Title:

Medications that relax the lower oesophageal sphincter and risk of oesophageal cancer: an analysis of two independent population-based databases

Short title:

Lower oesophageal sphincter relaxation and cancer risk

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Medications that decrease lower oesophageal sphincter pressure (benzodiazepines, calcium channel blockers, nitrates, xanthines and β2 agonists) increase acid reflux, an oesophageal adenocarcinoma risk factor. Previous studies of associations between these medications and cancer risk have reached inconsistent conclusions, potentially reflecting limited power. We conducted the largest study yet using two independent datasets. Medications that decrease sphincter pressure were not associated with increased oesophageal cancer, apart from β2 agonists. The β2 agonist association merits further investigation.

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ABSTRACT

Excessive lower oesophageal sphincter relaxation increases gastro-oesophageal acid reflux, an oesophageal adenocarcinoma risk factor. Medications that relax this sphincter (benzodiazepines, calcium channel blockers, nitrates, β2 agonists and xanthines) could promote cancer. These medications were investigated in two independent datasets. In the Scottish Primary Care Clinical Informatics Unit (PCCIU) database, a nested case-control study of oesophageal cancer was performed using GP prescription records. Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CIs) for medication use and oesophageal cancer. In UK Biobank, a cohort study was conducted using self-reported medication use. Cox regression was used to calculate hazard ratios (HRs) and 95% CIs for medication use and oesophageal cancer, and by tumour subtype. Overall, 1,979 oesophageal cancer patients were matched to 9,543 controls in PCCIU, and 355 of 475,768 participants developed oesophageal cancer in UK Biobank. None of the medications investigated were significantly associated with oesophageal cancer risk apart from β2 agonists, which were associated with increased oesophageal cancer risk in PCCIU (adjusted OR 1.38, 95% CI 1.12, 1.70) but not in UK Biobank (adjusted HR 1.21, 95% CI 0.70, 2.08). Medications that relax the lower oesophageal sphincter were not associated with oesophageal cancer, apart from β2 agonists. This increased cancer risk in β2 agonist users merits further investigation.

INTRODUCTION

Oesophageal cancer is the eighth most common cancer worldwide, accounting for 400,000 deaths each year.[1] Over recent decades survival from oesophageal cancer has remained poor (12% 5-year survival rate in Europe).[2]

Prolonged relaxation of the lower oesophageal sphincter results in increased gastro-oesophageal reflux,[3] a known risk factor for oesophageal adenocarcinoma.[4] Although the relationship between lower oesophageal sphincter tone and squamous cell carcinoma is less clearly established, non-acid gastro-oesophageal reflux has been associated with this cancer subtype.[5,6] Through smooth muscle relaxation mechanisms, several commonly used medications have been shown to relax the lower oesophageal sphincter, including benzodiazepines, calcium channel blockers, nitrates, β2 agonists and xanthines,[7–12] with the greatest reduction in pressure being caused by β2 agonists (30%).[10] Millions of these medications are prescribed each year for conditions such as anxiety, hypertension, angina and asthma, respectively.[13,14]

However, few epidemiological studies have explored the relationship between these medications and oesophageal cancer. Where studied, statistical power has been limited, as shown in a recent meta-analysis of these medications and oesophageal cancer risk, which included benzodiazepines (total of 406 cases), calcium channel blockers (total of 875 cases), nitrates (total of 980 cases), β2 agonists (total of 1,291 cases) and xanthines (total of 984 cases).[15–19] Additionally, three of these studies relied upon self-reported medication use, and are therefore prone to recall bias.[16,17,19] Furthermore, these studies have observed inconsistent results for some medications,

for example xanthines (specifically, theophylline).[17–19] Given the widespread use of these medications it is a priority to establish if they increase oesophageal cancer risk.

We conducted two large independent population-based studies from Scotland and England to explore the association between medications that reduce lower oesophageal sphincter tone and the risk of developing oesophageal cancer.

METHODS

PCCIU: Data source

The Primary Care Clinical Informatics Unit Research (PCCIU) database contains computerised GP records including clinical diagnoses and prescriptions for approximately 15% of Scotland.[20] The PCCIU contains over two million patients registered at 393 Scottish GPs. Access to the PCCIU data was approved by the Research Applications and Data Management Team, University of Aberdeen. Ethical approval for the PCCIU analysis was obtained from the School of Medicine, Dentistry and Biomedical Sciences Research Ethics Committee at Queen's University Belfast (reference number: 15.43).

PCCIU: Study design

A nested case-control study was conducted with cases defined as patients with a first ever diagnosis of oesophageal cancer (Read code category: B10) between January 1999 and April 2011. Up to five controls were randomly selected for each case matched on age, gender, year of diagnosis and general practice (GP). The index date for the cases was defined as the date of diagnosis of oesophageal cancer. The index date for the controls was the diagnosis date of their matched case. The start of the exposure period was the latest of 1st January 1996 (as prescriptions prior to this were less likely to have been electronically recorded) or the date of patient registration at a GP practice. Additionally, the start of the exposure period was truncated to the latest start date within each matched set of a case and controls to ensure all members of the matched set had an identical length of exposure period, removing the risk of time-window bias.[21] Cases and controls with a previous cancer diagnosis (other than non-

melanoma skin cancer), and those with less than three years of prescription records prior to index date, were excluded. The end of the exposure period was one year prior to the index date to avoid reverse causation due to increased exposure to healthcare professionals following symptoms of cancer.

PCCIU: Exposure data

The medication groups of interest were those that relax the lower oesophageal sphincter: benzodiazepines, calcium channel blockers, nitrates, β2 agonists and xanthines. Supplementary Table 1 contains a list of medications included which were identified from the British National Formulary (71st edition).[13] Medication use was determined from GP prescription records).

PCCIU: Confounders

Confounders were identified from GP records in the exposure period defined above. Based on the Charlson index,[22] twelve comorbidities were identified using GP diagnosis codes (including acute myocardial infarction, congestive cardiac failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease [COPD], connective tissue disease, peptic ulcer disease, diabetes mellitus, rheumatoid arthritis, chronic kidney disease and liver disease). Lifestyle risk factors for oesophageal cancer including smoking (never smoker, ex-smoker or current smoker), alcohol consumption (none, low [e.g., moderate or light drinker], or high intake [e.g., above recommended limits, chronic alcoholism]) and obesity (obese [BMI>30] or not obese) were extracted from GP records. Postcode of the GP practice was used to assign deprivation fifths using the Scottish Index of Multiple Deprivation.[23] Aspirin and statin use within the exposure period was identified, as

inverse associations have been shown with oesophageal cancer.[24,25]

PCCIU: Statistical analysis

We calculated descriptive statistics, comparing the demographics and clinical characteristics of cases and controls. Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for the association between medication use (in the exposure period) and risk of oesophageal cancer. In the main analysis, the matched design accounted for age, gender, general practice and year of diagnosis, with additional adjustments made for comorbidities (as described), and aspirin and statin use. As the patients were matched on general practice, they were inherently matched on deprivation level, as the available deprivation measure was based upon the address of their GP practice. In the main analysis for respiratory-based medications studied (β2 agonists and xanthines) additional adjustment for steroid-based inhaler medication were conducted, but a sensitivity analysis was also added not adjusting for these medications to avoid the potential for over-adjustment. Analyses were repeated by number of prescriptions and by medication (restricted to medications prescribed to at least 1% of the patients in the analysis) (Supplementary Table 1).

A sensitivity analysis was conducted additionally adjusting for lifestyle factors (smoking, alcohol and obesity) using both a complete case approach and multiple imputation. The imputation used ordered logit models with age, gender and deprivation, separately for cases and controls. Multiple imputation with chained equations is a simulation-based approach for handling missing data which can lead to valid statistical inferences.[26] Sensitivity analyses were also conducted investigating

the impact of excluding prescriptions in the two years prior to the index date and defining medication users as patients with at least three prescriptions. Finally, we repeated the analysis combining gastric cancer (based upon Read code category B11) and oesophageal cancers as GPs could have misclassified junctional oesophageal carcinomas as gastric cancer.[27]

UK Biobank: Data source

The UK Biobank contains approximately 500,000 individuals aged between 40 and 69 from England, Scotland and Wales recruited between 2006 and 2010. The UK Biobank is linked to cancer registry data from the Health and Social Care Information Centre (in England and Wales) and the Scottish Cancer Registry (in Scotland).[28] The UK Biobank was approved by the North West Multi-Centre Research Ethics Committee, and all participants provided written informed consent.

UK Biobank: Study design

A prospective cohort study was conducted. Cases of oesophageal cancer were identified from cancer-registry records (ICD code C15) up to 2014. Patients with a previous cancer diagnosis, apart from non-melanoma skin cancer, were excluded. Patients were followed from 1 year after baseline (removing cancers that may have been present at baseline) until the date of cancer or censoring on the earlier of death, emigration or 30th June 2014 (the date at which cancer registry data was complete).

UK Biobank: Exposure data

Self-reported use of medications outlined previously was determined at the baseline electronic touchscreen data entry system or interview.

UK Biobank: Confounders

All confounders were determined from the baseline visit. The twelve comorbidities previously mentioned were identified from patient interview/touch screen at baseline. In addition, other recognised risk factors retrieved from the UK Biobank database were hypertension, Alzheimer's disease, fruit and vegetable intake and educational degree. Lifestyle risk factors including smoking (never, former or current) and alcohol consumption (none, moderate [≤14 units per week], heavy [>14 units per week]) were determined from the electronic touchscreen data entry system, at baseline. BMI was calculated from height and weight measurements recorded at baseline by trained research staff, and categorised (underweight [<18.5], normal weight [18.5-24.99], overweight [25-29.99], obese [>30]). The Townsend score based upon postcode of residence was determined as a measure of deprivation.[29] Self-reported aspirin and statin use were also identified.

UK Biobank: Statistical analysis

The UK Biobank cohort was analysed using Cox regression with age as the underlying time scale (individuals were considered at risk from birth and under observation from age at baseline, left truncated) to calculate hazard ratios (HR) and 95% CIs for the association between medication use and oesophageal cancer. An initial adjusted analysis was conducted including gender, comorbidities, deprivation level, statin and aspirin use, for comparison with PCCIU estimates (not shown). The UK Biobank analysis contained further adjustment of other factors known to increase cancer risk which were not available in the PCCIU dataset, including lifestyle factors (including smoking, alcohol consumption and obesity), hypertension, Alzheimer's

disease, fruit and vegetable intake and educational degree. These adjustments made little difference to the estimates and only these estimates are shown. Similar to the PCCIU analysis, additional adjustment for steroid-based inhaler medication was included for patients using respiratory-based medications (β2 agonists and xanthines). Sensitivity analysis was conducted by histological subtype (adenocarcinoma or squamous cell carcinoma). A sensitivity analysis was conducted starting follow-up at 2 years after diagnosis. Sensitivity analyses were conducted for β2 agonists stratifying by asthma in order to reduce the risk of confounding by indication, and after adjustment for asthma. Finally, for comparison with β2 agonist association, a separate analysis of inhaled steroid medication was conducted (as these are used to treat asthma and COPD, but are not known to relax the lower oesophageal sphincter). Analysis was performed using STATA 14 (StataCorp LP, College Station, TX, USA).

RESULTS

PCCIU

In PCCIU there were 1,979 oesophageal cancer cases and 9,543 control patients (Table 1). The median exposure time was 5.5 years (range 3.0-15.1 years). Oesophageal cancer cases were more likely to smoke, have higher alcohol intake and be diagnosed with COPD and peptic ulcer disease.

Overall, a greater proportion of oesophageal cancer cases compared with controls used lower oesophageal sphincter relaxing medications (45.2% versus 39.1%). After adjustment for confounding, these medications were associated with a 23% increase in oesophageal cancer risk (adjusted OR 1.23 95% CI 1.10, 1.38) (Table 2). This association did not follow an exposure response as the adjusted OR for 1 to 12 prescriptions was 1.30 (95% CI 1.13, 1.48), whilst the adjusted OR for >12 prescriptions was 1.17 (95% CI 1.02, 1.35).

This association was largely driven by β2 agonists, which were associated with a 38% increase in oesophageal cancer risk (adjusted OR 1.38, 95% CI 1.12, 1.70). The adjusted OR for 1 to 12 prescriptions was 1.42 (95% CI 1.14, 1.77) but the adjusted OR for greater use was 1.26 (95% CI 0.94, 1.69). Further analysis of specific respiratory-based medications showed only those containing salbutamol were significantly associated with oesophageal cancer (adjusted OR 1.26, 95% CI 1.03, 1.54) (Supplementary Table 2). There was little evidence of an association between oesophageal cancer risk and the other medications that reduce lower oesophageal sphincter pressure, specifically benzodiazepines (adjusted OR 0.94, 95% CI 0.79,

1.11), calcium channel blockers (adjusted OR 1.05, 95% CI 0.92, 1.20), nitrates (adjusted OR 1.09, 95% CI 0.92, 1.29) and xanthines (adjusted OR 1.40, 95% CI 0.88, 2.22) (Table 2).

In sensitivity analyses, the associations were generally similar when the 2 years prior to diagnosis were removed, when a minimum of 3 prescriptions were investigated and when adjustments for lifestyle factors were included, using either complete case or multiple imputation (Table 3). Analysis excluding the additional adjustment for steroid-based inhaler medication conducted for respiratory-based medications (β2 agonists and xanthines) had minimal effect on results, with β2 agonist medication remaining statistically significantly associated with oesophageal cancer (adjusted HR 1.27, 95% CI 1.08, 1.48). Associations were also similar for combined gastric or oesophageal cancer (Supplementary Table 3).

UK Biobank

The UK Biobank cohort contained 475,768 participants of which 355 were diagnosed with oesophageal cancer (Table 1). The median follow-up time was 5.6 years (range 1.0-8.6 years). In UK Biobank those with oesophageal cancer were more likely to be male, older, smoke, have higher alcohol intake, have higher BMI, and have COPD, amongst other comorbidities.

Overall, in comparison to those without oesophageal cancer a greater proportion of people who developed oesophageal cancer used one or more lower oesophageal sphincter relaxing medication (23.1% versus 14.1%). After adjustment for confounders, there was no evidence of an association between use of one or more

medication which lower oesophageal sphincter pressure and oesophageal cancer (adjusted HR 1.29, 95% CI 0.97, 1.71) (Table 4). Further, there was also no evidence of association for specific medication classes and oesophageal cancer: benzodiazepines (adjusted HR 1.47, 95% CI 0.54, 3.96), calcium channel blockers (adjusted HR 0.94, 95% CI 0.64, 1.36), nitrates (adjusted HR 0.85, 95% CI 0.40, 1.82), β2 agonists (adjusted HR 1.21, 95% CI 0.70, 2.08) and xanthines (adjusted HR 2.46, 95% CI 0.58, 10.32) (Table 4).

Analyses by histological subtype also showed medications that relax the lower oesophageal sphincter are not associated with risk of oesophageal adenocarcinoma or squamous cell carcinoma. Further analyses demonstrated that there was no association between β2 agonist use and oesophageal cancer in patients with or without asthma (adjusted HR 1.69, 95% CI 0.76, 3.78 and adjusted HR 0.57, 95% CI 0.17, 1.92, respectively) (Table 5). Similarly, after additional adjustment for asthma, there was no evidence of β2 agonist association with oesophageal cancer (adjusted HR 1.24, 95% CI 0.66, 2.34). However, there was an association between β2 agonist use and oesophageal cancer when adjustment for steroid-based inhalers was removed (adjusted HR 1.66, 95% CI 1.16, 2.37) (Table 5).

Users of steroid based inhalers, prescribed for asthma, had a significantly increased risk of oesophageal cancer (adjusted HR 1.94, 95% CI 1.32, 2.86). Analyses by drug type revealed in the UK Biobank no specific individual mediation was associated with increased risk of developing oesophageal cancer (Supplementary Table 2).

DISCUSSION

In these two large independent population-based studies, there was little evidence of an association between oesophageal cancer risk and benzodiazepines, calcium channel blockers, nitrates or xanthines, despite the known reduction in oesophageal sphincter pressure associated with these medications. In contrast, β2 agonist use was associated with a 38% increased odds of oesophageal cancer in PCCIU but not in UK Biobank.

The lack of association between benzodiazepines, calcium channel blockers and nitrates (all known to lower oesophageal sphincter pressure) and oesophageal cancer is similar to the results collated in a 2012 meta-analysis which was based upon fewer cases (406, 875 and 980 cases, respectively).[30] Our study includes over 2,300 cases allowing us to rule out relatively small potential increases in risk. Our study provides reassurance that these medications are safe with respect to oesophageal cancer risk.

The previous meta-analysis observed an increase in oesophageal adenocarcinoma risk with theophylline (xanthine) use (OR 1.55, 95% CI 1.05, 2.28).[30] Our study did not find a statistically significant increased risk in oesophageal cancer associated with xanthine use, however there was limited use of this drug in either population studied and when oesophageal and gastric cancer were combined in the PCCIU dataset an increased risk was observed for short term use (under 1 year), suggesting further studies containing larger numbers of xanthine users would be of value.

In the PCCIU data, we found β2 agonists, such as salbutamol, were associated with increased risk of oesophageal cancer, results which are consistent with studies by Vaughn et al (OR 1.70, 95% CI 0.78, 3.71), Lagergren et al (OR 1.60, 95% CI 0.81, 3.15) and Ranka et al (OR 1.76, 95% CI 0.96, 3.23).[16,17,19] Our PCCIU findings are also similar to a recent cohort study of progression from Barrett's oesophagus to oesophageal cancer in which associations were observed with β2 agonist (adjusted HR 1.27, 95% CI 0.68, 2.38) and steroid inhaler use (adjusted HR 2.11, 95% CI 1.12, 3.97), although that study contained a total of only 55 oesophageal cancer cases within their Barrett's oesophagus cohort.[31]

The cause of the increased risk of oesophageal cancer with β2 agonist use in PCCIU is unknown. The lack of association in UK Biobank, the lack of dose response association, the association between other asthma medications (e.g. steroid-based) and oesophageal cancer risk provide evidence against a causal interpretation, particularly as several studies have shown marked increases in oesophageal cancer risk in asthma patients.[32–34] However, β2 agonists have been shown to decrease oesophageal sphincter pressure thus potentially increasing the risk of gastro-oesophageal reflux disease,[35] providing a potential mechanism by which they could increase oesophageal cancer risk. Two previous studies have observed an increase in the premalignant Barrett's oesophagus risk in users of β2 agonist[36,37] suggested this association could reflect reverse causality, where the symptoms of gastro-oesophageal reflux mimic asthma leading to the use of β2 agonists.[38,39] Alternatively, the increased oesophageal cancer risk with β2 agonist use could be real, particularly as studies have shown increased β2 agonist receptor expression contributes to tumour growth via the cyclic-

AMP pathway in cancer cell lines, including the oesophageal squamous-cell carcinoma subtype.[40,41]

The main strengths of the current analyses were the size (2,334 oesophageal cancer cases) and the use of data from two independent studies. Also, we were able to adjust for a wide range of confounders, particularly in UK Biobank, to rule out confounding by comorbidity diagnoses and lifestyle factors. Furthermore in UK Biobank we were able to investigate by histological subtype. Unfortunately in PCCIU this was not possible and consequently the inclusion of squamous cell carcinoma cases in the PCCIU analysis could attenuate associations, if lower oesophageal sphincter relaxing medications only caused adenocarcinoma. However, this potential attenuation will be limited as based upon our UK Biobank data over seventy percent of oesophageal cancer cases are likely to be adenocarcinoma. In PCCIU there was possible misclassification of gastric cardia cancers, however as the risk estimates for combined gastric and oesophageal cancer were similar to the individual cancers the impact of this potential confounding factor is reduced (Supplementary Table 3). Another significant strength is that the prescription data in PCCIU is from GP prescribing records and thus recall bias is eliminated.

We also cannot rule out residual confounding by incompletely recorded confounders or unknown exposures associated with both lower oesophageal sphincter relaxing medication use and oesophageal cancer. We did not adjust for PPI use, Barrett's oesophagus or oesophagitis because, although possible, these covariates are likely to be on the causal pathway between the medications and oesophageal cancer. Finally, dose response analyses could only be performed in the PCCIU dataset and were

conducted by number of prescriptions, but as the length of prescriptions may vary this could result in some measurement error in analysis of longer-term use.

In conclusion, there was little evidence that benzodiazepines, nitrates, and calcium channel blockers increase oesophageal cancer risk providing reassurance that these widely used medications are not associated with oesophageal cancer. The increased risk of oesophageal cancer with β2 agonist merits further investigation but as the association was limited to one dataset, and there was no exposure response relationship, a causal interpretation seems less likely.

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There are no conflicts of interest.

Author contributions

The study was conceived and designed by CRC, PM, LI, and AL. PM, CRC, LI and AL obtained the data from the Primary Care Clinical Informatics Unit Research, Scotland whereas LJM, ÚCMcM, CRC, BTJ, HGC obtained the UK Biobank data. ADS, JB, ATK, UCMcM and CRC analysed the data. ADS, JB, MO'R, BTJ and

CRC interpreted the results and drafted the manuscript. All authors reviewed the final manuscript and agree to submission.

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