



# Maintenance proton pump inhibition therapy and risk of oesophageal cancer

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## ABSTRACT

**Background:** The association of long-term use of proton pump inhibitors (PPIs) with oesophageal adenocarcinoma has been poorly defined. Our aim was to assess the risk of oesophageal cancer assessing confounding by indication.

**Methods:** This population-based cohort study included all 796,492 adults exposed to maintenance therapy with PPIs in Sweden in 2005–2012. Standardised incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated to assess the risk of oesophageal adenocarcinoma (and squamous cell carcinoma as a comparison) among long-term PPI users relative to the corresponding background population. The different indications for maintenance PPI therapy were analysed separately.

**Results:** Among all individuals using maintenance PPI therapy, the overall SIR of oesophageal adenocarcinoma was 3.93 (95% CI 3.63–4.24). The SIRs of adenocarcinoma were increased also among individuals without gastro-oesophageal reflux disease who used PPIs for indications not associated with any increased risk of oesophageal adenocarcinoma. For example, the SIRs among participants using maintenance PPI therapy because of maintenance treatment with non-steroidal anti-inflammatory drugs and aspirin were 2.74 (95% CI 1.96–3.71) and 2.06 (95% CI 1.60–2.60), respectively. The SIRs of oesophageal squamous cell carcinoma were increased for most investigated indications, but to a lesser degree than for oesophageal adenocarcinoma.

**Conclusion:** In conclusion, the long term use of PPIs is associated with increased risk of oesophageal adenocarcinoma in the absence of other risk factors. Long term use of PPIs should be addressed with caution.

## 1. Introduction

Proton pump inhibitors (PPIs) are used to reduce gastric acidity in patients with gastro-oesophageal reflux and peptic ulcers, and in the prevention of peptic ulcers [1]. PPIs are also increasingly used for various other abdominal disorders, and are among the most commonly prescribed medications worldwide [1]. Gastro-oesophageal reflux is of great interest, as strong risk factor for oesophageal adenocarcinoma, a cancer with increasing incidence and poor survival [1,2]. Some studies report a decreased cancer progression to invasive adenocarcinoma in individuals with Barrett oesophagus, a premalignant metaplasia caused by chronic gastro-oesophageal reflux, but bias from selection and confounding challenges these findings [3]. Other studies indicate rather an increased risk among PPI users even after adjusting for reflux-severity, but residual confounding by indication cannot be excluded [4,5]. Thus, the impact of PPIs on oesophageal adenocarcinoma development remains unclear. Maintenance PPI therapy is also used for indications not

known to increase the risk of oesophageal adenocarcinoma: in ulcer prevention among long-term users of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs), which are targets for chemoprevention of oesophageal cancer; [6–8] in the treatment of *Helicobacter pylori*, which is also associated with a decreased risk of oesophageal adenocarcinoma; [9,10] and in the treatment of gastroduodenal ulcers, dyspepsia and gastro-duodenitis. PPI maintenance use has recently been associated with an increased risk of mortality [11], and also of gastric cancer apparently independent of the underlying risk factors [12,13]. Interestingly, rodent studies in the 1980s already provided evidence that PPI may promote gastric carcinogenesis, findings which have been largely neglected [14,15]. Therefore, we aimed to assess how maintenance PPI use for indications not increasing the risk of oesophageal adenocarcinoma influences the risk of this cancer.

Abbreviations: CI, confidence interval; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; SIR, standardised incidence ratio

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## 2. Material and methods

### 2.1. Design

This was a nationwide Swedish population-based cohort study during the period 1st July 2005 to 31st December 2012, described in detail elsewhere [12]. It was designed to examine the risk of oesophageal adenocarcinoma among all Swedish residents exposed to maintenance PPI therapy, compared to the Swedish background population of the same sex, age and calendar period (7.1–7.6 million adults) [16]. The source cohort included all Swedish residents who received at least one dispensed prescription of one or more commonly prescribed drugs, including PPIs, menopausal hormone therapy, aspirin or other NSAIDs between 1st July 2005 and 31st December 2014, with follow-up for cancer until 31st December 2012 [12,17–20]. For comparison reasons, the risk of oesophageal squamous cell carcinoma was also evaluated. Only adults ( $\geq 18$  years) without a history of any cancer were included. The study was approved by the Regional Ethical Review Board in Stockholm (2014/1291-31/4).

### 2.2. Data collection

The data were derived from four nationwide high-quality Swedish registers: the Prescribed Drug Registry, the Cancer Registry, the Patient Registry and the Causes of Death Registry. Information on individuals was linked by means of the unique Swedish personal identity number assigned to each Swedish resident [21].

### 2.3. Exposure

The study exposure was maintenance use of any PPI. PPI use was retrieved from the Swedish Prescribed Drug Registry, which recorded all prescribed and dispensed medications in Sweden during the study period. PPIs were defined by the A02BC code of the Anatomical Therapeutic Chemical classification system (ATC). Maintenance use was defined as a cumulative defined daily dose (DDD) of at least six months (180 days) during the study period. According to the World Health Organization (WHO) definition, the DDD is the average daily maintenance dose for a drug when used for its main indication in adults, and is therefore an approximation of the actual use [22]. This cumulative DDD was estimated by adding the DDD per package, which takes both the potency and the quantity of the drug into account. PPIs are also available over-the-counter in Sweden, but only in smaller and more expensive packages for temporary use [23]. If no information was found for the indication for PPI use (25.0%), the indication was considered absent.

For comparison reasons, maintenance use of histamine-2-receptor antagonists (ATC code A02BA), which have similar indications as PPIs, was also assessed. Individuals who were exposed to maintenance use of both a PPI and a histamine-2-receptor antagonist during the study period were excluded.

### 2.4. Outcomes

The main outcome was a first episode of oesophageal adenocarcinoma according to the Swedish Cancer Registry. The comparison outcome was an episode of oesophageal squamous cell carcinoma. The anatomical location of oesophageal cancer was defined by the C15 diagnosis code of the International Classification of Diseases (ICD), 10th version, and adenocarcinoma and squamous cell carcinoma were defined by the histology codes 096 and 146, respectively. The Swedish Cancer Registry has 98% completeness in the recording of all oesophageal cancer, and 100% completeness in the recording of the histological type [24].

### 2.5. Confounding by indication

Confounding by indication was evaluated by separately analysing indications for PPI use, categorised according to their known associations with the risk of oesophageal adenocarcinoma (Appendix A). Indications with an expected increased risk included gastro-oesophageal reflux disease, and gastro-oesophageal reflux related disorders (Barrett's oesophagus and Zollinger-Ellison syndrome) [5,20]. Indications with an expected neutral risk (no known association with oesophageal cancer) were peptic ulcer disease, gastro-duodenitis and dyspepsia. Indications with an expected decreased risk included *Helicobacter pylori* infection or eradication (since the presence of *H. pylori* in the stomach has been associated with a reduction of gastro-oesophageal reflux<sup>9,10</sup>) and maintenance use ( $\geq 180$  days) of aspirin or other NSAIDs (which have been associated with a decreased risk of oesophageal cancer [8,25]). Additional subgroup analyses were performed for those only using NSAIDs or aspirin (without any other indications), and those with gastro-oesophageal reflux and maintenance use of NSAIDs or aspirin (expected lower risk than all individuals with gastro-oesophageal reflux). Individuals with more than one indication (33.6%) were assigned to the indication with the highest expected risk of oesophageal adenocarcinoma.

### 2.6. Statistical analyses

The risk of oesophageal adenocarcinoma (and squamous cell carcinoma) was compared between the maintenance PPI users and the entire Swedish background population of the same sex (male or female), age (categorised as  $< 40$ , 40–49, 50–59, 60–69, or  $\geq 70$  years), and calendar period (categorised as 2005–2006, 2007–2009, or 2010–2012). Standardised incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated by dividing the observed number of cases with the expected number, while accounting for changes in age and calendar categories [26]. The expected numbers were derived from the Swedish Cancer Registry and population statistics from Statistics Sweden [16]. Follow-up time was calculated from the dispense date of the first prescription of PPIs within the study period, until death, any cancer, or 31st December 2012, whichever occurred first. Sub-analyses were stratified for sex and age groups. To evaluate confounding by indication, stratified analyses were performed for each risk indication group for PPI use and for each indication identified in at least 10,000 PPI users in the cohort. Duration of use was estimated based on the sum of the defined daily dosage per packages prescribed before the diagnosis date of any cancer, and was categorised as  $< 1.0$  year, 1.0–2.9 years, 3.0–4.9 years, and  $\geq 5$  years.

A sensitivity analysis was performed excluding cases of oesophageal cancer occurring within one year after enrolment in the study. There were no missing data on the exposure, outcome, age, sex, or calendar period.

## 3. Results

### 3.1. Study participants

In total, 796,492 individuals received maintenance PPI therapy during the study period, resulting in 3.4 million person-years of follow-up (mean 4.4 years). Characteristics of the study participants are presented in Table 1.

Overall, 58.5% were female and 34.0% were 70 years or older. The most commonly identified indications for PPI use were maintenance therapy with aspirin (34.8%) and NSAIDs (30.4%), followed by gastro-oesophageal reflux (25.3%), gastro-duodenitis (13.2%), and peptic ulcer disease (10.0%). The other indications occurred in less than 10% of the PPI-users. Based on the risk categorization, 25.4% had indications with an expected increased risk of oesophageal adenocarcinoma, 12.3% had indications with an expected neutral risk, and 37.3% had

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