Analgesic Use and Risk of Renal Cell Carcinoma: A Case-Control, Cohort, and Meta-Analytic Assessment

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Abstract

Analgesics are the most commonly consumed drugs worldwide. Evidence that analgesics increase kidney cancer risk has been mixed. We investigated the association between renal cell carcinoma (RCC) and analgesic use in a large population-based case-control study and a post-trial observational cohort study. Findings were used to update a recent meta-analytic review. We analyzed data from 1,217 RCC cases and 1,235 controls in the US Kidney Cancer Study and 98,807 participants in the US Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO: n=137 RCCs). Self-reported acetaminophen, aspirin, and non-steroid anti-inflammatory drug (NSAID) use and duration information was assessed in relation to RCC. For the US Kidney Cancer Study, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. For PLCO, we computed hazard ratios (HRs) and 95%CIs using Cox regression. Among case-control participants, RCC risk was associated with over-the-counter acetaminophen use (OR=1.35, 95%CI=1.01–1.83). There was a positive trend with increasing

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duration (P-trend=0.01), with a two-fold risk for use ≥10 years (OR=2.01, 95%CI=1.30–3.12). No association with prescription acetaminophen use was detected. In PLCO, acetaminophen use was also associated with increased RCC risk (HR=1.68, 95%CI=1.19–2.39), although elevated risk was absent among the few long-term users. No association with RCC risk was detected for aspirin or NSAIDs use in either study. An association between acetaminophen use and kidney cancer was supported by meta-analytic cohort (n=4; summary relative risk=1.34; 95%CI=1.13–1.59; P-heterogeneity=0.40) and case-control (n=9, summary OR=1.20; 95%CI=1.01–1.42; P-heterogeneity=0.05) findings. In brief, acetaminophen use may increase the risk of developing RCC.

Keywords

Renal Cell Carcinoma; Kidney Cancer; Acetaminophen; Analgesics; Meta-Analysis

INTRODUCTION

Analgesics, used to reduce pain or fever, are the most commonly consumed drugs in the world (1, 2). Acetaminophen, ibuprofen, and aspirin are the most frequently used over-the-counter (OTC) and prescription drugs in the United States (US) (2, 3). For over two decades, analgesic consumption and availability has increased in the US (1-3). According to US National Health Interview Survey data, regular aspirin use increased nearly 60% between 2005 and 2010 (4). US Food and Drug Administration data also showed an approximate 30% increase in acetaminophen sales between 2004 and 2008 (5). While epidemiological studies have shown a protective effect against various cancers for several of these drugs (6, 7), findings have been inconsistent for kidney cancer (8-13).

Kidney cancer is the seventh- and ninth-most commonly diagnosed malignancy among US men and women, respectively, with an estimated 64,000 cases expected in 2015 (14-16). The most common form, renal cell carcinoma (RCC), accounts for over 80% of kidney cancers (17, 18). Although primary RCC risk factors such as male sex, African American race, family history of kidney cancer, cigarette smoking, hypertension, and excess body weight have been established, these factors account for only about half of cases (17, 18).

To gain a better understanding of the relationship between analgesic use and RCC risk, we analyzed OTC and prescription drug history information from participants in a large US population-based case-control study of Caucasians and African Americans. Because self-reported information on analgesic use obtained post-diagnosis could be subject to recall bias, we further examined this relationship in the prospective US Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO). Findings from both studies were subsequently used to update a recent meta-analytic review.

METHODS

US Kidney Cancer Study

Details regarding recruitment and data collection in the US Kidney Cancer Study have been described previously (19, 20). Briefly, between 2002 and 2007 we enrolled white and black participants, 20 to 79 years old, from Detroit, Michigan and Chicago, Illinois with

histologically confirmed incident RCC (International Classification of Diseases for Oncology (ICD-O), Third Edition, Code 64.9). Controls, selected from the general population, were frequency-matched to cases on age, sex, race (self-reported), and area of residence. Controls <65 years were identified from Department of Motor Vehicle (DMV) records. Controls aged 65 to 79 were identified from Centers for Medicare and Medicaid Services (CMS) files.

Although blacks have higher RCC rates than whites (18), in the current study more whites were diagnosed with RCC given the greater number of white residents. To increase enrollment of blacks, all eligible black cases were invited to participate, whereas only a subset of potentially eligible white cases were recruited. To further increase power for blacks, our targeted control:case matching ratio was 2:1 for blacks and 1:1 for whites. Among the 1,918 eligible cases identified, we were able to contact 1,571 cases for enrollment and recruit 1,217 cases for participation. Among the 2,718 potentially eligible controls identified, we were able to contact 2,269 controls for enrollment and recruit 1,235 for participation. Institutional Review Boards at collaborating institutions approved study procedures and all subjects provided written informed consent prior to data collection.

Data Collection—Demographics, diet, occupational history, smoking history, as well as medical and medication history data were collected using in-home, computer-assisted personal interviews. Approximately 60% of the cases were interviewed within six months of their diagnosis, and 84% were interviewed within one year of their diagnosis. Participants were queried about their use of the following medications for pain or fever, two years prior to the interview: OTC acetaminophen; prescription acetaminophen; OTC non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin; and prescription NSAIDs. Data on aspirin use for a heart regimen was also collected. Subjects were shown medication cards with names of different OTC and prescribed products. "Regular" use of OTC drugs was defined as use for at least once a week for three months or longer, at least two years prior to the interview. Regular use of prescription drugs and aspirin for a heart regimen was defined as use once a week for one month or longer, at least two years prior to interview. For participants acknowledging regular use, information on start age or year, stop age or year, and duration of use was obtained. The "once per week" criterion was not maintained for the duration-response analyses. Whether participants took the drug "regularly" throughout the entire duration that they used the product is unknown. Additionally, data were not collected on frequency or dose of these medications.

Statistical Analysis—We assessed ever/never and duration of acetaminophen and NSAIDs use separately for OTC and prescription drugs; subsequently, we examined OTC and prescription use combined. Categories for duration of use were classified as: no regular use (referent), <1 year, 1 to <5 years, 5 to <10 years, and 10 years.

For analytic purposes, we developed a set of sample weights to reduce potential biases arising from differential sampling rates for controls and cases, from survey non-response, and from deficiencies in coverage of the population at risk by DMV and CMS files for control selection. Sample weights for controls also included a post-stratification adjustment so that the weighted control distribution across matching variables corresponded exactly to

the weighted case distribution (21). We compared the sample-weighted frequency distribution of selected characteristics and known RCC risk factors between cases and controls using a Wald F-test (22). Unconditional logistic regression using post-stratified weights was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) associated with analgesic use. We performed trend tests by modeling the median of the exposure-response categories for duration of use as ordinal variables and applying the Wald Chi-Square test (22). Standard errors were estimated using the jackknife replicate weight method (23).

We adjusted regression models for sex, race, smoking (ever/never), age (20–44, 45–54, 55–64, 65–74, 75 years), body mass index (BMI; <25, 25 to <30, and 30 kg.m^{-2}), hypertension (yes/no), family history of cancer (no, yes non-kidney, yes kidney), education (<12 years, high school graduate, some college, college graduate), center (Detroit/Chicago), and dialysis treatment (ever/never). We conducted subgroup analyses by race, sex, median age (<60 years/ 60 years), BMI (<30 kg.m^{-2} / 30 kg.m^{-2}), hypertension (ever/never), smoking (ever/never), family history of cancer (yes/no), tumor grade (Fuhrman Nuclear Grade: I and II vs. III and IV), and histologic RCC subtypes (clear cell/papillary). Interactions were tested using a t-test and Wald test.

We conducted analyses in the US Kidney Cancer Study with SAS 9.2 and STATA 10.0 using procedures for sample weighted data. All analyses were also performed without sample weighting and results were similar to those presented (data not shown). Statistical significance was determined at a two-sided *P*-value<0.05.

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)

The multi-center randomized PLCO trial was designed to evaluate prostate, lung, colorectal, and ovarian cancer screening effectiveness on disease-specific mortality (24, 25). Between 1993 and 2001, nearly 155,000 men and women, aged 55 to 74, were enrolled from ten US centers. Anthropometric, medical, and lifestyle questionnaire data were collected at baseline. Between 2006 and 2007, a supplemental questionnaire was mailed to participants to gather additional information on family history of cancer, medical history, physical activity, and gender-specific health factors.

Our analysis excluded participants who had not returned both the baseline and supplemental questionnaires (n=52,345), had questionnaires completed by proxy (n=3,177), had reported a previous kidney cancer at baseline or were diagnosed with kidney cancer prior to completion of the supplemental questionnaire (n=408), or had missing follow-up data (n=163). Our final population included 98,807 subjects. PLCO participants were followed-up for all cancer diagnoses by annually mailed questionnaires, with subsequent confirmation through medical records. We identified 137 incident RCC (ICD-O, Second Edition, Code C649) cases from the date of supplemental questionnaire completion through December 31, 2009. Censoring events included death, loss to follow-up, renal pelvis or kidney cancer *in situ* diagnosis, or end of follow-up.

Data Collection—In addition to demographic factors, participants were asked the number of years they took acetaminophen, NSAIDs (excluding aspirin), and aspirin (including baby

aspirin) at least once per week in the supplemental questionnaire. Data on strength/dose was collected only for aspirin. The questionnaire did not distinguish between OTC and prescription forms or provide a list of common prescription products that contain these medications in combination with other drugs.

Statistical Analysis—We examined acetaminophen, NSAIDs, and aspirin use separately. Questionnaire data for duration of use was collected using the following categories: no regular use (referent), <10 years, 10 to <20 years, and 20 years. Given the small number of subjects with 20 years of use, we combined the upper two categories. Aspirin strength/dose was assessed as 81mg or 325mg.

We conducted analyses using SAS 9.2. Statistical significance was determined at a two-sided P-value<0.05. We calculated hazard ratios (HRs) and 95% CIs relating risk factors to RCC incidence using Cox proportional hazards models, with attained age (in days) as the time metric. We performed trend tests with ordinal variables by treating each category as a continuous term (0, 1, 2…) in the model; tests were based on the Wald statistics. We assessed proportional hazards assumptions by adding interaction terms between age and each analgesic exposure in the Cox models; no evidence of violations against proportionality was found. Final models were adjusted for sex, BMI (<25, 25 to <30, and 30kg.m^{-2}), hypertension (ever/never), race/ethnicity (white, black, Hispanic, Asian/Native Indian/Alaskan Pacific Islander), center, smoking (ever/never), and education (<12th grade, 12th grade or completed high school, post-high school training, some college, college, post-college graduate). We conducted subgroup analyses by sex, median age (<70 years/70+ years), hypertension (ever/never), smoking (ever/never), and BMI (<30 kg.m^{-2} / 30 kg.m^{-2}). Lastly, we repeated analyses excluding the first-two years of follow-up after completion of the supplemental questionnaire (54 cases remained) to evaluate the possibility of bias introduced by early symptoms of cancer influencing reported analgesic use.

Meta-Analyses

To follow up on our acetaminophen findings, we conducted a meta-analysis of relevant cohort and case-control studies. Studies written in English through December 2013 were identified in PubMed using the following key words: *analgesic use and (kidney) cancer risk, paracetamol use and (kidney) cancer risk,* and *acetaminophen use and (kidney) cancer risk.* References from identified publications were reviewed for additional studies. Including our current study, four cohort (11-13) and 12 case-control (26-36) studies on kidney cancer risk and acetaminophen use were identified. To ensure thoroughness of our meta-analysis, we designed and reported findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Supplemental Figure 1) (37).

Meta-analyses were conducted for cohort and case-control studies separately, using STATA version 10.0. For several studies, risk estimates were not provided; where possible, we calculated crude risk estimates using the number of subjects provided (i.e., unexposed/exposed) (11, 26, 28, 30, 31). Sensitivity analyses excluding these crude risk estimates from analyses did not significantly alter findings. The data were combined using random-effects models to estimate the summary relative risks (SRRs) or odds ratios (SORs) and 95% CIs.

Cochrane's Q test and Higgin's I^2 statistic were used to evaluate heterogeneity among the studies, while publication bias was assessed by Begg's and Egger's tests and through evaluation of funnel plots (38, 39).

RESULTS

US Kidney Cancer Study

Cases and controls were comparable with regard to sex and age, but cases had a higher BMI, prevalence of hypertension, history of smoking, a lower education level, and were more likely to have a family history of kidney cancer, and to have undergone dialysis treatment (Supplemental Table 1). Stratified analyses showed comparable distribution of characteristics by race and sex (data not shown).

Table 1 displays associations between analgesic use and RCC risk. Ever OTC acetaminophen use was associated with increased RCC risk (OR=1.35, 95% CI=1.01– 1.83). A positive trend with increasing duration of OTC acetaminophen use (*P*-trend=0.01) was also observed; subjects with 10 years of use had a two-fold increase in risk (OR=2.01, 95% CI=1.30–3.12). Findings for prescription acetaminophen were null. A borderline significant trend (*P*-trend=0.07) was observed for OTC and prescription acetaminophen use combined, with a significantly elevated risk for 10 years of use (OR=1.54, 95% CI=1.09– 2.16). RCC risk was not associated with OTC or prescription NSAIDs or with aspirin use for a heart regimen. Similar findings are shown by sex and race, with no evidence of interaction (Supplemental Table 2). Results for analgesic use did not differ (*P*-interaction>0. 05) by BMI, median age, smoking status, hypertension, tumor grade, or RCC histologic subtypes (data not shown).

PLCO

Among the 98,807 PLCO participants examined, 82% reported regular analgesic use (aspirin, 62.0%; non-aspirin NSAIDs, 30 9%; acetaminophen, 32.7%). Compared to non-analgesic users, participants with regular use typically had a higher BMI and were more likely to be white, to smoke, and to be hypertensive (Supplemental Table 3).

An elevated RCC risk was observed among regular acetaminophen users (HR=1.68, 95% CI=1.19– 2.39) (Table 2). Risk was elevated among participants with <10 years of use (HR=2.09, 95% CI=1.39–3.14) but not for those with 10 years (HR=1.08, 95% CI=0.55– 2.10). Findings for NSAIDs and aspirin were null. Results for analgesic use did not differ (*P*-interaction>0.05) by sex, race, BMI, median age, smoking status, hypertension, clear cell RCC histologic subtype, or after excluding the first-two years of follow-up (data not shown).

Meta-Analysis

Four cohort (11-13) and 12 case-control (26-36) studies were identified from the scientific literature. Supplemental Table 4 briefly describes each study. Three case-control studies (29-31) were excluded because the study populations were subsets of a large international study (32). Thus, 13 studies (four cohort, nine case-control) were included in our meta-analysis.

A forest plot in Figure 1 summarizes study-specific and summary associations between acetaminophen use and kidney cancer. The acetaminophen-kidney cancer SRR association for all studies combined was 1.25 (95% CI=1.10–1.41), with no evidence of between-study heterogeneity (P=0.08; I^2=37.73) or publication bias (P-Begg's=0.54; P-Egger's=0.42). The summary effect was slightly stronger for cohort (SRR=1.34, 95% CI=1.13–1.59; P-heterogeneity=0.40; I^2<0.01) than case-control (SOR=1.20, 95% CI=1.01–1.42; P-heterogeneity=0.05; I^2=48.61) findings. Publication bias was not detected for cohort (P-Begg's>0.99; P-Egger's=0.59) or case-control (P-Begg's=0.68; P-Egger's=0.49) studies. When restricting analysis to studies limited to RCC risk (n=11), the summary effect estimate remained significantly elevated for acetaminophen use (SRR=1.25, 95% CI=1.09–1.45; P-heterogeneity=0.05; I^2=46.01; P-Begg's=0.70; P-Egger's=0.49).

DISCUSSION

Our investigation of RCC risk and analgesic use in the US Kidney Cancer Study and the PLCO Screening Trial suggests that acetaminophen use may be associated with increased RCC risk. In the US Kidney Cancer Study, risk increased significantly with duration of OTC acetaminophen use, with a two-fold risk among subjects with at least ten years of use; this association was null among prescription acetaminophen users. In PLCO, risk was significantly elevated among ever acetaminophen users. Long-term acetaminophen use was not associated with risk, although RCC case numbers with ten or more years of use was small (n=10). Our meta-analytic findings support an association between acetaminophen use and kidney cancer, where comparable summary estimates were observed for cohort and case-control studies. Similar meta-analytic findings were observed when we restricted analyses to studies that examined RCC risk. Use of NSAIDs and aspirin was not associated with RCC risk in either of the two studies.

Three published cohort studies have investigated the association between acetaminophen use and kidney cancer risk (11-13). The largest of these studies reported a marginally significant 30% increase in RCC risk among acetaminophen users in the US Nurse's Health Study and Health Professionals Follow-up Study; but, no trend with duration of use was reported (12). In a second US cohort study, no relationship with ever or duration of acetaminophen use and RCC was shown (11). Among prescription acetaminophen users in a Danish cohort, a non-significantly elevated standardized incidence ratio of 1.3 was observed for RCC, with a significant positive trend with increasing numbers of prescriptions (P=0.04) (13). A meta-analysis of these cohort studies by Choueiri et al. showed a non-significant elevated kidney cancer risk of 1.19 (10). After incorporating our PLCO study results, the strength of pooled cohort findings increased, revealing a significant association between acetaminophen use and kidney cancer. For case-control studies, Choueiri et al. showed a significantly elevated summary effect for kidney cancer risk and acetaminophen use (RR=1.30, 95% CI=1.13–1.49) (10). After we excluded three case-control studies (29-31) that were subsets of a large international study (32) from Choueiri's review (10), pooled case-control findings for OTC or prescription acetaminophen use and kidney cancer risk remained elevated both with (SOR=1.20, 95% CI=1.01– 1.42; P-heterogeneity=0.05) and without (SOR=1.22, 95% CI= 0.99–1.49; P-heterogeneity=0.05) inclusion of our US Kidney Cancer Study findings, although borderline evidence of heterogeneity was detected. The Choueiri et al. review also examined

the effect of increased intake and duration on the acetaminophen-kidney cancer association. The overall RR across case-control and cohort studies combined (RR=1.28, 95% CI=1.15–1.44) increased to 1.68 (95% CI=1.22– 2.30) for high acetaminophen intake, but no relationship with duration was observed.

Although individual epidemiological study results have been inconsistent for acetaminophen use and kidney cancer risk, meta-analytic findings, which are more generalizable and less likely affected by small sample size, reveal a significant positive association that is biologically plausible (10). Approximately 90% of ingested acetaminophen is hepatically converted to nontoxic sulfates and glucuronide conjugates that are excreted in urine. The remaining amounts are oxidized in the liver and kidneys to reactive electrophilic N-acetyl-p-benzoquinoneimine (NAPQI) (40). At normal therapeutic doses, trace amounts of reactive NAPQI are formed. However, at higher doses, glutathione levels deplete, inhibiting formation of conjugates for excretion (40, 41). NAPQI is then available to form protein adducts, bind covalently to kidney and liver DNA, and disrupt cellular homeostasis (40, 41). Consequently, renal tubular necrosis may develop. Furthermore, long-term acetaminophen exposure at therapeutic doses has been correlated with chronic renal disease and analgesic nephropathy, and is thought to be dependent on prostaglandin endoperoxide synthesis (PGES), which exhibits a high affinity for acetaminophen (40). In the kidneys, PGES metabolically activates acetaminophen to NAPQI, increasing formation of reactive intermediates that cause tissue damage.

In the US Kidney Cancer Study, long-term OTC acetaminophen users had a statistically significant two-fold elevated RCC risk compared to non-users, but no association was observed among long-term prescription acetaminophen users. In the US, acetaminophen prescription products are typically found in combination with another analgesic, like codeine or hydrocodone. As these products have some dependence liability and/or abuse potential, they are generally prescribed for limited periods of time. Therefore, participants who reported long-term use of prescription acetaminophen products may have been taking these drugs on an "as needed" basis or for acute flare-ups rather than on a regular basis. These issues might also explain the null finding among long-term acetaminophen users in the PLCO study, which did not distinguish between OTC and prescription use. Alternately, the null association for long-term acetaminophen users in PLCO may be related to small case numbers.

Neither the US Kidney Cancer Study nor PLCO revealed any associations between RCC risk and use of NSAIDs (including aspirin) for pain or fever (US Kidney), use of aspirin as part of a heart regimen (US Kidney), use of aspirin for any indication (PLCO), or use of non-aspirin NSAIDs (PLCO). To date, two meta-analytic reviews on aspirin use and kidney cancer risk have been reported (9, 10). Both reviews observed non-significantly elevated risk, ranging from 1.1 to 1.2 for cohort and case-control studies, with significant heterogeneity between studies. For non-aspirin NSAIDs use, only one meta-analytic review has been published (10). Statistically significant 25% and 31% increased summary risk estimates were reported for all studies combined (n=5) and for cohort studies (n=2), respectively. A non-significant 1.14 summary estimate was observed for case-control studies. No significant evidence of heterogeneity was detected across the studies.

Our investigation of analgesic use and kidney cancer risk has several strengths. Strengths of both studies include their population-based design, data collection on specific types of analgesics, and the ability to control for known RCC risk factors as well as potential confounders like family history of cancer and education (a surrogate for socioeconomic status). Additional strengths of the US Kidney Cancer Study include the ability to assess risk for whites and blacks separately and inclusion of only histologically-confirmed RCC cancers. PLCO additional strengths include its large size and prospective design. Both studies are limited by a lack of data on analgesic dose and reliance on self-reported data. The potential misclassification of exposure due to inaccurate reporting would be non-differential in PLCO, where data were collected prior to diagnosis. However, since RCC can present as abdominal pain, it is possible that individuals may have used analgesics to treat early symptoms of RCC before diagnosis. Nonetheless, our analysis restricted to PLCO participants diagnosed greater than two years after completion of the supplementary questions does not suggest such bias. For the US Kidney Cancer Study, data on indication for analgesic use was not collected from participants and may have confounded results. Furthermore, inconsistencies in the results for OTC versus prescription drug use as well as for duration-response analyses may be related to the imprecise definition of "regular" drug use in both the US Kidney Cancer Study ("at least once a week for three months or longer" for OTC drugs and "at least once a week for one month or longer" for prescription drugs and aspirin) and in PLCO ("at least once per week"). The available exposure information in these studies did not allow for evaluation of intensity of use or assessment of consistency of use, and exposure misclassification in our definitions of regular use is likely to have biased our results towards the null. Another limitation of the US Kidney Cancer Study is the lack of statistical power to detect associations for analyses stratified by race and sex. The response rate among controls was not optimal, but the sample weights included adjustments for differential non-response rates among demographic categories that may have reduced bias in analyses due to non-response (21). An additional limitation of PLCO is the lack of data on OTC versus prescription analgesic use. With regard to our meta-analytic review, publication bias can potentially lead to summary estimates biased away from the null, although evidence of publication bias was not detected. Furthermore, variability of acetaminophen use definitions across studies and the inability to have a homogeneous definition of "regular" use was a limitation. However, our meta-analytic study did show consistently elevated summary risk estimates for both cohort and case-control studies with no significant evidence of heterogeneity. In addition, we were able to update previous meta-analytic findings by calculating summary risk estimates that incorporated our US Kidney Cancer case-control and PLCO cohort results.

In summary, findings from our population-based case-control study, multi-center randomized trial, and meta-analysis suggest that acetaminophen use may increase RCC risk. No evidence for an association between aspirin and NSAIDs use and RCC risk was observed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS:

Abbreviations Used:

BMI	body mass index
CI	confidence interval
CMS	Centers for Medicare and Medicaid Services
DMV	Department of Motor Vehicle
HR	hazard ratio
ICD-O	International Classification of Diseases for Oncology
NAPQI	N-acetyl-p-benzoquinoneimine
NSAIDs	non-steroid anti-inflammatory drugs
PGES	prostaglandin endoperoxide synthesis
PLCO	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
OR	odds ratio
OTC	over-the-counter
RCC	renal cell carcinoma
RR	relative risk
SOR	summary odds ratio
SRR	summary relative risk
US	United States

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Novelty and Impact:

Analgesics, like acetaminophen, aspirin, and non-steroid anti-inflammatory drugs (NSIADs), are the most commonly consumed drugs worldwide; yet, evidence that analgesics increase renal cell carcinoma (RCC) risk has been mixed. To better understand the relationship, the association between analgesic use and RCC was evaluated in a case-control study, and cohort study, and a meta-analytic review. Evidence from all three study designs suggests that acetaminophen use is associated with increased RCC risk. Associations with aspirin or NSAIDs were null.

Figure 1.
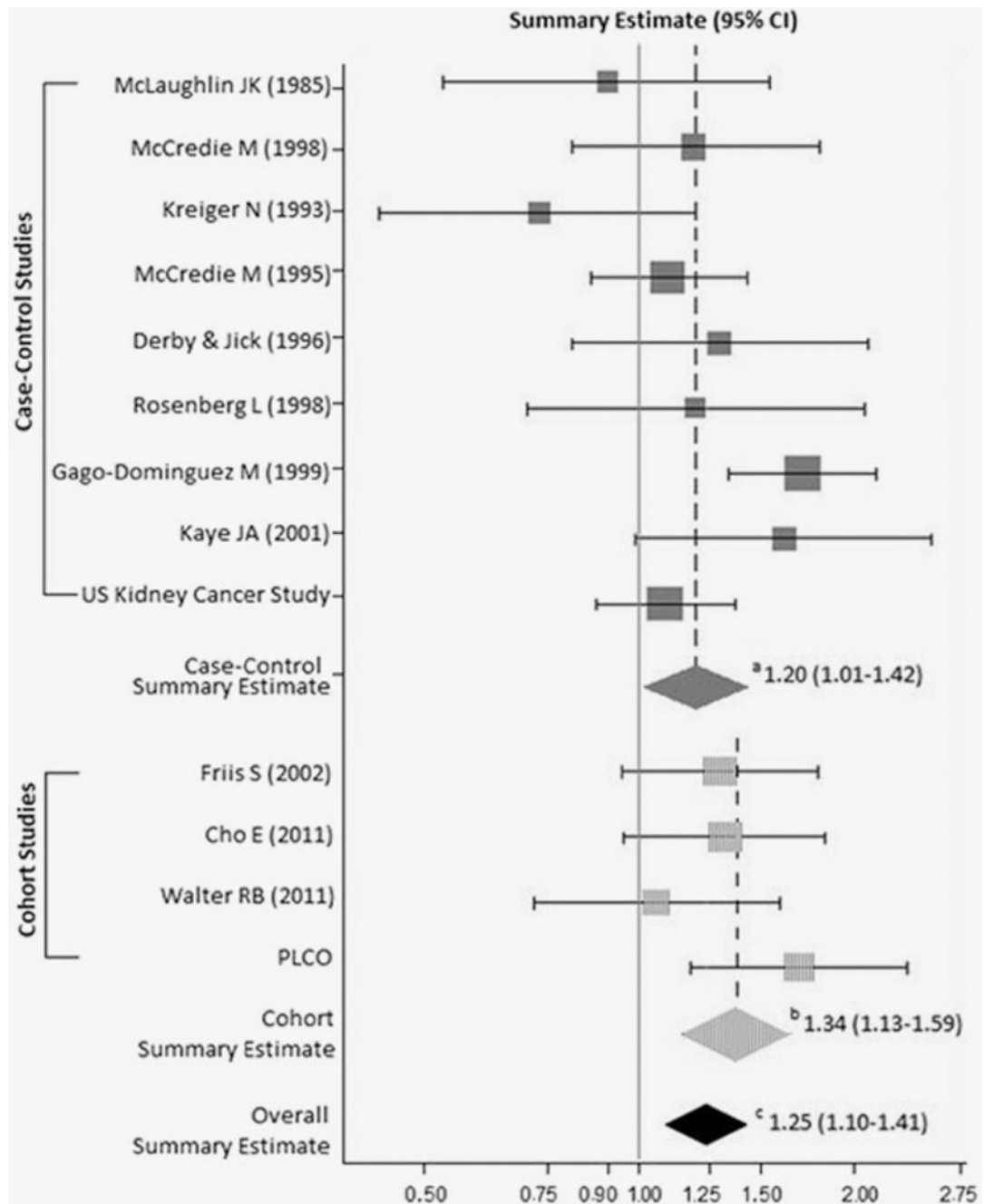Associations between regular use of acetaminophen and kidney cancer risk. [a]Case-control meta-analytic summary estimate. [b]Cohort meta-analytic summary estimate. [c]Combined overall (case-control and cohort) meta-analytic summary estimate.

Table 1.

Weighted RCC risk and "regular" use of analgesics in the US Kidney Cancer Study

Analgesics	Case, n	Control, n	OR[a]	95% CI[a]	
ACETAMINOPHEN USE AND DURATION					
Over the Counter					
No	1081	1144	1.00		
Yes	133	90	1.35	1.01	1.83
<1year	12	12	1.08	0.44	2.64
1 to <5 years	24	24	0.79	0.41	1.53
5 to <10 years	27	16	1.37	0.71	2.65
10+ years	63	34	2.01	1.30	3.12
P-trend					*0.01*
Prescription					
No	1014	1038	1.00		
Yes	198	190	0.96	0.74	1.24
<1year	64	80	0.88	0.63	1.22
1 to <5 years	55	50	1.19	0.74	1.93
5 to <10 years	27	19	1.13	0.59	2.19
10+ years	43	30	1.09	0.65	1.82
P-trend					*0.67*
Over the Counter or Prescription					
No	937	986	1.00		
Yes	275	242	1.09	0.87	1.37
<1year	61	80	0.86	0.61	1.21
1 to <5 years	64	62	1.03	0.67	1.59
5 to <10 years	37	30	1.06	0.59	1.89
10+ years	92	57	1.54	1.09	2.16
P-trend					*0.07*
NSAIDs (INCLUDING ASPIRIN) USE AND DURATION					
Over the Counter					
No	1076	1114	1.00		
Yes	137	120	1.01	0.76	1.34
<1year	16	11	1.28	0.58	2.81
1 to <5 years	34	30	0.94	0.56	1.57
5 to <10 years	23	22	0.89	0.43	1.85
10+ years	53	49	1.01	0.67	1.53

Analgesics	Case, n	Control, n	OR[a]	95% CI[a]	
P-trend					*0.93*
Prescription					
No	1031	1032	1.00		
Yes	182	197	0.87	0.66	1.16
<1year	50	63	0.78	0.53	1.15
1 to <5 years	56	64	0.95	0.61	1.48
5 to <10 years	32	29	0.91	0.50	1.69
10+ years	40	31	1.14	0.65	2.01
P-trend					*0.86*
Over the Counter and Prescription					
No	927	970	1.00		
Yes	283	261	1.07	0.86	1.35
<1year	56	60	1.04	0.70	1.54
1 to <5 years	80	72	1.14	0.78	1.64
5 to <10 years	46	33	1.50	0.85	2.64
10+ years	88	74	1.15	0.83	1.57
P-trend					*0.20*
ASPIRIN FOR HEART REGIMEN USE AND DURATION					
No	786	879	1.00		
Yes	401	325	1.15	0.92	1.42
<1year	37	47	0.75	0.43	1.29
1 to <5 years	149	125	1.09	0.81	1.47
5 to <10 years	100	74	1.22	0.85	1.75
10+ years	96	71	1.25	0.89	1.75
P-trend					*0.12*

Abbreviations: BMI- body mass index; CI- confidence interval; n- number; NSAIDs- non-steroid anti-inflammatory drugs; OR- odds ratio; OTC-over-the-counter; RCC- renal cell carcinoma.

The following data are unknown: OTC acetaminophen use (3 cases, 1 control) and duration (10 cases, 5 controls), prescription acetaminophen use (5 cases, 7 controls) and duration (14 cases, 18 controls), OTC NSAIDs use (4 cases, 1 control) and duration (15 cases, 9 controls), prescription NSAIDs use (4 cases, 6 controls) and duration (8 cases and 16 controls), and aspirin for a heart regimen use (30 cases, 31 controls) and duration (49 cases, 39 controls).

Due to missing start age or year, stop age or year, or duration of use data the following are unknown: overall acetaminophen duration (26 cases, 20 controls) and overall NSAIDs duration (20 cases, 26 controls).

[a]Weighted logistic regression adjusted for sex, race, hypertension, BMI, smoking status, age, education, study center, family history of cancer, and dialysis treatment.

Table 2.

RCC risk and "regular" use of analgesics in the PLCO Screening Trial

Analgesics	Cases, n	HR	95% CI	
RCC Cases	137			
ACETAMINOPHEN USE AND DURATION				
No	73	1.00		
Yes	59	1.68	1.19	2.39
<10 years	36	2.09	1.39	3.14
10+ years	10	1.08	0.55	2.10
P-trend				*0.06*
NSAIDs (EXCLUDING ASPIRIN) USE AND DURATION				
No	88	1.00		
Yes	41	1.03	0.71	1.51
<10 years	33	1.43	0.95	2.15
10+ years	4	0.43	0.16	1.17
P-trend				*0.69*
ASPIRIN USE, DURATION AND STRENGTH				
No	51	1.00		
Yes	84	0.82	0.58	1.17
<10 years	44	0.80	0.54	1.20
10+ years	29	0.83	0.52	1.32
P-trend				*0.38*
325mg strength	32	0.87	0.56	1.36
81mg strength	48	0.80	0.54	1.20
P-trend				*0.29*

Abbreviations: BMI- body mass index; CI- confidence interval; HR- Hazard Ratios; n- number; NSAIDs- non-steroid anti-inflammatory drugs; PLCO- Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; RCC- renal cell carcinoma.

The following data are unknown: acetaminophen use (5 cases) and duration (18 cases), NSAIDs use (9 cases) and duration (13 cases), and aspirin use (2 cases), duration (13 cases) and strength (6 cases).

Cox proportional hazard regression models adjusted for: BMI, education, race, smoking status, hypertension and center.