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Aspirin and other non-steroidal anti-inflammatory drug prescriptions and survival after the diagnosis of head and neck and oesophageal cancer

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ABSTRACT

Background: Aspirin and other NSAIDs are widely used as analgesics and the former is a preventative agent for vascular events. It is unclear whether their long-term use affects cancer risk. Data on the chemopreventative role of these drugs on the mortality in patients with upper aerodigestive tract cancer (UADT) are insufficient. The aim of this study was to investigate the effect of aspirin and other NSAIDs on survival in UADT cancer patients.

Methods: An observational cohort study of patients with UADT cancer was undertaken using Primary Care Clinical Informatics Unit (PCCIU) database of electronic medical records in Scotland. Information was available on all prescriptions of aspirin and other NSAIDs before and after diagnosis. The main outcome measure was all-cause mortality. Cox regression was used for statistical data analysis.

Results: There were 2392 patients diagnosed with UADT cancer between 1996 and 2010. Mean age of patients was 66 years (SD 12) and most were male (63%). Median survival in head and neck (HNC) patients was 94 months, while median survival in oesophageal cancer patients was 10 months. For HNC improved survival was observed with aspirin prescription (ever vs never hazard ratio (HR) 0.56 95% Confidence Interval (CI) 0.44, 0.71), there was no association with Cyclooxygenase 2 Inhibitors (COX-2) prescriptions. Improved survival was observed with other NSAIDs prescription (ever vs never HR 0.74 95% CI 0.60, 0.90). For oesophageal cancer patients, improved survival was observed with aspirin prescriptions (ever vs never HR 0.54 95% CI 0.45, 0.64), COX-2 prescriptions (HR 0.78 95% CI 0.62, 0.98) and other NSAIDs (HR 0.67 95% CI 0.56, 0.80).

Conclusions: Aspirin and other NSAIDs prescriptions after diagnosis are associated with a reduced all-cause mortality in UADT cancer patients.

Introduction

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 over million incident cases and over 700,000 deaths worldwide [1]. 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 [2]. European mean age-standardised 5-year relative survival was 39.9% for Head and Neck Cancer (HNC) and 12.4% for cancer of the oesophagus [3].

Prophylactic aspirin has been considered to be beneficial in reducing the risks of heart disease and cancer. Previous research showed the decreased risk of cancer of the UADT associated with the use of non-COX-2 inhibitors, NSAIDs and long-term aspirin therapy [4,5]. Analysis of individual patient data from randomised clinical trials of daily aspirin [7] showed a significant reduction in death due to cancer, however there were no data reported in this study on HNC. Observational study by Rachidi et al. [6] showed that post-diagnosis treatment of patients with head and neck squamous cell carcinoma with antiplatelet medications (including aspirin and other NSAIDs) was associated with better prognosis.

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.

2. Material and methods

An observational cohort study of patients with UADT cancer was undertaken using Primary Care Clinical Informatics Unit (PCCIU) database of electronic medical records in Scotland (http://

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www.abdn.ac.uk/pcciu/). PCCIU Research database includes data from more than 200 participating medical practices and approximately one million patients. Data reflect the computerized clinical record, including appointments, repeat and acute prescribing, call/recall, and screening. Ethical permission was not required as the data were anonymised and individuals could not be identified.

Patients with first time UADT cancer (oral cavity, oropharynx, hypopharynx, larynx and oesophagus) diagnosed in 1996 or later were identified using READ codes (http://systems.hscic.gov.uk/data/uktc/readcodes) as described in Table 1. Carcinoma in situ and patients aged <18 years at diagnosis were excluded. We used all the available eligible patients in the PCCIU database. Participants with cancer diagnosis before diagnosis with UADT cancer were excluded (READ codes B0%, B1%, B2%, B3%, B4%, B5%, B6%, B9%, BA%, BB%, By%).

Participants entered the study on the date of UADT cancer diagnosis and exited the study on the date of last appointment at their medical practice, date of deregistration with the practice or date of death. There was no information on cause of death.

To measure exposure, we identified prescriptions of oral aspirin, Cyclooxygenase 2 Inhibitors (COX-2) or other NSAIDs. Additional data in the database were available on patients' age at diagnosis, gender, practice deprivation (Carstairs index) [8], self-reported smoking status before diagnosis (never/ever) and most recent alcohol consumption (high consumption was defined as above the recommended limit of 2-3 units a day for women and 3–4 units a day for men). Information was also obtained on history of coronary heart disease (CHD), atrial fibrillation (AF) and stroke.

Analysis was conducted using IBM SPSS Statistics version 21 (IBM Corporation 2012) and STATA 13 (StataCorp LP, College Station, TX, USA 2013). We used Kaplan–Meier analysis to illustrate survival graphically and Log Rank test (Mantel–Cox) to test for equality of survival distributions for different levels of medication use.

Hazard ratios (HRs) with 95% confidence intervals (CIs) adjusted for the potential confounding factors (age, gender, deprivation, smoking and alcohol consumption) were estimated using Cox regression model. Proportional hazards assumption was tested using *stphtest* and *stphplot* procedures in STATA. Continuous variables were categorised using median or tertiles of the overall distribution as appropriate. Age was *a priori* categorised as following: 18–55, 56–65, 66–75 and 76–99 years. Multiple

Table 1
Description of patients with UADT cancer included in the study.

READ code	Site Malignant neoplasm	Head and neck cancer ($n = 1195$) *N* (%)	Oesophagus ($n = 1197$) *N* (%)
B0...	Lip, oral cavity and pharynx	100 (4.2)	
B01	Tongue	143 (6.0)	
B03	Gum	4 (.2)	
B04	Floor of mouth	51 (2.1)	
B05	Other & unspecified parts of mouth	87 (3.6)	
B06	Oropharynx	123 (5.1)	
B08	Hypopharynx	47 (2.0)	
B0z	Other and ill-defined sites within the lip, oral cavity and pharynx	161 (6.7)	
B21	Larynx	423 (17.7)	
B901	Neoplasm of uncertain behaviour of lip, oral cavity and pharynx	40 (1.7)	
B906	Neoplasm of uncertain behaviour of larynx	16 (.7)	
B10	Oesophagus		387 (16.2)
B100	Cervical oesophagus		3 (.1)
B101	Thoracic oesophagus		2 (.1)
B102	Abdominal oesophagus		12 (.5)
B104	Middle third of oesophagus		1 (.04)
B105	Lower third of oesophagus		29 (1.2)
B10y	Other specified part of oesophagus		1 (.04)
B10z	Oesophagus not otherwise specified		762 (31.9)
Age at diagnosis (years)			
Mean (SD)		62.3 (11.9)	69.3 (11.4)
Min, max		20, 95	25, 99
Gender			
M		839 (70.2)	771 (64.4)
F		356 (29.8)	426 (35.6)
Duration of follow up (months)			
Median (IQR)		34.9 (64.1)	9.0 (15.9)
Min, max		1, 181	1, 181
Follow up data for at least 12 months			
N (%)		919 (76.9)	470 (32.3)
Mortality			
N (%)		509 (42.6)	965 (80.6)
Survival (months)			
Median (95% CI)		94 (78, 120)	10 (9, 11)

IQR—interquartile range.