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Aspirin and non-steroidal anti-inflammatory drug use and the risk of upper aerodigestive tract cancer

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Background: Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) are widely used as analgesics and preventative agents for vascular events. It is unclear whether their long-term use affects cancer risk. Data on the chemopreventative role of these drugs on the risk of the upper aerodigestive tract cancer (UADT) are insufficient and mostly refer to oesophageal cancer. The aim of this study was to investigate the effect of aspirin and other NSAIDs on the risk of UADT cancers.

Methods: A nested case–control study using the Primary Care Clinical Informatics Unit (PCCIU) database. Conditional logistics regression was used for data analysis.

Results: There were 2392 cases of UADT cancer diagnosed between 1996 and 2010 and 7165 age-, gender- and medical practice-matched controls from 131 general medical practices. Mean age of cases was 66 years (s.d. 12) and most were male (63%). Aspirin was prescribed in a quarter of cases and controls, COX-2 inhibitors in 4% of cases and 5% of controls and other NSAIDs in 33% of cases and 36% of controls. Aspirin prescription was associated with a nonsignificant risk reduction of cancer of UADT (adjusted OR = 0.9, 95% CI = 0.8, 1.0), head and neck (HN; adjusted OR = 0.9, 95% CI = 0.7, 1.1) or the oesophagus (adjusted OR = 0.8, 95% CI = 0.7, 1.0). Similar results were found for COX-2 inhibitors prescription. Prescription of other NSAIDs was associated with significantly reduced risk of cancer of UADT (adjusted OR = 0.8, 95% CI = 0.7, 0.9), HN (adjusted OR = 0.8, 95% CI = 0.7, 0.9) and the oesophagus (adjusted OR = 0.8, 95% CI = 0.7, 0.9). An increased volume of aspirin prescriptions was associated with a significant risk reduction (test for trend $P < 0.001$).

Conclusions: The decreased risk of cancer of the UADT associated with the use of non-COX-2 inhibitors, NSAIDs and long-term aspirin therapy warrants further exploration of the benefits *vs* risks of the use of these agents.

Cancer of the upper aerodigestive tract (UADT; oral cavity, pharynx, larynx and oesophagus combined) is, globally, the fourth most common cancer and cause of cancer mortality, with an estimated 1 033 004 incident cases and 712 489 deaths worldwide in 2008 (Ferlay *et al*, 2010). While a decrease in mortality was noted in the European Union (EU) overall between 1993 and 2004, a persistent rise was observed in central and eastern European countries (Garavello *et al*, 2010).

Major risk factors for UADT cancer are tobacco consumption, heavy alcohol drinking and poor nutrition, specifically lower fruit and vegetable consumption (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2004, 2010; Lagiou *et al*, 2009). Other possible risk factors include poor oral hygiene, alcohol in mouthwash and genetic factors (Warnakulasuriya, 2009).

Human papillomavirus (HPV) has been shown to have an aetiological role in head and neck cancers (which include oral cavity, oropharynx, hypopharynx and larynx) irrespective of tobacco and alcohol use (Mork *et al*, 2001) and may be responsible for the increase in incidence of oropharyngeal squamous cell carcinoma (Mehanna *et al*, 2010) in the United States between 1999 and 2006, United Kingdom between 1989 and 2006 whereas oropharyngeal cancer had the greatest rate of

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increase of any cancer in Scotland in 1987–2006 (Junor *et al*, 2010).

Recent analysis of individual patient data from randomised clinical trials of daily aspirin (Rothwell *et al*, 2011) showed a significant reduction in death due to cancer. Few studies have investigated the role of non-steroidal anti-inflammatory drugs (NSAIDs) specifically for UADT cancer (Bosetti *et al*, 2003; Friis *et al*, 2006; Macfarlane *et al*, 2012) and the results are not consistent. A recent systematic review of NSAIDs and aspirin use and risk of head and neck cancer did not derive a definitive conclusion, suggesting the need for further studies (Wilson *et al*, 2011).

The aim of this study was to investigate the effect of aspirin and other NSAIDs use on the risk of UADT cancers. Specific objectives were to investigate risk by cancer sub-site, duration of use and type of NSAIDs.

MATERIALS AND METHODS

We conducted a nested case–control study using the Primary Care Clinical Informatics Unit (PCCIU) (http://www.abdn.ac.uk/pcciu/) database, which contained information from a sample of general medical practices in Scotland.

The data set consists of complete copies of clinical data for all registered patients. The UK National Health Service (NHS) requires registration with a medical practice to access healthcare services. At the time of data extraction, participating practices systematically used electronic medical records for registration of patients, morbidity recording and prescriptions. The current data includes records up to October 2010 and covers around 15% of the Scottish population. The data set included age, sex and socio-economic status, and is representative of all the Scottish patients (Elder *et al*, 2007).

Ethical permission was not required as the data were anonymised and individuals could not be identified.

Cases and controls. Cases were defined as first time UADT cancer cases (oral cavity, oropharynx, hypopharynx, larynx and oesophagus) diagnosed in 1996 or later. Carcinoma *in situ* and cases aged <18 years at diagnosis were excluded. We used all the available eligible cases in the PCCIU database.

We aimed to identify three controls per case individually matched by age (within 5 years), gender, medical practice and duration of observation in the database, that is, controls should not have follow-up observation time less than cases. In addition, period of exposure considered for controls was truncated so that was not systematically longer than that for the matched controls. Index date for controls was selected from the date of diagnosis of matching cases. Controls aged <18 years at index date were excluded.

Both cases and controls with previous history of cancer were excluded (Dregan *et al*, 2012).

Definition of exposure. We identified prescriptions of oral aspirin, COX-2 inhibitors or other NSAIDs. Any prescriptions before 1990 (because after 1990 the prescriptions were more likely to have been generated electronically and therefore more complete and reliable) and any prescriptions within a year before the diagnosis or index date were disregarded. Topical NSAID preparations were excluded. List of other NSAIDs is shown in Appendix 1.

We defined patients as users if they had at least one prescription. Age at first and last prescription, time between last and first prescription, time between diagnosis and first and last prescriptions and total number of prescriptions were obtained. We also calculated the number of prescriptions per year as the total number of prescriptions divided by time between the last and first prescription.

Confounding factors. Additional data in the database were available on age, gender and practice deprivation (Carstairs index; Carstairs and Morris, 1989). Body mass index (BMI; at least 1 year before the diagnosis/index date) was calculated from height and weight, which were recorded in the database as well as self-reported smoking status and alcohol consumption. Information was obtained on previous history (at least 1 year before diagnosis/index date) of coronary heart disease (CHD), atrial fibrillation (AF), stroke and lipid-lowering medications. We also investigated the family history of cancer.

Statistical analysis. Conditional logistic regression was used to estimate odds ratios (ORs) with 95% confidence intervals (CIs). Stratified analysis was conducted using logistic regression adjusted for age, gender and clustering within practices. Crude ORs and adjusted for the potential confounding variables listed above were calculated. Continuous variables were categorised using median or tertiles of the overall distribution. The χ^2-test was used for comparison of proportions.

We investigated patterns of missing data and performed both complete data analysis and analysis using multiple imputation (MI). MI ($n=50$ imputations) was performed using MI procedure in STATA 13 (StataCorp LP, College Station, TX, USA, 2013) for smoking, alcohol consumption and BMI with age, gender and deprivation used in the imputation, separately for cases and controls, using chained logit model. Briefly, MI is a simulation-based approach for analysing incomplete data. MI procedure first replaces missing values with multiple sets of simulated values to complete the data, then applies standard analyses to each completed data set, and finally adjusts the obtained parameter estimates for missing-data uncertainty. The objective of MI is not to predict missing values as close as possible to the true ones but to handle missing data in a way resulting in valid statistical inference (Marchenko, 2011).

Propensity score was used to reduce the impact of selection bias and confounding. Briefly, propensity score is the probability of treatment assignment conditional on observed baseline characteristics (Austin, 2011). The propensity score allows analysis of observational (nonrandomised) studies so that it mimics some of the particular characteristics of a randomised controlled trial. Out of four available methods (matching on the propensity score, stratification on the propensity score, inverse probability of treatment weighting using the propensity score, and covariate adjustment using the propensity score) the inverse probability of aspirin treatment weighting was used. Propensity score (probability that patients had received aspirin prescription) was calculated from logistic regression model with aspirin prescription as outcome and potential confounding factors as predictors. Weight in the model for patients prescribed aspirin was the inverse of the propensity score values whereas the weight for patients not receiving aspirin prescription was the inverse of (1 − the propensity score).

Analysis was conducted using IBM SPSS Statistics version 21 (IBM Corp., Released 2012, Armonk, NY, USA) and STATA 13.

RESULTS

We identified 2392 cases of UADT cancer (1195 of HNC and 1197 oesophageal cancer) and 7165 controls from 131 general medical practices between 1996 and 2010. The majority (2381) of cases had three matched controls and 11 cases had two controls. Mean age of cases was 66 years (s.d. 12) and most were male (67%).

The proportion of incomplete data for BMI, smoking and alcohol was 43%, 24% and 35% respectively among cases and 38%, 23% and 34% respectively among controls. Complete data were

available for 1201 (50%) of cases and 3862 (54%) of controls. Among cases, complete data were available for 48% of HNC cases and for 52% of oesophageal cancer cases. Overall, there was no significant difference in data completeness by gender (χ^2 $P=0.511$), however, there was variation by age group ($P<0.001$) with the highest proportion of complete data in 66–75 years age group (57%) and the lowest in 18–55 age group (47%). There was a significant difference in data completeness by deprivation ($P<0.001$) with the highest completeness proportion in the highest deprivation category (59%). There was a significant difference ($P<0.001$) in data availability by stroke (65% *vs* 53%), CHD (67% *vs* 51%), aspirin prescription (71% *vs* 47%), COX-2 inhibitors (76% *vs* 52%) and other NSAIDs (68% *vs* 45%; data not shown).

Deprivation was strongly related to risk of UADT cancer (Table 1; OR = 2.3, 95% CI = 1.6, 3.2) in most deprived category compared with least deprived; test for trend $P<0.001$. Lower BMI was associated with increased risk of UADT cancer (OR = 2.6, 95% CI = 1.5, 4.3) in patients with BMI = 15.5–18.4 compared with BMI = 30–54; test for trend $P<0.001$. Individuals categorised as 'ever smokers' had a significantly higher risk of UADT cancer compared with 'never smokers' (Table 1; OR = 2.4, 95% CI = 2.1, 2.7). Individuals with a high level of alcohol consumption (OR = 1.7; 95% CI = 1.4, 2.1) were at greater risk of UADT cancer than low or non-alcohol consumers. History of CHD and stroke was associated with increased UADT cancer risk: OR = 1.2, 95% CI = 1.0, 1.4 and OR = 1.4, 95% CI = 1.1, 1.8, respectively. No association was found for history of AF (OR = 1.0, 95% CI = 0.8, 1.3), family history of cancer (OR = 1.1; 95% CI = 0.8, 1.5) or lipid-lowering drug prescription (OR = 1.0; 95% CI = 0.9, 1.2; Table 1).

Aspirin was prescribed in a quarter of cases and controls, COX-2 inhibitors were prescribed in 4% of cases and 5% of controls and other NSAIDs were prescribed in 33% of cases and 36% of controls (Table 2). Aspirin prescription was associated with nonsignificant reduction in risk of cancer of UADT (adjusted OR = 0.9, 95% CI = 0.8, 1.0), HN (adjusted OR = 0.9, 95% CI = 0.8, 1.2) and oesophagus (adjusted OR = 0.9, 95% CI = 0.7, 1.1; Table 2). Similar results were found for COX-2 inhibitors prescriptions. Prescription of other NSAIDs was associated with reduced risk of cancer of UADT (adjusted OR = 0.8, 95% CI = 0.7, 0.9), HN (adjusted OR = 0.8, 95% CI = 0.7, 0.9) and the oesophagus (adjusted OR = 0.8; 95% CI = 0.7, 0.9; Table 2). There was no significant difference in the above OR estimates between cancer of the head and neck and oesophagus ($P>0.05$; Table 2), therefore, these two sites were combined.

Aspirin prescription was significantly associated with older age, deprivation, BMI, smoking, alcohol consumption, history of CHD, AF, stroke and lipid-lowering drug prescription ($P<0.001$; data not shown in tables).

Further analysis of aspirin prescription (ever) showed no change in OR estimates when weighting by propensity score was used in the model (for UADT cancer OR = 0.9; 95% CI = 0.7, 1.0). Using multiple imputation and additional adjustment for BMI, smoking and alcohol consumption resulted in similar estimate (OR = 0.9; 95% CI = 0.8, 1.0; data not shown in tables).

When considering patients with complete data only, aspirin prescriptions were not associated with decreased risk of UADT cancer (OR = 1.0, 95% CI = 0.9, 1.2).

There was a significant reduction associated with aspirin prescriptions for females (OR = 0.7, 95% CI = 0.6, 0.9) but not for males (OR = 1.0, 95% CI = 0.9, 1.2; test for heterogeneity $P=0.019$; Table 3). There were no differences in OR estimates for aspirin by age, deprivation, BMI, smoking or alcohol (test for heterogeneity $P>0.05$; Table 3), however, significant risk reduction associated with aspirin prescriptions was observed among patients with missing data for BMI, smoking and alcohol (Table 3). There was no difference in estimates between males and females when multiple imputation and propensity score were used ($P>0.05$, data not shown in tables).

There was no significant reduction associated with UADT cancer risk for age at first and last aspirin prescription, time between last and first prescription, time between diagnosis and first and last prescription and number of prescriptions per year (Table 4). However there was a significant decrease in risk of UADT cancer with increased number of prescriptions (OR = 0.8, 95% CI = 0.6, 0.9) in those with total number of prescription between 29 and 147 compared with never prescription, test for trend $P=0.017$ (Table 4). This result was not significant when analysed separately for cancer of the head and neck and oesophageal cancer (OR = 0.77, 95% CI = 0.5, 1.1 and OR = 0.81, 95% CI = 0.6, 1.1, respectively; data not shown in tables).

DISCUSSION

This first large Scotland-based general practice-derived case–control study showed a decrease in risk of UADT cancer with a high volume of aspirin prescriptions, that is, >29, as well as with the prescription of other NSAIDs (not COX-2 inhibitors). The majority of the UK population is registered with a general medical practice; therefore these results are likely to be representative of the general population.

While our study overall did not show a significant association between ever aspirin prescription and risk of UADT cancer, when considered by total number of prescriptions, aspirin was associated with a reduced risk of UADT cancer for high total number of prescriptions and ever use of other NSAIDs. This finding supports results of a review of aspirin and cancer risk (Wilson *et al*, 2011), which showed that aspirin use was associated with a reduced risk of cancer of the oesophagus and multicentre study of UADT cancer, which showed that regular aspirin use (at least once a week for a year) was not associated with risk of UADT cancer overall but was associated with a reduced risk for cancer of oesophagus (OR = 0.5, 95% CI = 0.3–0.9), hypopharynx (OR = 0.5, 95% CI = 0.3–1.0) and larynx (OR = 0.7, 95% CI = 0.5–1.0; Macfarlane *et al*, 2012).

Analysis of individual patient data from eight randomised trials of daily aspirin *vs* no aspirin (Rothwell *et al*, 2011) showed a significant reduction in death due to cancer (OR = 0.8, 95% CI = 0.7, 0.9). There were no data reported specifically on head and neck cancer, but there was a nonsignificant decrease in risk of death due to oesophageal cancer (hazard ratio (HR) = 0.8 (95% CI = 0.3, 2.2) for 0–5 years of follow-up and HR = 0.43 (95% CI = 0.1, 1.7) for 5 years follow-up or longer). The overall protective effect of aspirin was more evident for adenocarcinomas (HR = 0.5, 95% CI = 0.4, 0.8 for 5 years of follow-up or longer). The protective effect of aspirin in this combined analysis did not appear to increase at doses >75 mg daily.

Biologically, aspirin and other NSAIDs suppress the production of prostaglandins and thromboxanes by irreversible inactivation of the cyclooxygenase (COX) enzyme which is involved in the mechanism of carcinogenesis (Thun *et al*, 2002). Other mechanisms include the induction of apoptosis through COX-independent pathways, the inhibition of NFjb factor and the upregulation of tumour suppression genes (Hernández-Díaz and García Rodríguez, 2007).

We have evaluated aspirin and other NSAIDs separately and found stronger chemopreventive effect of other NSAIDs for both HNC and oesophageal cancer. It was suggested that different types of NSAIDs might have different effects due to residual confounding and biological mechaisms (Hernández-Díaz and García Rodríguez, 2007; Vinogradova *et al,* 2011).

Table 1. Relationship between socioeconomic, behavioural and medical factors and risk of UADT cancer

Characteristics	Cases $n=2392$ N (%)	Controls $n=7176$ N (%)	OR (95% CI)[a] Test for trend P-value
Carstairs deprivation category			
1 (Least deprived)	94 (3.9)	365 (5.1)	1.00
2	199 (8.3)	665 (9.3)	1.19 (0.85, 1.67)
3	404 (16.9)	1356 (18.9)	1.20 (0.89, 1.61)
4	785 (32.8)	2294 (32.0)	1.56 (1.18, 2.06)
5	380 (15.9)	1043 (14.6)	1.73 (1.28, 2.34)
6	259 (10.8)	738 (10.3)	1.80 (1.30, 2.51)
7 (Most deprived)	271 (11.3)	704 (9.8)	2.26 (1.59, 3.22)
			$P<0.001$
Body mass index			
30.0–54.0	260 (19.1)	1051 (23.7)	1.00
25.0–29.9	520 (38.1)	1832 (41.4)	1.13 (0.94, 1.35)
18.5–24.9	552 (40.4)	1498 (33.8)	1.42 (1.18, 1.71)
15.5–18.4	33 (2.4)	49 (1.1)	2.55 (1.52, 4.28)
Missing	1027	2735	$P<0.001$
Smoking			
Never	453 (24.9)	2411 (43.7)	1.00
Ever	1370 (75.1)	3109 (56.3)	2.40 (2.10, 2.73)
Missing	569	1645	
Alcohol consumption			
No	329 (21.1)	1033 (21.8)	1.00
Low (within recommended limits)	884 (56.8)	3057 (64.6)	0.89 (0.75, 1.04)
High (above recommended limits)	344 (22.1)	645 (13.6)	1.70 (1.37, 2.11)
Missing	835	2430	
Coronary heart disease (at least 12 months before diagnosis/index date)			
No	2007 (83.9)	6156 (85.9)	1.00
Yes	385 (16.1)	1009 (14.1)	1.18 (1.04, 1.35)
Atrial fibrillation (at least 12 months before diagnosis/index date)			
No	2305 (96.4)	6911 (96.4)	1.00
Yes	87 (3.6)	254 (3.6)	1.02 (0.80, 1.32)
Stroke (at least 12 months before diagnosis/index date)			
No	2293 (95.9)	6946 (96.9)	1.00
Yes	99 (4.1)	219 (3.1)	1.38 (1.08, 1.76)
Family history of cancer			
No	2341 (97.9)	7020 (98.0)	1.00
Yes	51 (2.1)	145 (2.0)	1.06 (0.76, 1.48)
Lipid-lowering drug prescription (at least 12 months before diagnosis/index date)			
Never	1943 (81.2)	5832 (81.4)	1.00
Ever	449 (18.8)	1333 (18.7)	1.01 (0.89, 1.15)

Abbreviations: CI = confidence interval; OR = odds ratio; UADT = upper aerodigestive tract cancer.
[a]From conditional logistic regression (unadjusted).

With respect to methodological quality, the study included cancers over several sites in the UADT. No information was available regarding the histological subtype or cancer stage. While these are a heterogeneous group of neoplasms, they have similar aetiologies: regular alcohol consumption and tobacco smoking (Lagiou *et al*, 2009; IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2010). To investigate potential aetiological differences, we conducted additional analyses separately for head and neck cancer and cancer of the oesophagus and did not find significant differences in risk estimates.

Matching controls on sex, age, medical practice and index date removed effects from these confounding factors.

NSAID exposure was measured in terms of prescriptions issued. In the current study we did not have information on dose or indication for use of aspirin or other NSAIDs. The issue of a prescription does not mean that the medicine was actually used.

Table 2. NSAID prescription and UADT cancer risk

	All UADT cancers			Head and Neck cancer			Oesophageal cancer			
Prescription	Cases $n=2392$ *N* (%)	Controls $n=7165$ *N* (%)	OR (95% CI)[a]	Cases $n=1195$ *N* (%)	Controls $n=3580$ *N* (%)	OR (95% CI)[a]	Cases $n=1197$ *N* (%)	Controls $n=3585$ *N* (%)	OR (95% CI)[a]	*P*-value[b]
Aspirin										
Never	1798 (75.2)	5397 (75.3)	1.00	936 (78.3)	2862 (79.9)	1.00	862 (72.0)	2535 (70.7)	1.00	
Ever	594 (24.8)	1768 (24.7)	0.90 (0.78, 1.04)	259 (21.7)	718 (20.1)	0.93 (0.76, 1.15)	335 (28.0)	1050 (29.3)	0.87 (0.72, 1.05)	0.122
COX-2										
Never	2289 (95.7)	6783 (94.7)	1.00	1150 (96.2)	3403 (95.1)	1.00	1139 (95.2)	3380 (94.3)	1.00	
Ever	103 (4.3)	382 (5.3)	0.84 (0.67, 1.06)	45 (3.8)	177 (4.9)	0.80 (0.56, 1.13)	58 (4.9)	205 (5.7)	0.88 (0.64, 1.21)	0.620
Other NSAID										
Never	1612 (67.4)	4563 (63.7)	1.00	817 (68.4)	2314 (64.6)	1.00	795 (66.4)	2249 (62.7)	1.00	
Ever	780 (32.6)	2602 (36.3)	0.83 (0.75, 0.93)	378 (31.6)	1266 (35.4)	0.82 (0.70, 0.96)	402 (33.6)	1336 (37.3)	0.84 (0.73, 0.98)	0.825

Abbreviations: CHD = coronary heart disease; CI = confidence interval; COX-2 = cyclooxygenase-2; HNC = head and neck cancer; NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; UADT = upper aerodigestive tract cancer.
[a]From conditional logistic regression adjusted for deprivation, CHD, stroke, aspirin, COX-2 inhibitors and other NSAID.
[b]*P*-value to test the null hypothesis of no difference in estimates between HNC and oesophageal cancer.

Questionnaire-based study conducted in UK general medical practices which compared prescribed NSAIDs and described by patients reported mean (s.d.) compliance (percentage of intended dose taken) of 0.73 (0.55) for ibuprofen, 0.76 (0.56) for diclofenac and 0.76 (0.55) for Naproxen (Hawkey *et al*, 2000). It is unlikely, however, that non-adherence would differ systematically between cases and controls in our study.

The results will not have been influenced by recall bias because prescriptions were recorded prospectively before the index date. No data were available regarding the use of over-the-counter medications, which contain aspirin and NSAIDs, and this will have underestimated exposure to these medicines. COX-2 inhibitors can only be obtained by prescription in the UK. However the reported prevalence of aspirin prescription is comparable to prevalence of self-reported aspirin use in other studies conducted in the UK (Macfarlane *et al*, 2012; 22% in cases and 26% in controls).

Hernández-Díaz and García Rodríguez (2007) in the study of NSAIDs and risk of lung cancer performed a sensitivity analysis to quantify the impact of misclassification due to unrecorded over-the-counter use or to noncompliance. They concluded that the protective effect could not be explained by the unrecorded use. Yood *et al* (2007) concluded from their sensitivity analysis that prescription data can give valid estimates of association even though some of the drugs are available over the counter.

Prescriptions for cases before diagnosis could relate to early cancer symptoms before the recorded diagnosis. However we excluded any prescriptions within 1 year of diagnoses.

We defined ever users as those with at least one prescription. Another study of prescriptions (Vinogradova *et al,* 2011) similarly defined users as those with at least one prescription, whereas Friis *et al* (2006) defined users as those with two or more prescriptions. Studies which collected information using questionnaires defined users as those who ever took aspirin before the onset of illness (Jayaprakash *et al,* 2006) or as regular users (use at least once a week for a year; Macfarlane *et al,* 2012). In our study, among ever users cases and controls, there were 11% and 12% with only one prescription, respectively. Defining users as those with at least two prescriptions resulted in adjusted OR of 0.87 (0.78, 1.55) which is similar to our estimates when users were defined as those with at least one prescription.

We adjusted for potential confounders such as deprivation, BMI, smoking, alcohol consumption, medical history and family history of cancer. However the quality of some of this information was poor. For example, there was a large amount of missing data and inconsistency in recording of smoking and alcohol consumption. In addition, we did not have information on other risk factors for UADT, such as poor nutrition (especially low fruit and vegetable consumption), history of HPV infection, poor oral hygiene and genetic factors. However, analyses of US healthcare utilisation data sets indicate that these potential confounders have limited influence in studies of NSAID use and various health outcomes (Schneeweiss *et al*, 2005). Analysis of the relationship between confounding factors and UADT cancer in our study showed similar association. For example, increased risk was associated with increased deprivation (Conway *et al*, 2010), low BMI (Gaudet *et al*, 2010), smoking (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2004) and alcohol consumption (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2010). We also used multiple imputation to replace the missing values for confounding factors.

Systematic review of observation studies of NSAIDs use and upper gastrointestinal tract bleeding and perforation (Hernández-Díaz and Rodríguez, 2000) showed an increased pooled relative risk of 3.8 (95% CI = 3.6, 4.1). However Rothwell *et al* (2012) in the study of individual patient data from 51 randomised trials of short-term effects of daily aspirin on cancer incidence, mortality and non-vascular death showed that the reduced risk of major vascular events was initially offset by an increased risk of major bleeding, but effects on both outcomes diminished with increasing follow-up, leaving only the reduced risk of cancer from 3 years onwards. Case-fatality from major extracranial bleeds was also lower on aspirin than on control (OR = 0 · 32, 95% CI = 0 · 12–0 · 83).

The incidence of oral cancer is increasing in many countries (Jemal *et al*, 2010; Chaturvedi *et al*, 2013) and the lack of efficient therapy and the considerable associated morbidity and mortality make chemoprevention a realistic possibility (Jemal, 2012), particularly since this might be targeted to high-risk individuals with leukoplakia or other precursor lesions (Nelson, 2006). NSAIDs have shown promise as chemopreventive agents for oral cancer in experimental studies (Goodin and Shiff, 2004). Further

Table 3. Aspirin use and UADT cancer risk by demographic and behavioural factors

Characteristics	OR (95% CI) Test for heterogeneity *P*-value
Gender	
M	1.02 (0.86, 1.22)[a]
F	0.72 (0.56, 0.91)
	P = 0.019
Age (years)	
18–55	0.78 (0.46, 1.32)[b]
56–65	0.91 (0.68, 1.21)
66–75	0.96 (0.77, 1.19)
76 +	0.81 (0.64, 1.02)
	P = 0.269
Carstairs deprivation category	
1 (Least deprived)	0.90 (0.45, 1.77)
2	0.86 (0.53, 1.41)[b]
3	0.94 (0.69, 1.40)
4	0.87 (0.68, 1.10)
5	0.77 (0.55, 1.08)
6	1.14 (0.78, 1.69)
7 (Most deprived)	0.85 (0.57, 1.27)
	P = 0.438
Body mass index	
30.0–54.0	1.08 (0.77, 1.50)[b]
25.0–29.9	1.32 (1.02, 1.71)
18.5–24.9	0.88 (0.66, 1.17)
15.5–18.4	0.75 (0.13, 4.26)
	P = 0.164
Missing	0.65 (0.51, 0.84)
Smoking	
Never	1.00 (0.76. 1.32)[b]
Ever	0.88 (0.74, 1.05)
	P = 0.108
Missing	0.54 (0.37, 0.79)
Alcohol consumption	
No or low(within recommended limits)	0.97 (0.82, 1.15)[b]
High (above recommended limits)	0.92 (0.62, 1.37)
	P = 0.978
Missing	0.74 (0.56, 0.97)

Abbreviations: CHD = coronary heart disease; CI = confidence interval; F = female; M = male; NSAID = non-steroidal anti-inflammatory drug; OR = odds ratio; UADT = upper aerodigestive tract cancer.
[a]From conditional logistic regression adjusted for deprivation, CHD, stroke and other NSAIDs.
[b]From unconditional logistic regression adjusted for age, gender, deprivation, CHD, stroke and other NSAIDs taking into account aggregation within medical practices.

Table 4. Aspirin prescription and UADT cancer risk

Characteristics[a]	Cases *n* = 2392 *N* (%)	Controls *n* = 7165 *N* (%)	OR (95% CI)[b]	Test for trend (*P*-value)
Age at first prescription (years)				
Never	1798 (75.2)	5397 (75.3)	1.00	0.112
26–61	181 (7.6)	539 (7.5)	0.84 (0.68, 1.04)	
62–70	216 (9.0)	625 (8.7)	0.90 (0.74, 1.09)	
71–93	197 (8.2)	604 (8.5)	0.87 (0.70, 1.08)	
Age at last prescription (years)				
Never	1798 (75.2)	5397 (75.3)	1.00	0.185
27–66	176 (7.4)	577 (8.0)	0.76 (0.62, 0.93)	
67–74	210 (8.8)	557 (7.8)	1.05 (0.85, 1.28)	
75–98	208 (8.7)	634 (8.9)	0.84 (0.67, 1.05)	
Time between last and first prescription (years)				
Never	1798 (75.2)	5397 (75.3)	1.00	0.102
< 1.5	187 (7.8)	586 (8.2)	0.86 (0.71, 1.04)	
1.6–5.3	203 (8.5)	591 (8.3)	0.89 (0.73, 1.09)	
5.4–19.2	204 (8.5)	591 (8.3)	0.86 (0.69, 1.06)	
Time between diagnosis and first prescription (years)				
Never	1798 (75.2)	5397 (75.3)	1.00	0.061
1–3	199 (8.3)	574 (8.0)	0.91 (0.75, 1.09)	
4–6	159 (6.6)	497 (7.0)	0.84 (0.68, 1.04)	
7–20	236 (9.9)	697 (9.7)	0.85 (0.70, 1.04)	
Time between diagnosis and last prescription (years)				
Never	1798 (75.2)	5397 (75.3)	1.00	0.300
> 1	445 (18.6)	1365 (19.1)	0.83 (0.71, 0.97)	
2–14	149 (6.2)	403 (5.6)	0.99 (0.81, 1.23)	
Total number of prescriptions				
Never	1798 (75.2)	5397 (75.3)	1.00	0.017
1–7	202 (8.4)	571 (8.0)	0.95 (0.79, 1.15)	
8–28	198 (8.3)	603 (8.4)	0.83 (0.68, 1.01)	
29–147	194 (8.1)	594 (8.3)	0.79 (0.64, 0.99)	
Average number of prescriptions per year[c]				
Never	1798 (75.2)	5397 (75.3)	1.00	0.122
0.4–4	155 (6.5)	443 (6.2)	0.88 (0.70, 1.09)	
5–7	207 (8.7)	642 (9.0)	0.82 (0.67, 1.00)	
8–40	232 (9.7)	683 (9.5)	0.90 (0.75, 1.07)	

Abbreviations: BMI = body mass index; CHD = coronary heart disease; CI = confidence interval; F = female; M = male; OR = odds ratio; UADT = upper aerodigestive tract cancer.
[a]Categories created from continuous variable using median or tertiles of the overall distribution.
[b]From conditional logistic regression adjusted for deprivation, BMI (<25), smoking (ever), alcohol consumption (high), CHD, stroke.
[c]Total number of prescriptions divided by time between last and first prescription.

exploration of the benefits *vs* risks of the use of these agents is needed.

CONCLUSION

There is evidence of decreased risk of UADT cancer associated with the use of NSAIDs (non-COX-2 inhibitors) and number of aspirin prescriptions. These findings are important and should be a priority for further investigation using major studies and other data sources.

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AUTHOR CONTRIBUTIONS

TVM had the original idea for this study, contributed to the study design, undertook all the statistical analyses and wrote the first draft of the paper. MCW and KL contributed to the development of the idea, design and interpretation and worked on further drafts of the paper.

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APPENDIX 1	
Aceclofenac	Lederfen
Acemetacin	Lodine
Arthrotec	Mefenamic acid
Azapropazone	Meloxicam
Brexidol	Mobic
Brufen	Mobiflex
Caprin	Motifene
Clinoril	Motrin
Co-codaprin	Nabumetone
Codafen continus	Napratec
Dexketoprofen	Naprosyn
Diclofenac	Naproxen
Diclomax	Nycopren
Diflunisal	Oruvail
Dolobid	Piroxicam
Etodolac	Ponstan
Feldene	Preservex
Fenbid	Relifex
Fenbufen	Rheumox
Fenoprofen	Rhumalgan CR
Flurbiprofen	Sulindac
Froben	Surgam
Froben-p42	Synflex
Ibuprofen	Tenoxicam
Indomax SR	Tiaprofenic acid
Indometacin	Volsaid retard
Keral	Voltarol
Ketoprofen	