



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 (≥ 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^{9,10}) and maintenance use (≥ 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 ≥ 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 ≥ 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

Table 1

Descriptive characteristics of the study cohort exposed to maintenance therapy with proton pump inhibitors (PPIs) categorised by indications with different expected risks of oesophageal adenocarcinoma.

	Number (%)	Indications with increased risk Number (%)	Indications with neutral risk Number (%)	Indications with decreased risk Number (%)
Total	796,492 (100)	202,543 (25.4)	97,643 (12.3)	296,859 (37.3)
Sex				
Men	330,652 (41.5)	92,579 (45.7)	42,452 (43.5)	115,277 (38.8)
Women	465,840 (58.5)	109,964 (54.3)	55,191 (56.5)	181,582 (61.2)
Age, in years				
< 40	88,775 (11.2)	21,790 (10.8)	8218 (8.4)	21,258 (7.2)
40–49	103,784 (13.0)	26,507 (13.1)	9587 (9.8)	33,890 (11.4)
50–59	155,625 (19.5)	42,002 (20.7)	15,520 (15.9)	56,540 (19.1)
60–69	177,610 (22.3)	50,916 (25.1)	20,839 (21.3)	67,153 (22.6)
≥ 70	270,698 (34.0)	61,328 (30.3)	43,479 (44.5)	118,018 (39.8)
Calendar period				
2005–2006	437,230 (54.9)	124,071 (61.3)	55,775 (57.1)	157,671 (53.1)
2007–2009	227,141 (28.5)	52,620 (26.0)	27,634 (28.3)	88,194 (29.7)
2010–2012	132,121 (16.6)	25,852 (12.8)	14,234 (14.6)	50,994 (17.2)
Indications for PPI use				
Gastro-oesophageal reflux	201,744 (25.3)	201,744 (99.6)	–	–
Barrett's oesophagus	6040 (0.8)	6040 (3.0)	–	–
Zollinger-Ellison syndrome	31 (0.0)	31 (0.0)	–	–
Peptic ulcers	79,546 (10.0)	28,504 (14.1)	51,042 (52.3)	–
Gastro-duodenitis	104,903 (13.2)	47,870 (23.6)	57,033 (58.4)	–
Dyspepsia	43,879 (5.5)	17,955 (8.9)	25,924 (26.6)	–
Helicobacter pylori	58,340 (7.3)	19,695 (9.7)	16,571 (16.8)	22,074 (7.4)
NSAIDs use (≥ 180 days)	241,777 (30.4)	52,445 (25.9)	26,161 (26.8)	163,171 (55.0)
Aspirin use (≥ 180 days)	276,941 (34.8)	65,917 (32.5)	42,406 (43.4)	168,618 (56.8)
Number of indications				
0	199,447 (25.0)	–	–	–
1	329,771 (41.4)	65,619 (32.4)	22,375 (22.9)	241,777 (81.5)
> 1	267,274 (33.6)	136,924 (67.6)	75,268 (77.1)	55,082 (18.6)
Oesophageal cancer				
All	1055 (0.13)	470 (0.23)	80 (0.08)	236 (0.08)
Adenocarcinoma	649 (0.08)	330 (0.16)	43 (0.04)	133 (0.04)
Squamous cell carcinoma	353 (0.04)	113 (0.06)	34 (0.03)	94 (0.03)
Duration of follow-up				
Total	3,464,831	967,066	403,495	1,262,846
Mean (standard deviation)	4.4 (2.4)	4.8 (2.3)	4.1 (2.4)	4.3 (2.4)

indications with an expected decreased risk.

3.2. Risk of oesophageal adenocarcinoma in PPI-users

Oesophageal adenocarcinoma was found in 649 individuals using PPI maintenance therapy. The overall SIR of oesophageal adenocarcinoma was 3.93 (95% CI 3.63–4.24) in both sexes combined, 4.22 (95% 3.87–4.58) in men and 2.89 (95% 2.36–3.50) in women (Table 2). Regarding age groups, the SIR was highest among PPI-users younger

Table 2

Standardised incidence ratios (SIRs) and 95% confidence intervals (CIs) of oesophageal cancer in all individuals exposed to proton pump inhibitors (PPIs), stratified by sex and age group.

	Oesophageal adenocarcinoma		Oesophageal squamous cell carcinoma	
	Number	SIRs (95% CI)	Number	SIRs (95% CI)
Total	649	3.93 (3.63–4.24)	353	2.77 (2.49–3.07)
Sex				
Men	546	4.22 (3.87–4.58)	221	3.16 (2.76–3.60)
Women	103	2.89 (2.36–3.50)	132	2.30 (1.92–2.72)
Age, in years				
< 40	4	28.19 (7.59–72.18)	2	12.50 (1.40–45.13)
40–49	25	9.83 (6.36–14.52)	13	9.66 (5.14–16.53)
50–59	99	6.28 (5.10–7.65)	52	4.94 (3.69–6.48)
60–69	219	4.59 (4.00–5.24)	130	3.19 (2.66–3.78)
≥ 70	302	3.05 (2.72–3.41)	156	2.09 (1.78–2.45)

than 40 years (SIR = 28.19, 95% CI 7.95–72.18), and lowest among those 70 years or older (SIR = 3.05, 95% CI 2.72–3.41). A sensitivity analyses excluding participants with oesophageal adenocarcinoma occurring within one year after enrolment onto the study also showed an increased SIR of oesophageal adenocarcinoma (SIR = 1.83, 95% CI 1.63–2.05). Among individuals using maintenance PPIs for indications with an expected increased risk, neutral risk, and decreased of oesophageal adenocarcinoma, the SIRs were 6.92 (95% CI 6.20–7.71), 1.89 (95% CI 1.36–2.54), and 2.07 (95% CI 1.73–2.46), respectively (Table 3). An increased risk was found for each separate indication, including maintenance use of aspirin (SIR = 2.06, 95% CI 1.60–2.60) and NSAIDs (SIR = 2.74, 95% CI 1.96–3.71) without any other indication. As shown in Table 4, the risk remained increased even in individuals exposed to PPI for a longer duration.

3.3. Risk of oesophageal squamous cell carcinoma in PPI-users

Oesophageal squamous cell carcinoma was found in 353 of the maintenance PPI-users, resulting in an overall SIR of 2.77 (95% CI 2.49–3.07). The patterns of SIRs by sex and age were similar as for adenocarcinoma, but less pronounced (Table 2). The SIRs were 3.13 (95% CI 2.58–3.76), 1.99 (95% CI 1.38–2.78), and 1.88 (95% CI 1.52–2.30) for indications with an expected increased risk, unclear risk and expected decreased risk of oesophageal adenocarcinoma, respectively. The SIRs for several of the separate indications showed evidence for an increased risk, except dyspepsia (SIR = 1.36, 95% CI 0.88–2.00) and maintenance NSAIDs use (SIR = 1.27, 95% CI 0.74–2.03). As shown in Table 4, the risk of squamous cell carcinoma was lower among long-term users, in particular those with an estimated duration of ≥ 5

Table 3
Standardised incidence ratios (SIRs) and 95% confidence intervals (CIs) of oesophageal cancer in all individuals exposed to proton pump inhibitors (PPIs), stratified by indication.

	Total	Adenocarcinoma		Squamous cell carcinoma	
		Number of cases (%)	SIRs (95% CI)	Number of cases (%)	SIRs (95% CI)
All	796,492	649 (0.08)	3.93 (3.63–4.24)	353 (0.04)	2.77 (2.49–3.07)
Indications with increased risk of oesophageal adenocarcinoma					
All	202,543	330 (0.16)	6.92 (6.20–7.71)	113 (0.06)	3.13 (2.58–3.76)
Gastro-oesophageal reflux	201,744	316 (0.16)	6.87 (6.13–7.67)	113 (0.06)	3.35 (2.76–4.03)
Indications with neutral risk of oesophageal adenocarcinoma					
All	97,643	43 (0.04)	1.89 (1.36–2.54)	34 (0.03)	1.99 (1.38–2.78)
Peptic ulcers	79,546	63 (0.08)	2.91 (2.24–3.72)	37 (0.05)	2.37 (1.67–3.27)
Gastro-duodenitis	104,903	81 (0.08)	3.34 (2.66–4.16)	54 (0.05)	2.93 (2.20–3.82)
Dyspepsia – disruption of gastric function	43,879	37 (0.08)	1.53 (1.08–2.11)	25 (0.04)	1.36 (0.88–2.00)
Indications with decreased risk of oesophageal adenocarcinoma					
All	296,859	133 (0.04)	2.07 (1.73–2.46)	94 (0.03)	1.88 (1.52–2.30)
<i>Helicobacter pylori</i> infection/eradication	58,340	29 (0.05)	2.43 (1.63–3.49)	26 (0.04)	2.95 (1.93–4.32)
NSAIDs use (≥ 180 days)	241,777	109 (0.05)	1.83 (1.50–2.21)	60 (0.02)	1.34 (1.03–1.73)
Aspirin use (≥ 180 days)	276,941	231 (0.08)	2.79 (2.44–3.17)	120 (0.04)	1.97 (1.63–2.36)
Sub-groups of indications with expected decreased risk					
Only NSAIDs use (≥ 180 days)	111,841	41 (0.04)	2.74 (1.96–3.71)	17 (0.02)	1.27 (0.74–2.03)
Only aspirin use (≥ 180 days)	119,142	69 (0.06)	2.06 (1.60–2.60)	53 (0.04)	2.17 (1.63–2.84)
NSAIDs use (≥ 180 days) and gastro-oesophageal reflux	52,272	43 (0.08)	3.69 (2.67–4.97)	19 (0.04)	1.98 (1.19–3.10)
Aspirin use (≥ 180 days) and gastro-oesophageal reflux	65,626	122 (0.19)	5.41 (4.50–6.47)	34 (0.05)	2.08 (1.44–2.90)

*NSAIDs, non-steroidal anti-inflammatory drugs. One individual could have different indications, except for the group exposed only to NSAIDs or aspirin. Each individual is categorised in the highest risk category applicable. Indications with an expected increased risk include gastro-oesophageal reflux, Barrett oesophagus and Zollinger-Elison syndrome; those with an expected neutral risk include peptic ulcers, gastro-duodenitis and dyspepsia; those with an expected decreased risk include *Helicobacter pylori*, NSAIDs or aspirin maintenance use.

Table 4
Standardised incidence ratios (SIRs) by estimated duration of use and 95% confidence intervals (CIs) of oesophageal cancer in all individuals exposed to proton pump inhibitors (PPIs) per estimated duration of treatment.

Duration	Adenocarcinoma		Squamous cell carcinoma	
	Number of cases/Total	SIR (95% CI)	Number of cases/Total	SIR (95% CI)
< 1.0 year	412/	13.76	252/	10.96
	225,178	(12.46–15.15)	53225,178	(9.65–12.40)
1.0-2.9 years	106/	2.24	56/241,342	1.56
	241,342	(1.84–2.71)		(1.18–2.03)
3.0-4.9 years	63/	2.22	19/108,624	0.88
	108,624	(1.70–2.83)		(0.53–1.37)
≥ 5.0 years	68/	1.11	26/221,348	0.54
	221,348	(0.86–1.41)		(0.35–0.79)

years (SIR 0.54, 95%CI 0.35–0.79).

3.4. Risk of oesophageal cancer in H2 receptor antagonist-users

Among 20,177 individuals exposed to maintenance therapy with histamine-2-receptor antagonists only (without taking any PPIs), there was no increased risk of oesophageal adenocarcinoma (SIR = 0.39, 95% CI 0.04–1.40, n = 2) or oesophageal squamous cell carcinoma (SIR = 0.50, 95% CI 0.06–1.88, n = 2).

4. Discussion

This study found evidence of an increased risk of oesophageal adenocarcinoma (and squamous cell carcinoma) among individuals using maintenance PPI therapy, also among those who used PPIs for indications not associated with any increased risk of oesophageal adenocarcinoma.

A main strength of the study was the ability to separately analyse PPI-use for indications not associated with any increased risk of oesophageal adenocarcinoma. This minimised the risk of confounding by indication which has been a major limitation in previous research on this topic. However, we could not identify an underlying indication for 25% of the patients, yet we can assume that the indications have been

registered for those with the most severe symptoms. Other methodological advantages include the large sample size, population-based design and high quality data sources. Since the exposure was defined as maintenance use of PPIs (at least 180 days), over-the-counter availability of PPIs (small and expensive packages) and low compliance should not have caused considerable misclassification of PPI use. The fact that the comparison population also included a percentage of PPI users should have diluted the positive associations rather than contributing to them. Limitations included the lack of information on PPI exposure before the study period and the limited duration of follow-up, making assessment of duration of PPI treatment unreliable. However, we attempted to assess reverse causality by excluding cases occurring within a year after enrolment, which showed similar results. The analyses assessing estimated duration based on the defined daily dosages per package, showed increased risk even among long-term users – yet the apparent decreasing trend does not rule out a causal relationship between PPI and oesophageal cancer. Residual confounding, e.g. by lifestyle factors and body mass index cannot be ruled out, and severity of gastro-oesophageal reflux is not recorded in the Health Registries.

Some previous studies suggest a reduced risk of oesophageal adenocarcinoma following PPI use in individuals with Barrett’s oesophagus [27]. Yet, other studies contradict these findings [28–30]. Selection bias is an issue since patients with Barrett’s oesophagus who do not use PPIs is likely a highly selected group, e.g. with low compliance or interest in their health. Moreover, it is unlikely that PPI use would entirely eliminate the cancer risk because of the previously caused damage [31]. Importantly, if PPIs would decrease the risk of oesophageal adenocarcinoma, we would expect a reduced risk at least among individuals using aspirin or other NSAIDs which have cancer protective properties [6–8]. Our findings are in line with studies that have indicated an increased risk of oesophageal adenocarcinoma among PPI-users. Admittedly, confounding by indication (reflux) has been a concern, but some of these studies did adjust their results for severity of reflux [4,5].

The lack of any increased risk of oesophageal adenocarcinoma (and squamous-cell carcinoma) among maintenance users of H2-receptor antagonists lends support to the hypothesis that this association may be due to PPI medication *per se*, and not related to other factors that predisposes to using anti-acidic medications [32]. PPIs affect the final step of acid secretion in the gastric mucosa, so they inhibit acid secretion and do not suppress it the way H2-receptor antagonists do. In

healthy individuals, the half-life of PPIs is only one hour, yet acid secretion is inhibited for 48 h because of irreversible binding to the H₂K-ATPase [33]. A direct carcinogenic effect of PPI use on the oesophageal mucosa may be unlikely, and we hypothesize that the increased oesophageal cancer risk is instead due to a disruption of the gastro-intestinal microbiome [34]. The blocked gastric acid secretion could decrease the defence against pathogenic bacteria [35,36], and increase bacterial colonization (including non-gastric microorganisms) [37,38]. In particular, the potential increase of bacteria that produce nitrosamines may play a role, since nitrosamines are well-established risk factors for gastric and potentially also oesophageal cancer of both histological types [39]. Other possible pathways include bile salt toxicity because of the increased pH in the stomach, which may cause mucosal metaplasia in the oesophagus [40]. All these potential mechanisms could help explain our finding of an increased risk of both adenocarcinoma and squamous cell carcinoma of the oesophagus.

Of all patients diagnosed with oesophageal cancer in Sweden during the study period, 36.8% were exposed to maintenance use with PPIs. Even our most conservative estimates (SIR = 1.53 for dyspepsia) indicate that 5.4% of the oesophageal cancer in the population could be attributed to PPI use (population attributable fraction), or 34.6% of all oesophageal cancer in the PPI maintenance users (attributable fraction), assuming a causal relation and a prevalence of PPI maintenance use among the total adult Swedish population of 10.7%.

To assess generalizability and validity of these results, further investigations in other settings with other distributions of risk factors for oesophageal cancer is necessary. Yet, we believe that a more restrictive attitude towards maintenance use of PPIs may be indicated.

To conclude, an increased risk of oesophageal cancer was found

among PPI maintenance users, even among individuals using PPIs for indications not associated with a risk of oesophageal adenocarcinoma.

Authorship contribution

NB is the guarantor of the article. Literature search: NB; Design of the study: all authors; Data collection and preparation for analyses: NB; Data analysis: NB; Data interpretation: all authors; Writing of first draft: NB, revised and approved by all authors. The final version of the article is approved by all authors.

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Conflicts of interest

None.

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Appendix A. International Classification of Diseases (ICD) and Anatomical Therapeutic Chemical classification system (ATC) codes to describe the indications for proton pump inhibitors.

	ICD-7 (Since 1955)	ICD-8 (Since 1968)	ICD-9 (Since 1987)	ICD-10 (Since 1997)
Reflux codes	784,3; 539,11–539,12; 560,4	530,93–530,94; 551,3; 784,3	530B-C; 553D; 787B	K20-21; K44; R12
Barrett's oesophagus codes	–	–	–	K227
Peptic ulcer disease	540–541	531–533	531–533	K25-K27
Zollinger-Ellison syndrome/ Hypergastrinemia	–	–	251F	E16.4
Gastro-duodenitis	543	535	535	K29
Dyspepsia/disruption of gastric function	544	536	536	K30-K31
<i>Helicobacter pylori</i> infection	–	–	–	B96.8 or B98.0
	ATC			
Non-steroidal anti-inflammatory drugs	M01A			
Aspirin	B01AC06, N02BA			
<i>Helicobacter pylori</i> eradication	A02BD, or A02BC (PPI) in combination with 2 out of 3 antibiotics (Amoxicillin [J01CA04]; Clarithromycin [J01FA09], or metronidazole [J01XD]); or combined with metronidazole [J01XD], doxycycline [J01AA02] and bismuth [A02BX05]; or with amoxicillin [J01CA04] and levofloxacin [J01MA12].			

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