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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.

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1. 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

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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the UK's Clinical Practice Research Datalink (CPRD), a large medical records database.

2. Materials and methods

2.1. Data source

This nested case-control study was conducted using data from CPRD, a large, population-based, automated medical records 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).

2.2. 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.

2.3. 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 $\geq$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.

2.4. 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.

3. 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