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Associations of NSAID and paracetamol use with risk of primary liver cancer in the Clinical Practice Research Datalink

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Abstract

Liver cancer incidence has been rising rapidly in Western countries. Nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol are widely-used analgesics that may modulate the risk of liver cancer, but population-based evidence is limited. We conducted a case-control study (1195 primary liver cancer cases and 4640 matched controls) within the United Kingdom's Clinical Practice Research Datalink to examine the association between the use of prescription NSAIDs and paracetamol and development of liver cancer. Multivariable-adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression. Overall, ever-use of NSAIDs was not associated with risk of liver cancer (aOR = 1.05, 95% CI = 0.88–1.24), regardless of recency and intensity of use. Use of paracetamol was associated with a slightly increased risk of liver cancer (aOR = 1.18, 95% CI = 1.00–1.39), particularly among individuals with body mass index < 25 kg/m^2 (aOR = 1.56, 95% CI = 1.17–2.09). Our results suggest that NSAID use was not associated with liver cancer risk in this population. Ever-use of paracetamol may be associated with slightly higher liver cancer risk, but results should be interpreted cautiously due to methodological limitations. Given that paracetamol is a widely-used analgesic, further examination of its relationship with liver cancer is warranted.

Keywords

Analgesics; liver cancer; case-control study; medical records database

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INTRODUCTION

Primary liver cancer is the second leading cause of cancer death worldwide [1]. Although it's relatively rare in the Western countries, its incidence has been rising rapidly in both the United Kingdom (UK) [2] and the United States (US) [3]. Furthermore, the effectiveness of surveillance and treatment of liver cancer is low [4], and the prognosis of liver cancer is poor [5]. Thus, it is of considerable clinical and public health importance to determine preventive strategies to reduce the disease burden of liver cancer.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely-used medications with analgesic, antipyretic, and anti-inflammatory properties. As liver cancer develops on a background of chronic inflammation [6], NSAIDs may be chemopreventive against liver cancer based on their anti-inflammatory properties. Experimental studies have shown that NSAIDs may inhibit liver cancer cellular growth and induce cell apoptosis by modifying cyclooxygenase (COX) enzymatic pathways which mediate inflammation [7, 8]. Two reports from large observational studies suggested that NSAID use, specifically aspirin, was associated with reduced risk of liver cancer [9, 10], but NSAID use was self-reported in these studies. Associations between prescription NSAID use and liver cancer have not been previously described.

Paracetamol (acetaminophen) is another type of widely-used moderately-effective analgesic. Paracetamol overdose may induce hepatotoxicity and subsequent acute liver failure [11]. Patients with chronic liver disease may be especially susceptible to the adverse effects of paracetamol because of altered liver function [12]. We hypothesized that paracetamol-induced liver injury may predispose individuals to higher risk of liver cancer. Several animal studies have demonstrated the hepatocarcinogenicity of paracetamol [13], but evidence to evaluate the hepatocarcinogenicity in humans is scarce.

Thus, we examined the associations between prescription NSAID and paracetamol use and the development of liver cancer in the UK's Clinical Practice Research Datalink (CPRD), a large medical records database.

MATERIALS AND METHODS

Data source

This nested case-control study was conducted using data from CPRD, a large, population-based, automated medical record database with information on approximately 8.5% of the UK population [14]. Diagnoses, physical findings, symptoms, and administrative events are recorded using Read codes [15], and the data are considered reasonably complete and accurate with regard to clinical illnesses diagnosed by the GP or a specialist [16, 17]. Specifically, over 90% of information from manual medical records is recorded electronically [16, 17], and 95% of all electronically identified primary cancers were confirmed as incident cancer cases [18]. Detailed information for all prescribed medications is also available. This study was approved by the National Institutes of Health Human Research Protection Program and the Independent Scientific Advisory Committee of the CPRD (Protocol 12_127R2).

Study population

As previously described [19], cases and controls were drawn from persons in the CPRD from 1988 through 2011 who were between the ages of 10 and 90 years. Cases met the following criteria: 1) first time diagnosis of primary liver cancer, 2) no code of liver metastases and no prior diagnosis of cancers most likely to have liver metastasis (lung, stomach, breast, colon, or pancreatic cancer), and 3) no diagnosis of any other cancer (except for nonmelanoma skin cancer) in the three years prior to the index date. The index date was defined as one year before the date of liver cancer diagnosis. All cases were required to have at least two years of history in the CPRD prior to the index date. Of the 1195 cases, 86.7% had supporting clinical codes indicating presence of liver cancer, such as diagnostic exams, treatment, palliative care, and referrals to specialty care.

For each case, controls were selected from individuals who were in the CPRD at the case's index date and had no cancer diagnosis (except nonmelanoma skin cancer) prior to that date. Controls were matched to cases at a four-to-one ratio on age (year of birth), sex, general practice, and number of years in the CPRD prior to the case's index date. We then defined the controls' index date to be the same as the matched case's index date. Only three eligible controls could be identified for 59 of the cases, only two for 24 cases, and only one for 11 cases, resulting in a total of 4640 controls.

In addition to the full case-control match, we completed an additional match based on the presence of chronic liver disease. For the 170 cases with a history of chronic liver disease, 680 controls selected among individuals with liver disease in the CPRD were matched to these cases at a four-to-one ratio using the same matching factors as in the primary match. Similarly, the remaining 1025 cases without liver disease were matched to 4100 controls without chronic liver disease. This approach allows sufficient sample size for stratified analyses by chronic liver disease.

Exposure definition

Ever-use of NSAIDs was defined as having two or more NSAID prescriptions recorded prior to the index date of the individual, while non-use was defined as one or no NSAID prescriptions prior to the index date. The same definition was used for paracetamol use. Current use was defined as use that ended within one year prior to the index date, while past use was defined as use that ended more than one year prior to the index date. Total number of prescriptions was evaluated for ever users, and separately for current and past users. It was categorized as 2–9, 10–19, 20–39, and ≥40 prescriptions, written up to the index date. To assess the intensity of medication use, we calculated the time between first and last use of each medication (categorized as <2 years, 2–5 years, and >5 years) and examined the association between total number of prescriptions and liver cancer risk within each time period category.

In addition to analyzing NSAID as a single entity, we also examined subtypes of NSAIDs individually, i.e., aspirin, COX-2 selective inhibitors, and other NSAIDs, using non-use of NSAIDs as the comparison group.

Statistical analysis

We conducted conditional logistic regression to calculate the crude and adjusted odds ratio (cOR and aOR) and 95% confidence interval (CI) for associations between NSAID and paracetamol use and liver cancer risk. In multivariable models, we adjusted for body mass index (BMI), smoking, alcohol-related disorders, hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, diabetes, rare metabolic disorders, anti-diabetic medications, and statin use, selected *a priori* based on previous literature. In addition, models for NSAIDs were adjusted for paracetamol use, and models for paracetamol were adjusted for any NSAID use. For covariates with missing values, "unknown" categories were created for the analyses.

Four sensitivity analyses were conducted for both NSAID and paracetamol use, including 1) restricting the analysis to cases with clinical codes for liver cancer treatment (e.g., surgery, chemotherapy, or palliative care) and their matched controls; 2) using an index date of 2 years prior to the case's date of diagnosis, rather than 1 year; 3) restricting the analysis to participants without cardiac impairments; and 4) excluding participants under age 40. In addition, we conducted a sensitivity analysis to examine the use of 36 or more prescriptions of NSAIDs (overall and by subtype) vs. no use, because there is evidence that the effect of low dose aspirin use on the incidence of cancer does not start until after about 3 years of sustained use [20], and in the UK, 36 prescriptions would be equivalent to three years of use as NSAID prescriptions tend to be written for one month at a time. Furthermore, we tested for effect modifications by important covariates, including age at index date, sex, BMI and smoking status, using likelihood ratio tests. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). All statistical tests were two-sided, and p values of less than 0.05 were considered statistically significant.

RESULTS

As shown in Table 1, the mean age of the study participants was 67 years, and 71.6% were men. Eligible liver cancer cases (n = 1195) were more likely than matched controls (n = 4640) to be obese, to be current or former smokers, to be infected with HBV and/or HCV, and to have chronic liver disease, rare metabolic disorders, alcohol-related disorders, diabetes, hypertension, and congestive heart failure.

Table 2 shows the results of the analysis of NSAID use with liver cancer risk. There was no association between liver cancer risk and ever-use of NSAIDs after multivariable adjustment (aOR = 1.05, 95% CI = 0.88–1.24). The attenuation of OR in the multivariable model, compared to the crude model, was primarily driven by adjustment of history of diabetes, antidiabetic medication use, and paracetamol use. Similarly, there were no associations with liver cancer risk when NSAID use was stratified by the total number of prescriptions or the recency and intensity of use. Analyses of individual subtypes of NSAIDs and liver cancer risk also found no associations with one exception: ketoprofen use was associated with lower risk (aOR = 0.27, 95% CI = 0.07–0.99), although the CI was relatively wide (Table 3). As with the analyses of the whole dataset, analyses stratified on the presence of chronic liver disease also yielded no significant associations (Supplementary Table 1).

Table 4 shows the association of paracetamol use with liver cancer risk. Ever-use of paracetamol was associated with a slightly increased risk of liver cancer (aOR = 1.18, 95% CI = 1.00–1.39). This association was most evident for current use (aOR = 1.30, 95% CI = 1.08–1.56) and long-term use (time between first and last prescription > 5 years; aOR = 1.26, 95% CI = 1.03–1.54). The increased risk of liver cancer associated with paracetamol use was also observed among individuals without chronic liver disease, but not among those with chronic liver disease (Supplementary Table 2). We noted a statistically significant interaction between paracetamol use and BMI ($p_{interaction} < 0.01$), with increased risk observed only among those with BMI < 25 kg/m^2 (aOR = 1.56, 95% CI = 1.17–2.09) but not among those with BMI≥25 kg/m^2 (aOR = 0.95, 95% CI = 0.77–1.17) (Supplementary Table 3).

In sensitivity analyses, we observed no material deviation from the main results after restricting the analyses to cases with supporting clinical codes and their controls, restricting to participants without cardiac impairments, excluding participants under age 40, or changing the index date to 2 years prior to date of diagnosis (results for paracetamol after changing the index date shown in Supplementary Table 4, other results not shown). In addition, when we evaluated sustained NSAID use in a sensitivity analysis, 36 or more prescriptions of NSAIDs were not associated with the risk of liver cancer (data not shown).

DISCUSSION

In the current study, we examined the association between NSAID and paracetamol use, as recorded in the CPRD's electronic clinical records, and risk of liver cancer. Overall, NSAID use was not associated with risk of liver cancer, although there was a suggestion of decreased risk associated with ketoprofen use. Paracetamol use was associated with a slightly increased risk of liver cancer, which was most evident in heavy and long-term users.

Previous US-based large cohort studies suggested that NSAID use, specifically aspirin, was associated with lower risk of hepatocellular carcinoma (HCC) [9, 10]. In contrast, our study suggests a lack of association between NSAID use and liver cancer risk in the CPRD. An important difference between our study and the previous cohort studies is that NSAID use was obtained via prescription data in clinical records in our study, whereas the previous cohort studies used questionnaire-based information on self-reported past use of aspirin or other NSAIDs with only one time-point of exposure. Although using prescription data avoids any recall bias, an inherent limitation is missing information on over-the-counter (OTC) medication use. Notably, the proportion of participants with aspirin use is much lower in our study (28% among controls) compared to cohort studies using self-reported NSAIDs (e.g., 73% in the NIH-AARP study) [10]. Whether this difference reflects recall bias (and consequent overestimation of NSAID use) in the previous studies or missing OTC exposure in our study is unclear. However, there is no evidence of massive OTC purchase of NSAIDs in the UK especially in the older population. A validation study interviewed women in CPRD who had no records of prescription NSAIDs, and reported that 30% of them had OTC use of aspirin or ibuprofen, most of which were rare or occasional use [21]. Furthermore, a simulation study suggested that missing OTC drug exposure is not a large source of bias under realistic conditions of NSAID use; for example, assuming the true RR

is 0.75 between NSAID use and a given outcome, with 70% of the population using NSAIDs and 30% of the NSAID use being OTC, the observed RR would be approximately 0.83, slightly biased towards the null [22]. Thus, we believe that the discrepancy between our study results and those of previous cohort studies, which relied on self-reported NSAID use, may only be partially explained by missing OTC exposure in our study.

To our knowledge, the associations of paracetamol use with the risk of primary liver cancer have only been examined in one Danish cohort, and the authors observed higher liver cancer incidence among paracetamol users compared to expected incidence among those not receiving paracetamol prescriptions (standardized incidence ratio 1.5, 95% CI 1.0–2.2) [24]. Similarly, in our study, we observed slightly higher risk of liver cancer with paracetamol use, particularly among those who had received many prescriptions for paracetamol, or those who received a moderate number of paracetamol over a short period of time. The mechanisms underlying this association may involve paracetamol-induced hepatotoxicity, following a complex sequence of events such as the depletion of glutathione, increased oxidative stress, mitochondrial dysfunction, and eventual liver necrosis [25]. These changes in liver morphology may have implications in hepatocarcinogenesis. Several animal studies have provided evidence for the carcinogenicity of paracetamol, especially in the liver [13]. For example, there is evidence that mice receiving high-dose of dietary paracetamol for 18 months had increased benign and malignant liver tumors at the end of the treatment period [26].

Alternatively, given that paracetamol use was associated with liver cancer risk among current users at relatively low number of prescription (e.g., 10–19), but not among past users even at high number of prescription (e.g., ≥40), it is possible that reverse causation may partially explain the observed excess liver cancer risk with paracetamol use, because paracetamol may be used to treat mild-to-moderate pain in early stages of liver cancer, likely before diagnosis [27]. If this is the case, we would expect that changing the index date from 1 year to 2 years prior to the date of diagnosis might attenuate the association, but results were essentially unchanged in this sensitivity analysis (OR 1.20, 95% CI 1.02–1.42 for ever-use of paracetamol; Supplementary Table 4). Nevertheless, we cannot rule out the possibility that some current users already had pre-clinical liver cancer and used paracetamol to treat the pain, and this potential reverse causation warrants further investigation.

In our study, paracetamol was only associated with increased risk of liver cancer among individuals with BMI < 25 kg/m^2. The mechanisms underlying the interaction between paracetamol and BMI are unclear, but may involve differences in drug metabolism and clearance according to body size, as leaner individuals may tolerate paracetamol toxicity to a lesser extent than heavier individuals. In addition, it is likely that the etiology of liver cancer arising from excess adiposity may be different from that arising from other risk factors, such as HBV or HCV infection, in the absence of excess adiposity. It is also possible that this finding is due to chance, as we examined a number of potential effect modifiers and made multiple comparisons.

A major strength of this study is that the CPRD is a large, well-established, validated, longitudinal primary-care database, and is known for diagnostic accuracy of cancer

outcomes and complete prescription pharmaceutical data. NSAID and paracetamol use was obtained from prescription data, which minimized information bias from self-report. Also, we attempted to reduce exposure misclassification by excluding cases and controls with less than two years of recorded medical history prior to their index date. However, this study also has a number of limitations. Exposure misclassification due to a lack of OTC data may have biased our estimates for both NSAIDs and paracetamol towards the null; however the bias is usually not large [22]. There is also potential for outcome misclassification, as a diagnosis of liver cancer was not confirmed by linkage to a cancer registry, although previous validation studies have shown that cancer diagnoses within the CPRD are reasonably complete [16]. In addition, the completeness of data for covariates may vary across patients and time [28]. Confounding by indication/contra-indication is also a concern. For example, patients at highest liver cancer risk (e.g., those with cirrhosis and portal hypertension with thrombocytopenia) may be advised to avoid NSAID use due to risk of gastrointestinal bleeding and renal failure [29] , and these patients may be more likely to receive paracetamol rather than NSAIDs; however, results did not change materially when restricting the analyses to individuals without chronic liver disease (Supplementary Tables 1 and 2). Some participants may be using NSAIDs to treat pre-existing chronic inflammatory conditions, which may predispose them to higher risk of liver cancer, however data were not available on chronic inflammatory conditions as indications of NSAID use.

In conclusion, we observed no association between prescription NSAID use and liver cancer risk in the CPRD population, contrary to findings from previous studies based on self-report. This association should be further examined in future studies with both prescription and OTC medication data. In addition, we observed a slightly increased risk of liver cancer among ever-users of prescription paracetamol, but these results should be interpreted cautiously due to potential methodological limitations. As paracetamol is widely used for analgesia, its potential role in liver cancer development has strong public health relevance, and thus warrants further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	body mass index
CI	confidence interval
COX	cyclooxygenase
CPRD	Clinical Practice Research Datalink

GP	general practitioner
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
NSAID	Nonsteroidal anti-inflammatory drug
OR	odds ratio
OTC	over-the-counter

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- Prescription NSAID use is not associated with risk of primary liver cancer.
- Ever-use of paracetamol is associated with slightly higher liver cancer risk.
- Paracetamol—liver cancer association is stronger among leaner individuals.

Table 1

Characteristics of cases and controls and their univariate associations with liver cancer, CPRD

	Cases (n = 1195)		Controls (n = 4640)		Univariate OR[a]
	n	%	n	%	OR (95% CI)
Index year[b]					
1991–1994	59	4.9	230	5.0	-
1995–1999	140	11.7	546	11.8	–
2000–2004	306	25.6	1190	25.6	-
2005–2010	690	57.7	2674	57.6	-
Age at index (years)[b]					
< 40	28	2.3	112	2.4	-
40 – 49	63	5.3	252	5.4	-
50 – 59	217	18.2	850	18.3	-
60 – 69	304	25.4	1188	25.6	-
70 – 79	407	34.1	1591	34.3	-
80 – 89	176	14.7	647	13.9	-
Mean ± SD	67.2 ± 12.1		67.0 ± 12.1		-
Sex[b]					
Male	856	71.6	3322	71.6	-
Female	339	28.4	1318	28.4	-
Length of history before index date (years)[b]					
Mean ± SD	10.9 ± 5.3		11.1 ± 5.3		-
BMI					
< 18.5 (Underweight)	20	1.7	52	1.1	1.62 (0.94–2.80)
18.5 – 24.9 (Normal)	308	25.8	1302	28.1	1.00 (ref)
25.0 – 29.9 (Overweight)	372	31.1	1609	34.7	0.99 (0.84–1.17)
30.0+ (Obese)	320	26.8	817	17.6	1.73 (1.44–2.07)
Unknown	175	14.6	860	18.5	0.79 (0.63–0.99)
Mean ± SD	27.7 ± 5.3		27.0 ± 4.8		-
Smoking status					
Non smoker	384	32.1	1942	41.9	1.00 (ref)

	Cases (n = 1195)		Controls (n = 4640)		Univariate OR[a]
	n	%	n	%	OR (95% CI)
Current smoker	304	25.4	815	17.6	1.98 (1.65–2.36)
Former smoker	425	35.6	1458	31.4	1.56 (1.32–1.84)
Unknown	82	6.9	425	9.2	0.86 (0.63–1.16)
Alcoholism	189	15.8	189	4.1	5.28 (4.16–6.70)
HBV and/or HCV infection	74	6.2	5	0.1	70.2 (25.7–192)
Chronic liver disease	170	14.2	23	0.5	32.8 (20.6–52.1)
Rare metabolic disorders[c]	26	2.2	9	0.2	12.5 (5.65–27.7)
Diabetes	346	29.0	463	10.0	3.85 (3.27–4.55)
Type 1	36	3.0	31	0.7	5.76 (3.46–9.58)
Type 2	265	22.2	398	8.6	3.44 (2.87–4.13)
Type Unspecified	45	3.8	34	0.7	6.34 (3.97–10.1)
Ischemic heart disease	210	17.6	775	16.7	1.07 (0.90–1.28)
Hypertension	512	42.9	1701	36.7	1.34 (1.17–1.54)
Congestive heart failure	77	6.4	223	4.8	1.39 (1.05–1.83)
Stroke	66	5.5	203	4.4	1.27 (0.95–1.70)
Transient ischemic attack	51	4.3	171	3.7	1.18 (0.85–1.63)
Dyslipidemia	157	13.1	718	15.5	0.80 (0.66–0.98)
Statin use (2+ prescriptions)	302	25.3	1242	26.8	0.91 (0.77–1.07)
Antidiabetic medication use (2+ prescriptions)	208	17.4	277	6.0	3.47 (2.84–4.24)

Abbreviations: BMI = body mass index; CI = confidence interval; CPRD = Clinical Practice Research Datalink; HBV = hepatitis B virus; HCV = hepatitis C virus; OR = odds ratio; SD = standard deviation.

[a] Using conditional logistic regression to account for matching.

[b] Matching variables.

[c] Rare metabolic disorders include haemachromatosis, Wilson Disease, porphyrias, and alpha-1 antitrypsin deficiency.

Table 2

Association of NSAID use with liver cancer risk, CPRD

	Cases (n = 1195) No.	Controls (n = 4640) No.	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
NSAID use				
0–1 prescriptions	438	1886	1.00 (Ref)	1.00 (Ref)
2+ prescriptions	757	2754	1.24 (1.08–1.43)	1.05 (0.88–1.24)
No. of prescriptions				
2–9	297	1158	1.15 (0.97–1.37)	1.01 (0.83–1.23)
10–19	139	432	1.46 (1.17–1.83)	1.30 (1.00–1.69)
20–39	126	481	1.20 (0.96–1.52)	0.97 (0.74–1.27)
≥40	195	683	1.33 (1.07–1.65)	1.00 (0.77–1.31)
P_{trend}			0.03	0.81
Recency of NSAID use				
0–1 prescriptions	438	1886	1.00 (Ref)	1.00 (Ref)
Current NSAID use	449	1701	1.19 (1.01–1.39)	0.98 (0.81–1.18)
No. of prescriptions				
2–9	96	408	1.03 (0.81–1.32)	0.86 (0.65–1.14)
10–19	85	300	1.28 (0.98—1.67)	1.21 (0.89–1.64)
20–39	97	382	1.18 (0.91–1.52)	0.94 (0.70–1.27)
≥ 40	171	611	1.32 (1.06–1.66)	1.01 (0.77–1.33)
P_{trend}			0.04	0.89
0–1 prescriptions	438	1886	1.00 (Ref)	1.00 (Ref)
Past NSAID use	308	1053	1.33 (1.12–1.59)	1.15 (0.94–1.40)
No. of prescriptions				
2–9	201	750	1.24 (1.02–1.50)	1.11 (0.89–1.39)
10–19	54	132	1.93 (1.37–2.71)	1.51 (1.02–2.23)
20–39	29	99	1.36 (0.88–2.10)	1.09 (0.68–1.77)
≥ 40	24	72	1.60 (0.98–2.61)	1.06 (0.61–1.87)
P_{trend}			0.04	0.95
Intensity of NSAID use				
Time between first and last prescription: <2 years				

	Cases (n = 1195) No.	Controls (n = 4640) No.	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
0–1 prescriptions	438	1886	1.00 (Ref)	1.00 (Ref)
2+ prescriptions	143	484	1.30 (1.05–1.61)	1.16 (0.91–1.48)
No. of prescriptions				
2–9	122	417	1.30 (1.03–1.63)	1.18 (0.91–1.52)
10–19	17	54	1.39 (0.79–2.43)	1.10 (0.57–2.10)
20–39	4	13	1.38 (0.43–4.39)	1.19 (0.34–4.18)
≥ 40	0	0	NA	NA
P_{trend}			0.08	0.35
Time between first and last prescription: 2–5 years				
0–1 prescriptions	438	1886	1.00 (Ref)	1.00 (Ref)
2+ prescriptions	170	579	1.30 (1.06–1.59)	1.15 (0.91–1.45)
No. of prescriptions				
2–9	69	284	1.07 (0.80–1.43)	0.90 (0.65–1.25)
10–19	43	119	1.62 (1.12–2.35)	1.66 (1.10–2.51)
20–39	42	123	1.55 (1.07–2.24)	1.32 (0.86–2.00)
≥40	16	53	1.33 (0.74–2.38)	1.16 (0.60–2.22)
P_{trend}			0.02	0.24
Time between first and last prescription: >5 years				
0–1 prescriptions	438	1886	1.00 (Ref)	1.00 (Ref)
2+ prescriptions	444	1691	1.19 (1.00–1.41)	0.92 (0.75–1.14)
No. of prescriptions				
2–9	106	457	1.05 (0.82–1.35)	0.88 (0.66–1.17)
10–19	79	259	1.38 (1.04–1.83)	1.14 (0.82–1.58)
20–39	80	345	1.05 (0.80–1.39)	0.81 (0.58–1.11)
≥40	179	630	1.31 (1.04–1.64)	0.95 (0.72–1.25)
P_{trend}			0.03	0.80

Abbreviations: CI = confidence interval; CPRD = Clinical Practice Research Datalink; OR = odds ratio.

[a] Using conditional logistic regression to account for matching.

[b] Using conditional logistic regression to account for matching, and additionally adjusted for body mass index, smoking status, alcohol-related disorders, hepatitis B or C virus infection, diabetes, rare metabolic disorders, and use of paracetamol, antidiabetic medications, and statins.

Table 3

Associations of NSAID subtypes with liver cancer risk, CPRD

	Cases (n = 1195) No.	Controls (n = 4640) No.	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
0–1 prescriptions of NSAIDs	438	1886	1.00 (Ref)	1.00 (Ref)
Aspirin	376	1294	1.35 (1.11–1.65)	1.11 (0.86–1.44)
COX–2 inhibitors (Coxibs)	68	245	1.42 (0.92–2.19)	0.98 (0.55–1.72)
Rofecoxib	35	119	1.13 (0.64–2.02)	0.84 (0.41–1.71)
Celecoxib	34	103	2.11 (1.12–3.97)	1.61 (0.74–3.53)
Etoricoxib	11	46	3.89 (1.16–13.1)	2.33 (0.38–14.3)
Propionic acid derivatives	335	1238	1.18 (0.97–1.43)	0.97 (0.76–1.24)
Ibuprofen	255	933	1.17 (0.94–1.46)	0.91 (0.70–1.20)
Naproxen	82	307	1.10 (0.78–1.57)	0.97 (0.63–1.49)
Ketoprofen	11	51	0.68 (0.25–1.86)	0.27 (0.07–0.99)
Tiaprofenic Acid	8	22	1.55 (0.39–6.21)	1.63 (0.31–8.48)
Fenamic acid derivatives	12	47	1.23 (0.53–2.84)	1.33 (0.52–3.39)
Mefenamic Acid	12	46	1.23 (0.53–2.84)	1.34 (0.52–3.42)
Acetic acid derivatives	328	1162	1.16 (0.95–1.41)	0.89 (0.70–1.14)
Diclofenac	281	1015	1.13 (0.91–1.39)	0.83 (0.64–1.09)
Indomethacin	47	120	1.30 (0.80–2.11)	1.08 (0.60–1.92)
Etodolac	5	40	0.72 (0.21–2.41)	0.47 (0.13–1.70)
Nabumetone	8	25	1.43 (0.34–5.93)	0.79 (0.17–3.74)
Enolic acid (Oxicam) derivatives	44	183	1.31 (0.80–2.13)	0.97 (0.53–1.77)
Piroxicam	16	72	0.77 (0.35–1.70)	0.57 (0.23–1.43)
Meloxicam	28	105	1.74 (0.94–3.21)	1.31 (0.62–2.75)

Abbreviations: CI = confidence interval; COX, cyclooxygenase; CPRD = Clinical Practice Research Datalink; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio.

[a] Using conditional logistic regression to account for matching.

[b] Using conditional logistic regression to account for matching, and additionally adjusted for body mass index, smoking status, alcohol-related disorders, hepatitis B or C virus infection, diabetes, rare metabolic disorders, and use of paracetamol, antidiabetic medications, and statins.

Table 4

Association of paracetamol use with liver cancer risk, CPRD

	Cases (n = 1195) No.	Controls (n = 4640) No.	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Paracetamol use				
0–1 prescriptions	579	2610	1.00 (Ref)	1.00 (Ref)
2+ prescriptions	616	2030	1.46 (1.27–1.68)	1.18 (1.00–1.39)
No. of prescriptions				
2–9	267	1054	1.21 (1.02–1.44)	1.05 (0.87–1.27)
10–19	109	299	1.78 (1.39–2.28)	1.39 (1.04–1.84)
20–39	87	281	1.56 (1.19–2.04)	1.20 (0.89–1.62)
≥40	153	396	2.03 (1.61–2.56)	1.48 (1.13–1.93)
P_{trend}			< 0.01	< 0.01
Recency of paracetamol use				
0–1 prescriptions	579	2610	1.00 (Ref)	1.00 (Ref)
Current paracetamol use	403	1179	1.66 (1.42–1.95)	1.30 (1.08–1.56)
No. of prescriptions				
2–9	108	389	1.31 (1.03–1.66)	1.09 (0.83–1.43)
10–19	78	199	1.90 (1.43–2.52)	1.48 (1.07–2.04)
20–39	75	236	1.59 (1.20–2.12)	1.23 (0.90–1.69)
≥40	142	355	2.09 (1.65–2.66)	1.51 (1.15–1.99)
P_{trend}			< 0.01	< 0.01
0–1 prescriptions	579	2610	1.00 (Ref)	1.00 (Ref)
Past paracetamol use	213	851	1.20 (1.00–1.44)	1.03 (0.84–1.27)
No. of prescriptions				
2–9	159	665	1.15 (0.94–1.41)	1.03 (0.82–1.29)
10–19	31	100	1.53 (1.01–2.33)	1.19 (0.73–1.94)
20–39	12	45	1.39 (0.72–2.65)	1.01 (0.48–2.12)
≥ 40	11	41	1.42 (0.72–2.81)	1.06 (0.47–2.39)
P_{trend}			0.21	0.79
Intensity of paracetamol use				
Time between first and last prescription: <2 years				

	Cases (n = 1195) No.	Controls (n = 4640) No.	Crude OR (95% CI)[a]	Adjusted OR (95% CI)[b]
0–1 prescriptions	579	2610	1.00 (Ref)	1.00 (Ref)
2+ prescriptions	118	413	1.31 (1.05–1.65)	1.15 (0.89–1.49)
No. of prescriptions				
2–9	99	386	1.19 (0.94–1.52)	1.05 (0.80–1.38)
10–19	15	24	2.85 (1.47–5.55)	2.22 (1.03–4.74)
20–39	4	3	5.23 (1.15–23.7)	4.47 (0.95–21.1)
≥ 40	0	0	NA	NA
P_{trend}			< 0.01	0.15
Time between first and last prescription: 2–5 years				
0–1 prescriptions	579	2610	1.00 (Ref)	1.00 (Ref)
2+ prescriptions	130	482	1.25 (1.00–1.56)	1.08 (0.85–1.38)
No. of prescriptions				
2–9	65	294	1.05 (0.79–1.40)	1.00 (0.73–1.37)
10–19	34	79	1.96 (1.28–2.99)	1.64 (1.00–2.68)
20–39	20	82	1.19 (0.72–1.97)	0.93 (0.54–1.60)
≥ 40	11	27	1.81 (0.87–3.73)	1.11 (0.50–2.49)
P_{trend}			0.05	0.69
Time between first and last prescription: >5 years				
0–1 prescriptions	579	2610	1.00 (Ref)	1.00 (Ref)
2+ prescriptions	368	1135	1.67 (1.40–1.99)	1.26 (1.03–1.54)
No. of prescriptions				
2–9	103	374	1.38 (1.07–1.77)	1.09 (0.82–1.44)
10–19	60	196	1.55 (1.13–2.13)	1.17 (0.82–1.68)
20–39	63	196	1.66 (1.22–2.28)	1.26 (0.88–1.81)
≥ 40	142	369	2.05 (1.61–2.62)	1.51 (1.14–2.00)
P_{trend}			< 0.01	0.01

Abbreviations: CI = confidence interval; CPRD = Clinical Practice Research Datalink; OR = odds ratio.

[a] Using conditional logistic regression to account for matching.

[b] Using conditional logistic regression to account for matching, and additionally adjusted for body mass index, smoking status, alcohol-related disorders, hepatitis B or C virus infection, diabetes, rare metabolic disorders, and use of nonsteroidal anti-inflammatory drugs, antidiabetic medications, and statins.