95% CI) | Adjustment factors |
|---|---|---|---|---|---|---|---|
| Mclaughlin et al. (1985)[19] | USA | Population-based case-control | RCC | 495/697 | Any use vs. no use<br>Long duration (>3 yr) of any use vs. no use | 0.6 (0.4-0.9) M<br>1.6 (0.9-2.8) F<br>0.5 (0.2-1.0) M<br>1.8 (0.7-4.1) F | Age, smoking |
| McCredie et al.[a] (1988)[20] | Austrailia | Population-based case-control | Kidney cancer | 360/985 | Regular use vs. no use | 1.2 (0.7-1.9) | Age, sex, smoking, phenacetin, paracetamol, antihypertensive drugs, urological disease |
| McCredie et al.[b] (1993)[21] | Austrailia | Population-based case-control | RCC | 489/523 | Regular use as a single drug (taken at least 20 times during lifetime) vs. no use | 1.0 (0.7-1.4) | Age, sex, smoking, obesity, method of interview |
| Chow et al. (1994)[23] | USA | Population-based case-control | RCC | 440/691 | Any use vs. no use<br>High intake (>5 kg) vs. no use | 0.9 (0.6-1.2)<br>0.8 (0.5-1.2) M<br>1.0 (0.6-1.9) F<br>0.6 (0.3-1.2)<br>0.8 (0.4-1.6) M<br>0.4 (0.2-1.1) F | Age, smoking, BMI |
| Mellemgaard et al. (1994)[24] | Denmark | Population-based case-control | RCC | 368/396 | Any use vs. no use<br>High intake (>10 kg) vs. no use | 1.4 (0.9-2.1)<br>1.4 (0.8-2.7) M<br>1.3 (0.7-2.6) F<br>3.7 (1.0-13.8)<br>3.1 (0.3-29) M<br>4.0 (0.8-20.3) F | Age, smoking (male), BMI (female), history of hypertension, socioeconomic status |
| McCredie et al.[c] (1995)[25] | Austrailia, Denmark, Germany, Sweden, USA | Population-based case-control | RCC | 1,732/2,309 | Regular use (≥0.1kg) vs. no use<br>High intake (>5 kg) vs. no use | 1.1 (0.9-1.3)<br>1.0 (0.8-1.3) M<br>1.2 (0.9-1.5) F<br>1.2 (0.9-1.7)<br>1.2 (0.7-1.9) M<br>1.3 (0.8-2.1) F | Age, sex, BMI, smoking, study center |
| Gago-Dominguez et al. (1999)[28] | USA | Population-based case-control | RCC | 1,204/1,204 | Regular use (≥2/wk for at least a month) vs. no use<br>High intake (≥8g/wk) vs. no use<br>Long duration (≥10 yr) of daily use (>325 mg) vs. no use | 1.5 (1.2-1.8)<br>1.9 (1.3-2.8)<br>4.3 (1.6-11.3) | Age, sex, race, smoking, BMI, education, history of hypertension, regular use of amphetamines |
| Tavani et al. (2010)[30] | Italy | Hospital-based case-control | RCC | 755/1,297 | Regular use (≥6 months) vs. no use<br>High intake (≥7 times/wk) vs. no use<br>Long duration (≥ 3 yr) of regular use vs. no use | 0.98 (0.69-1.38)<br>1.12 (0.74-1.68) M<br>0.74 (0.38-1.41) F<br>0.97 (0.66-1.41)<br>1.04 (0.67-1.63) | Age, sex, study center, year of interview, education, smoking, alcohol intake, history of diabetes and hypertension |
| Paganini-Hill et al. (1989)[31] | USA | Cohort (6.5y follow-up) | Kidney cancer RCC | 25/ 13,987 | Regular use (daily use) | 4.0 (1.4-11.6)<br>6.3 (2.2-17) M<br>2.1 (0.53-8.5) F | Age, sex |

| Study (year) | Country | Design | Outcome | No. of cases/controls or subjects | Exposure definition | RR (95% CI) | Adjustment factors |
|---|---|---|---|---|---|---|---|
| | | | | | vs. no use | 6.3 (2.0-20) | |
| Schreinemachers & Everson (1994)[32] | USA | Cohort (12.4 y follow-up) | Kidney cancer | 32/ 14,407 | Any use in the last 30 days vs. no use | 0.60 (0.29-1.24) | Age, sex |
| Friis et al. (2003)[34] | Denmark | Cohort (1989-1997) | Kidney cancer | 67/ 29,470 | Any use vs. no use ( in general population) High intake (≥10 prescriptions) vs. no use (in general population) Long duration (5-9 yr) of any use vs. no use (in general population) | 1.4 (1.1-1.7) 1.6 (1.1-2.1) M 1.1 (0.7-1.6) F 1.7 (1.0-2.5) 1.7 (1.1-2.7) | Age, sex |
| Jacobs et al. (2007)[36] | USA | Cohort (1992-2003) | Kidney cancer | 365/ 146,113 | Any use vs. no use Long-duration (≥5 yr) of current daily use (≥325 mg) vs. no use | 0.99 (0.81-1.20) 1.13 (0.69-1.87) | Age, sex, smoking, BMI, race, education, physical activity, use of hormone replacement therapy, history of mammography, history of colorectal endoscopy, history of PSA testing, use of nonaspirin NSAIDs, history of heart attack, diabetes, and hypertension |
| Cho et al. (2011)[9] | USA, | Cohort (1990-2006, NHS; 1986-2006, HPFS) | RCC | 333/126,928 | Regular use (≥2/wk) vs. no use Long duration (≥10 yr) of regular use vs. no use | 0.96 (0.75-1.23) 0.99 (0.71-1.37) M 0.93 (0.64-1.35) F 1.13 (0.73-1.74) 1.05 (0.58-1.87) M 1.24 (0.64-2.40) F | Age, calendar year, smoking, BMI, history of hypertension, physical activity, fruit, vegetable, alcohol intakes, parity (female) |

M: Male, F: Female, RCC: Renal Cell Carcinoma, wk: week,BMI: Body Mass Index, NHS: Nurses' Health Study, HPFS: Health Professionals Follow-Up Study, PSA: Prostate Specific Antigen.

## Table 3

Characteristics of studies included in the meta-analysis of non-aspirin NSAIDs and risk of kidney cancer

| Study (year) | Country | Design | Outcome | No. of cases/controls or subjects | Exposure definition | RR (95% CI) | Adjustment factors |
|---|---|---|---|---|---|---|---|
| Chow et al. (1994)[23] | USA | Population-based case-control | RCC | 440/691 | Any use vs. no use | 1.0 (0.6-1.7)<br>1.0 (0.5-2.0) M<br>1.0 (0.4-2.3) F | Age, smoking, BMI |
| Gago-Dominguez et al. (1999)[28] | USA | Population-based case-control | RCC | 1,204/1,204 | Regular use vs. no use<br>High intake (≥8g/wk) vs.<br>no use | 1.4 (1.1-1.8)<br>1.9 (1.1-3.5) | Age, sex, race, smoking, BMI, education,<br>history of hypertension, regular use of amphetamines |
| Kaye et al. (2001)[29] | USA | Population-based case-control | Kidney cancer | 109/434 | Any use vs. no use | 0.9 (0.6-1.4) | Age, sex, general practice, duration of prescription history in the database,<br>index<br>date |
| Sorensen et al. (2003)[35] | Denmark | Cohort (1989-1997) | Kidney cancer | 144/<br>172,057 | Any use vs. no use (in general population)<br>High intake (≥10 prescriptions) vs. no use<br>(in general population) | 1.2 (1.0-1.5)<br>1.4 (0.9-2.1) | Age, sex |
| Cho et al. (2011)[9] | USA, | Cohort (1990-2006, NHS; 1986-2006, HPFS) | RCC | 333/126,928 | Regular use (≥2/wk) vs.<br>no use<br>Long duration (≥10 yr) of<br>regular use vs. no use | 1.51 (1.12-2.04)<br>1.33 (0.76-2.32) M<br>1.59 (1.11-2.27) F<br>2.92 (1.71-5.01)<br>1.98 (0.76-5.12) M<br>3.51 (1.83-6.74) F | Age, calendar year, smoking, BMI, history<br>of hypertension, physical activity, fruit,<br>vegetable, alcohol intakes, parity (female) |

M: Male, F: Female, RCC: Renal Cell Carcinoma, wk: week,BMI: Body Mass Index, NHS: Nurses' Health Study, HPFS: Health Professionals Follow-Up Study, NSAIDs: Non-steroidal-anti-inflammatory drugs