Chemoprevention of Oesophageal Squamous-Cell Carcinoma and Adenocarcinoma: A Multicentre Retrospective Cohort Study

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Keywords

Oesophageal cancer · Chemoprevention · Risk stratification · Medication · Aspirin

Abstract

Background: Oesophageal cancer comprises 2 different histological variants: oesophageal squamous-cell carcinoma (ESCC) and adenocarcinoma (EAC). While there are multiple therapeutic options for both types, patients with advanced or metastatic oesophageal cancer still suffer from poor prognosis. **Aims:** The study aimed to examine the association between the risk of oesophageal cancer and medications and to estimate the chemopreventive effects of commonly used drugs. **Methods:** A multicentre retrospective cohort study was conducted using data from 9 hospital databases of hospitalized patients between 2014 and 2019. The primary outcomes were ESCC and EAC. The association of oesophageal

cancer with drug use and clinical factors was evaluated. Odds ratios (ORs) were adjusted for age, sex, Charlson comorbidity index scores, and smoking with/without gastro-oesophageal reflux disease. **Results:** The use of proton pump inhibitors (PPIs) (adjusted OR [aOR] 0.48, $p < 0.0001$), aspirin (aOR 0.32, $p < 0.0001$), cyclooxygenase-2 inhibitor (COX2I) (aOR 0.70, $p = 0.0005$), steroid (aOR 0.19, $p < 0.0001$), statin (aOR 0.43, $p < 0.0001$), and metformin (aOR 0.42, $p < 0.0001$) was associated with a lower risk of ESCC than that in non-use. The use of aspirin (aOR 0.33, $p = 0.0006$) and steroids (aOR 0.54, $p = 0.022$) was associated with a lower risk of EAC than that in non-use. **Conclusion:** COX2Is, statins, metformin, and PPIs could help in prevention of ESCC, and aspirin and steroids may be chemopreventive for both types of oesophageal cancer.

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Introduction

Oesophageal squamous-cell carcinoma (ESCC) and adenocarcinoma (EAC) are important causes of cancer-related deaths worldwide [1]. Recently, the incidence of ESCC has increased in Eastern Asia and Eastern and Southern Africa, whereas the incidence of EAC has increased in North America and Europe. Several risk factors for these cancers have been discussed [2]. Smoking and alcohol are the main risk factors for ESCC, whereas gastro-oesophageal reflux disease (GERD) and Barrett's oesophagus, due to gastric acid, are the predominant risk factors for EAC [3–5]. These factors cause chronic inflammation and subsequent DNA damage in the oesophageal epithelium, resulting in cancer development. Given that several drugs have potential anti-inflammatory and anti-DNA damage effects, they may have anti-carcinogenic effects in oesophageal cancer.

In a randomized control study in Western countries, aspirin and esomeprazole, a strong proton pump inhibitor (PPI), prolonged the time to EAC development in patients with Barrett's oesophagus [6]. In a meta-analysis, non-steroidal anti-inflammatory drugs, including aspirin, were associated with a lower risk of ESCC [7]. In another meta-analysis, statins were shown to have a potential chemopreventive effect in both ESCC and EAC [8]. In addition, a population-based cohort study [9] suggested that metformin is associated with a decreased risk of ESCC. However, more comprehensive studies are needed to identify the association between oesophageal cancer and clinical parameters, including medications. Thus, a multicentre retrospective cohort study was performed to evaluate the chemopreventive effects of ESCC and EAC; we found that aspirin, PPI, and several other drugs are associated with lower risk of oesophageal cancers, particularly when these drugs are combined.

Methods

Study Design, Setting, and Patients

This retrospective case-control study was performed using a combination of diagnostic procedure databases from 9 hospitals. The study period was from April 2014 to March 2019. The combined databases provided records for all inpatients at Tonan Hospital and for all inpatients and outpatients at the University of Tokyo Hospital, Shuto General Hospital, Fukui Prefectural Hospital, Nerima Hikarigaoka Hospital, St. Luke's International Hospital, Toyonaka Municipal Hospital, Ishikawa Prefectural Central Hospital, and Nagasaki Minato Medical Center. They contained data on diagnosis, comorbidities, and adverse events, recorded using the International Classification of Diseases, tenth revision (ICD-

10), as well as on drugs and procedures, coded using the original Japanese system. This study was approved by the Institutional Review Board of the University of Tokyo Hospital (No. 2019161NI). All patients gave their informed consent prior to their inclusion in the study.

Outcomes and Variables

The primary outcomes were ESCC and EAC. Oesophageal cancers were defined as ICD-10 codes C150–C159. We assessed the use of PPIs, including omeprazole, lansoprazole, rabeprazole, and esomeprazole; non-steroidal anti-inflammatory drugs, including cyclooxygenase-2 inhibitors (COX2I); aspirin; steroids; statins including pitavastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin; fibrates including fenofibrate, bezafibrate, ciprofibrate, and clofibrate; other lipid-lowering agents; and metformin. Details of the codes for these medications are shown in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000520924). Use of PPIs was defined as a prescription for >90 days to eliminate the influence of endoscopic treatment-related PPI use.

We also evaluated the following clinical factors: age, sex, smoking status, and comorbidities. Age was dichotomized as > 70 and ≤70 years. The following comorbidities (based on ICD-10 codes) were included: atrial fibrillation, acquired immunodeficiency syndrome, arterial thrombosis, carotid disease, cerebrovascular disease, chronic heart failure, chronic kidney disease (stage 5), dementia, diabetes mellitus with or without complications, deep-vein thrombosis, GERD, hemiplegia, dyslipidaemia, ischaemic heart disease, liver disorder (mild/severe), malignancy with or without metastasis, peripheral vascular disease, pulmonary disease, rheumatic disease, transient ischaemic attack, peptic ulcer disease, unstable angina, and valvular disease. The Charlson comorbidity index was calculated using these data [10]. The details of the ICD-10 codes are provided in online supplementary Table 2.

Statistical Analysis

Univariable and multivariable logistic models were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for ESCC and EAC. The multivariable logistic models were adjusted for age, sex, smoking, Charlson comorbidity index, and GERD. A subgroup analysis was performed for smoking patients. Additional logistic model analyses were performed to estimate the effect of drug combinations. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SAS software (ver. 9.4; SAS Institute, Cary, NC, USA).

Results

Patient Characteristics

A total of 308,793 patients, including 1,911 ESCC, 195 EAC, and 306,687 non-oesophageal cancer patients, were analysed. Patient characteristics are shown in Table 1. Patients with oesophageal cancer, including ESCC and EAC, had higher proportions of elderly, male, history of smoking, and GERD than those in non-oesophageal cancer patients.

Table 1. Baseline characteristics (number of patients (%) or mean $\pm$ standard deviation)

Characteristics	ESCC (n = 1,911)	EAC (n = 195)	No ESCC or EAC (n = 306,687)
Male	1,550 (81.11)	160 (82.05)	149,461 (48.73)
Age >70 years	998 (52.22)	80 (41.03)	115,128 (37.54)
Smoking	1,231 (64.42)	118 (60.51)	99,692 (32.51)
Medications			
PPI	359 (18.79)	32 (16.41)	27,279 (8.89)
NSAIDs, N	751 (39.30)	77 (39.49)	106,937 (34.87)
Aspirin	116 (6.07)	10 (5.13)	25,708 (8.38)
COX2I (only celecoxib)	115 (5.44)	11 (5.64)	16,737 (5.46)
Steroid	77 (4.03)	17 (8.72)	27,063 (8.82)
Statin, N	166 (8.69)	28 (14.36)	34,035 (11.10)
Strong statin	141 (7.38)	25 (12.82)	28,969 (9.45)
Fibrate	23 (1.20)	3 (1.54)	2,496 (0.81)
Other lipid-lowering agents	17 (0.89)	5 (2.56)	3,947 (1.29)
Metformin	37 (1.94)	9 (4.62)	7,848 (2.56)
Comorbidities			
Atrial fibrillation	38 (1.99)	2 (1.03)	2,657 (0.87)
AIDS	0 (0.00)	0 (0.00)	113 (0.04)
Arterial thrombosis	15 (0.78)	1 (0.51)	1,443 (0.47)
Carotid disease	9 (0.47)	1 (0.51)	862 (0.28)
Cerebrovascular disease	108 (5.65)	6 (3.08)	12,721 (4.15)
Chronic heart failure	108 (5.65)	7 (3.59)	19,739 (6.44)
Chronic kidney disease <stage 5	35 (1.83)	7 (3.59)	7,595 (2.48)
Chronic kidney disease stage 5	4 (0.21)	1 (0.51)	870 (0.28)
Dementia	28 (1.47)	0 (0)	6,710 (2.19)
DM without COMP	322 (16.85)	39 (20.00)	34,563 (11.27)
DM with COMP	39 (2.04)	4 (2.05)	8,796 (2.87)
DVT	16 (0.84)	2 (1.03)	2,538 (0.83)
GERD	710 (37.15)	50 (25.64)	23,819 (7.77)
Hemiplegia	4 (0.21)	0 (0)	708 (0.23)
HTN	515 (26.95)	40 (20.51)	57,461 (18.74)
HL	203 (10.62)	15 (7.69)	30,666 (10.00)
Ischaemic heart diseases	27 (1.41)	0 (0)	3,812 (1.24)
LD (mild level)	129 (6.75)	12 (6.15)	10,327 (3.37)
LD (severe level)	16 (0.84)	0 (0)	1,255 (0.41)
Malignancy without metastasis	553 (28.94)	55 (28.21)	19,787 (6.45)
Malignancy with metastasis	237 (12.40)	18 (9.23)	9,631 (3.14)
PVDs	34 (1.78)	2 (1.03)	5,299 (1.73)
PD	129 (6.75)	11 (5.64)	14,447 (4.71)
RDs	6 (0.31)	2 (1.03)	1,480 (0.48)
TIA	3 (0.16)	0 (0)	285 (0.09)
PUDs	671 (35.11)	74 (37.95)	24,146 (7.87)
UAGs	138 (7.22)	19 (9.74)	14,261 (4.65)
VDs	20 (1.05)	6 (3.08)	3,768 (1.23)
Charlson comorbidities index	2.22 $\pm$ 2.57	1.95 $\pm$ 2.18	0.84 $\pm$ 1.65

ESCC, oesophageal squamous-cell carcinoma; EAC, oesophageal adenocarcinoma; DM, diabetes mellitus; NSAIDs, non-steroidal anti-inflammatory drugs; COX2I, cyclooxygenase-2 inhibitor; PPI, proton pump inhibitor; GERD, gastro-oesophageal reflux disease; COMP, complications; DVT, deep-vein thrombosis; HTN, hypertension; HL, hyperlipidaemia; LD, liver disorder; PVD, peripheral vascular disease; PD, pulmonary disease; RD, rheumatic diseases; TIA, transient ischaemic attack; PUD, peptic ulcer disease; UAG, unstable angina diseases; VD, valvular diseases; AIDS, acquired immunodeficiency syndrome.

Table 2. Clinical factors associated with ESCC (n = 308,598)

Factor	ESCC (n = 1,911)	No ESCC (n = 306,687)	Crude OR (95% CI)	Adjusted OR [†] (95% CI)	p value
Female	361 (0.23)	157,226 (99.77)	1	1	
Male	1,550 (1.03)	149,461 (98.97)	4.52 (4.03–5.07)	2.87 (2.54–3.25)	<0.0001
Age ≤70	913 (0.47)	191,559 (99.53)	1	1	
Age >70	998 (0.86)	115,128 (99.14)	1.82 (1.66–1.99)	1.15 (1.13–1.17)	<0.0001
Non-smoking	680 (0.33)	206,995 (99.67)	1	1	
Smoking	1,231 (1.22)	99,692 (98.78)	3.76 (3.42–4.13)	2.25 (2.04–2.49)	<0.0001
No PPI	1,614 (0.57)	279,408 (99.43)	1	1	
PPI	297 (1.08)	27,279 (98.92)	1.89 (1.67–2.14)	0.48 (0.42–0.56)	<0.0001
No NSAIDs	1,160 (0.58)	199,750 (99.42)	1	1	
NSAIDs	751 (0.70)	106,937 (99.30)	1.21 (1.10–1.33)	0.80 (0.72–0.88)	<0.0001
No aspirin	1,795 (0.63)	280,979 (99.37)	1	1	
Aspirin	116 (0.45)	25,708 (99.55)	0.71 (0.59–0.85)	0.32 (0.26–0.39)	<0.0001
No COX2I	1,807 (0.62)	289,950 (99.38)	1	1	
COX2I	104 (0.62)	16,737 (99.38)	1.00 (0.82–1.22)	0.70 (0.57–0.86)	0.0005
No steroid	1,834 (0.65)	279,624 (99.35)	1	1	
Steroid	77 (0.28)	27,063 (99.72)	0.43 (0.35–0.55)	0.19 (0.15–0.24)	<0.0001
No statin	1,745 (0.64)	272,652 (99.36)	1	1	
Statin	166 (0.49)	34,035 (99.51)	0.76 (0.65–0.89)	0.43 (0.37–0.51)	<0.0001
No strong statin	1,770 (0.63)	277,718 (99.37)	1	1	
Strong statin	141 (0.48)	28,969 (99.52)	0.76 (0.64–0.91)	0.41 (0.35–0.49)	<0.0001
No fibrate	1,888 (0.62)	304,191 (99.38)	1	1	
Fibrate	23 (0.91)	2,496 (99.09)	1.49 (0.98–2.24)	0.89 (0.59–1.36)	0.595
No other lipid-lowering agent	1,894 (0.62)	302,740 (99.38)	1	1	
Other lipid-lowering agents	17 (0.43)	3,947 (99.57)	0.69 (0.43–1.11)	0.40 (0.25–0.64)	0.0002
No metformin	1,874 (0.62)	298,839 (99.38)	1	1	
Metformin	37 (0.47)	7,848 (99.53)	0.75 (0.54–1.04)	0.42 (0.30–0.58)	<0.0001
Non-Af	1,873 (0.61)	304,030 (99.31)	1	1	
Af	38 (1.41)	2,657 (98.59)	2.32 (1.68–3.21)	1.02 (0.73–1.42)	0.919
Non-AIDS	1,911 (0.62)	306,574 (99.96)	1	1	
AIDS	0 (0)	113 (100)	NA	NA	–
Non-AT	1,896 (0.62)	305,244 (99.38)	1	1	
AT	15 (1.03)	1,443 (98.97)	1.67 (1.01–2.79)	0.72 (0.43–1.21)	0.218
Non-CD	1,902 (0.62)	305,825 (99.38)	1	1	
CD	9 (1.03)	862 (98.97)	1.68 (0.87–3.24)	0.60 (0.31–1.17)	0.135
Non-CVD	1,803 (0.61)	293,966 (99.39)	1	1	
CVD	108 (0.84)	12,721 (99.16)	1.38 (1.14–1.68)	0.61 (0.50–0.75)	<0.0001
Non-CHF	1,803 (0.62)	286,948 (99.38)	1	1	
CHF	108 (0.54)	19,739 (99.46)	0.87 (0.72–1.06)	0.35 (0.29–0.43)	<0.0001
Non-CKD <stage 5	1,876 (0.62)	299,092 (99.38)	1	1	
CKD <stage 5	35 (0.46)	7,595 (99.54)	0.74 (0.53–1.03)	0.34 (0.24–0.48)	<0.0001
Non-CKD stage 5	1,907 (0.62)	305,817 (99.38)	1	1	
CKD stage 5	4 (0.46)	870 (99.54)	0.74 (0.28–1.97)	0.20 (0.073–0.53)	0.0013
Non-dementia	1,883 (0.62)	299,977 (99.38)	1	1	
Dementia	28 (0.42)	6,710 (99.58)	0.67 (0.46–0.97)	0.48 (0.33–0.70)	0.0002
Non-DM (COMP–)	1,589 (0.58)	272,124 (99.42)	1	1	
DM (COMP–)	322 (0.92)	34,563 (99.08)	1.60 (1.42–1.80)	0.64 (0.57–0.73)	<0.0001
Non-DM (COMP+)	1,872 (0.62)	297,891 (99.38)	1	1	
DM (COMP+)	39 (0.44)	8,796 (99.56)	0.71 (0.51–0.97)	0.25 (0.18–0.34)	<0.0001
Non-DVT	1,895 (0.62)	304,149 (99.38)	1	1	
DVT	16 (0.63)	2,538 (99.37)	1.01 (0.62–1.66)	0.59 (0.36–0.97)	0.036
Non-GERD	1,201 (0.42)	282,868 (99.58)	1	1	
GERD	710 (2.89)	23,819 (97.11)	7.02 (6.39–7.71)	4.44 (4.01–4.91)	<0.0001
Non-hemiplegia	1,907 (0.62)	305,979 (99.42)	1	1	
Hemiplegia	4 (0.56)	708 (99.44)	0.91 (0.34–2.43)	0.44 (0.16–1.20)	0.1080

Table 2 (continued)

Factor	ESCC (n = 1,911)	No ESCC (n = 306,687)	Crude OR (95% CI)	Adjusted OR [†] (95% CI)	p value
Non-HTN	1,396 (0.56)	249,226 (99.44)	1	1	
HTN	515 (0.89)	57,461 (99.11)	1.60 (1.45–1.77)	0.67 (0.60–0.75)	<0.0001
Non-HL	1,708 (0.62)	289,950 (99.38)	1	1	
HL	203 (0.66)	30,666 (99.34)	1.07 (0.92–1.24)	0.50 (0.43–0.58)	<0.0001
Non-IHD	1,884 (0.62)	302,875 (99.38)	1	1	
IHD	27 (0.70)	3,812 (99.30)	1.14 (0.78–1.67)	0.39 (0.27–0.57)	<0.0001
Non-mild LD	1,782 (0.60)	296,360 (99.40)	1	1	
Mild LD	129 (1.23)	10,327 (98.77)	2.08 (1.74–2.49)	0.88 (0.73–1.06)	0.179
Non-severe LD	1,895 (0.62)	305,432 (99.38)	1	1	
Severe LD	16 (1.26)	1,255 (98.74)	2.06 (1.25–3.37)	0.48 (0.29–0.80)	0.0044
Non-malignancy (metastasis–)	1,358 (0.47)	286,900 (99.53)	1	1	
Malignancy (metastasis–)	553 (2.72)	19,787 (97.28)	5.90 (5.34–6.53)	2.78 (2.43–3.18)	<0.0001
Non-malignancy (metastasis+)	1,674 (0.56)	297,056 (99.44)	1	1	
Malignancy (metastasis+)	237 (2.40)	9,631 (97.60)	4.37 (3.81–5.01)	1.01 (0.79–1.28)	0.952
Non-PVD	1,877 (0.62)	301,388 (99.38)	1	1	
PVD	34 (0.64)	5,299 (99.36)	1.03 (0.73–1.45)	0.36 (0.26–0.51)	<0.0001
Non-PD	1,782 (0.61)	292,240 (99.39)	1	1	
PD	129 (0.89)	14,447 (99.11)	1.46 (1.22–1.75)	0.71 (0.59–0.85)	0.0002
Non-RD	1,905 (0.62)	305,207 (99.38)	1	1	
RD	6 (0.40)	1,480 (99.60)	0.65 (0.29–1.45)	0.45 (0.20–1.01)	0.053
Non-TIA	1,908 (0.62)	306,402 (99.38)	1	1	
TIA	3 (1.04)	285 (98.96)	1.69 (0.54–5.28)	0.68 (0.21–2.15)	0.507
Non-PUD	1,240 (0.44)	282,541 (99.56)	1	1	
PUD	671 (2.70)	24,146 (97.30)	6.33 (5.76–6.96)	3.83 (3.46–4.25)	<0.0001
Non-UAG	1,773 (0.60)	292,426 (99.40)	1	1	
UAG	138 (0.96)	14,261 (99.04)	1.60 (1.34–1.90)	0.66 (0.55–0.79)	<0.0001
Non-VD	1,891 (0.62)	302,919 (99.38)	1	1	
VD	20 (0.53)	3,768 (99.47)	0.85 (0.55–1.32)	0.54 (0.35–0.85)	0.0073

ESCC, oesophageal squamous-cell carcinoma; OR, odds ratio; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; COX2I, cyclooxygenase-2 inhibitor; PPI, proton pump inhibitor; Af, atrial fibrillation; AIDS, acquired immunodeficiency syndrome; AT, arterial thrombosis; CD, carotid disease; CVD, cerebrovascular disease; CHF, chronic heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; COMP, complications; DVT, deep-vein thrombosis; GERD, gastro-oesophageal reflux disease; HTN, hypertension; HL, hyperlipidaemia; LD, liver disorder; PE, pulmonary embolism; PVD, peripheral vascular disease; PD, pulmonary disease; RD, rheumatic diseases; TIA, transient ischaemic attack; PUD, peptic ulcer disease; UAG, unstable angina diseases; VD, valvular diseases. [†] OR adjusted for age >70 years, sex, smoking, GERD, and Charlson comorbidity index.

Factors Associated with ESCC

The factors associated with ESCC are listed in Table 2. The use of PPI (adjusted OR [aOR] 0.48, 95% CI 0.42–0.56), aspirin (aOR 0.32, 95% CI 0.26–0.39), COX2I (aOR 0.70, 95% CI 0.57–0.86), steroid (aOR 0.19, 95% CI 0.15–0.24), statin (aOR 0.43, 95% CI 0.37–0.51), and metformin (aOR 0.42, 95% CI 0.30–0.58) were associated with a lower risk of oesophageal SCC than that in non-use. These results were similar in the subgroup of smoking patients (Table 3) and in another logistic model analysis adjusted for propensity score calculated by age, sex, smoking, and comorbidity (online suppl. Table 3).

Factors Associated with EAC

The factors associated with the EAC are shown in Table 4. The use of aspirin (aOR 0.33, 95% CI 0.17–0.62) and steroids (aOR 0.54, 95% CI 0.32–0.91) was associated with a lower risk of EAC than that in non-use. These results were similar in the subgroup of smoking patients (Table 5) and in another logistic model analysis adjusted for propensity score calculated by age, sex, smoking, and comorbidity (online suppl. Table 3).

Drug Combination Model for ESCC and EAC

The drug combination models for ESCC and EAC are shown in Table 6. Drug combinations of PPI and aspirin

Table 3. Clinical factors associated with ESCC in smoking patients (*n* = 100,923)

Factor	ESCC (<i>n</i> = 1,231)	No ESCC (<i>n</i> = 99,692)	Crude OR (95% CI)	Adjusted OR [†] (95% CI)	<i>p</i> value
Female	143 (0.52)	27,331 (99.48)	1	1	
Male	1,088 (1.48)	72,361 (98.52)	2.87 (2.41–3.42)	2.41 (2.02–2.87)	<0.0001
Age ≤70	637 (1.05)	60,042 (98.95)	1	1	
Age >70	594 (1.48)	39,650 (98.52)	1.41 (1.26–1.58)	1.10 (0.98–1.23)	0.122
No PPI	1,053 (1.16)	89,424 (98.84)	1	1	
PPI	178 (1.70)	10,268 (98.30)	1.47 (1.25–1.73)	0.47 (0.39–0.56)	<0.0001
No NSAIDs	762 (1.18)	63,900 (98.82)	1	1	
NSAIDs	469 (1.29)	35,792 (98.71)	1.10 (0.98–1.23)	0.75 (0.66–0.85)	<0.0001
No aspirin	1,153 (1.27)	89,488 (98.73)	1	1	
Aspirin	78 (0.76)	10,204 (99.55)	0.59 (0.47–0.75)	0.34 (0.27–0.42)	<0.0001
No COX2I	1,160 (1.21)	94,787 (98.79)	1	1	
COX2I	71 (1.43)	4,905 (98.57)	1.18 (0.93–1.51)	0.79 (0.62–1.02)	0.068
No steroid	1,192 (1.30)	90,781 (98.70)	1	1	
Steroid	39 (0.44)	8,911 (99.56)	0.33 (0.24–0.46)	0.15 (0.11–0.21)	<0.0001
No statin	1,133 (1.28)	87,144 (98.72)	1	1	
Statin	88 (0.77)	12,548 (99.23)	0.60 (0.49–0.74)	0.39 (0.31–0.48)	<0.0001
No strong statin	1,149 (1.28)	88,546 (98.72)	1	1	
Strong statin	82 (0.73)	11,146 (99.27)	0.57 (0.45–0.71)	0.36 (0.29–0.46)	<0.0001
No fibrate	1,214 (1.22)	98,567 (98.78)	1	1	
Fibrate	17 (1.49)	1,125 (98.51)	1.23 (0.76–1.99)	0.93 (0.57–1.52)	0.774
No other lipid-lowering agent	1,221 (1.23)	98,157 (98.77)	1	1	
Other lipid-lowering agents	10 (0.65)	1,535 (99.35)	0.52 (0.28–0.98)	0.35 (0.19–0.66)	0.0011
No metformin	1,208 (1.24)	96,325 (98.76)	1	1	
Metformin	23 (0.68)	3,367 (99.32)	0.55 (0.36–0.82)	0.38 (0.25–0.57)	<0.0001
Non-Af	1,203 (1.21)	98,528 (98.79)	1	1	
Af	28 (2.35)	1,164 (97.65)	1.97 (1.35–2.88)	1.15 (0.78–1.68)	0.491
Non-AIDS	1,231 (1.22)	99,632 (98.78)	1	1	
AIDS	0 (0.00)	60 (0.06)	NA	NA	–
Non-AT	1,221 (1.22)	99,084 (98.78)	1	1	
AT	10 (1.62)	608 (98.38)	1.34 (0.71–2.50)	0.75 (0.40–1.41)	0.364
Non-CD	1,224 (1.22)	99,233 (98.78)	1	1	
CD	7 (1.50)	459 (98.50)	1.24 (0.59–2.61)	0.66 (0.31–1.40)	0.279
Non-CVD	1,154 (1.21)	94,480 (98.79)	1	1	
CVD	77 (1.46)	5,212 (98.54)	1.21 (0.96–1.53)	0.69 (0.54–0.88)	0.0024
Non-CHF	1,165 (1.25)	91,829 (98.75)	1	1	
CHF	66 (0.83)	7,863 (99.17)	0.66 (0.52–0.85)	0.34 (0.26–0.43)	<0.0001
Non-CKD <stage 5	1,208 (1.24)	96,584 (98.76)	1	1	
CKD <stage 5	23 (0.73)	3,108 (99.27)	0.59 (0.39–0.90)	0.35 (0.23–0.53)	<0.0001
Non-CKD stage 5	1,228 (1.22)	99,310 (98.78)	1	1	
CKD stage 5	3 (0.91)	382 (99.22)	0.64 (0.21–1.98)	0.23 (0.074–0.73)	0.013
Non-dementia	1,216 (1.23)	97,916 (98.77)	1	1	
Dementia	15 (0.84)	1,776 (99.16)	0.68 (0.41–1.14)	0.49 (0.29–0.82)	0.0067
Non-DM (COMP–)	1,009 (1.18)	84,328 (98.82)	1	1	
DM (COMP–)	222 (1.42)	15,364 (98.58)	1.21 (1.04–1.40)	0.65 (0.56–0.76)	<0.0001
Non-DM (COMP+)	1,210 (1.24)	96,053 (98.76)	1	1	
DM (COMP+)	21 (0.57)	3,639 (99.43)	0.46 (0.30–0.71)	0.21 (0.14–0.33)	<0.0001
Non-DVT	1,219 (1.22)	98,801 (98.78)	1	1	
DVT	12 (1.33)	891 (98.67)	1.09 (0.62–1.94)	0.71 (0.40–1.26)	0.242
Non-GERD	788 (0.87)	89,832 (99.13)	1	1	
GERD	443 (4.30)	9,860 (95.70)	5.12 (4.55–5.77)	3.82 (3.37–4.33)	<0.0001
Non-hemiplegia	1,228 (1.22)	99,443 (98.78)	1	1	
Hemiplegia	3 (1.19)	249 (98.81)	0.98 (0.31–3.05)	0.52 (0.16–1.64)	0.261
Non-HTN	877 (1.14)	75,984 (98.86)	1	1	
HTN	354 (1.47)	23,708 (98.53)	1.29 (1.14–1.47)	0.72 (0.63–0.82)	<0.0001

Table 3 (continued)

Factor	ESCC (n = 1,231)	No ESCC (n = 99,692)	Crude OR (95% CI)	Adjusted OR [†] (95% CI)	p value
Non-HL	1,085 (1.24)	86,478 (98.76)	1	1	
HL	146 (1.09)	13,214 (98.91)	0.88 (0.74–1.05)	0.53 (0.45–0.64)	<0.0001
Non-IHD	1,213 (1.23)	97,678 (99.36)	1	1	
IHD	18 (0.89)	2,014 (99.11)	0.72 (0.45–0.15)	0.37 (0.23–0.59)	<0.0001
Non-mild LD	1,145 (1.19)	95,357 (98.81)	1	1	
Mild LD	86 (1.95)	4,335 (98.05)	1.65 (1.32–2.06)	0.90 (0.72–1.13)	0.374
Non-severe LD	1,218 (1.21)	99,128 (98.79)	1	1	
Severe LD	13 (2.25)	564 (97.75)	1.88 (1.08–3.26)	0.62 (0.35–1.09)	0.093
Non-malignancy (metastasis–)	859 (0.93)	91,314 (99.07)	1	1	
Malignancy (metastasis–)	372 (4.25)	8,378 (95.75)	4.72 (4.17–5.34)	3.00 (2.55–3.53)	<0.0001
Non-malignancy (metastasis+)	1,082 (1.22)	95,448 (98.88)	1	1	
Malignancy (metastasis+)	149 (3.39)	4,244 (96.61)	3.10 (2.60–3.69)	0.81 (0.60–1.08)	0.154
Non-PVD	1,201 (1.22)	96,969 (98.78)	1	1	
PVD	30 (1.09)	2,723 (98.91)	0.89 (0.62–1.28)	0.46 (0.32–0.67)	<0.0001
Non-PD	1,135 (1.19)	93,924 (98.81)	1	1	
PD	96 (1.64)	5,768 (98.36)	1.38 (1.12–1.70)	0.77 (0.62–0.96)	0.019
Non-RD	1,226 (1.22)	99,283 (98.78)	1	1	
RD	5 (1.21)	409 (98.79)	0.99 (0.41–2.40)	0.69 (0.28–1.67)	0.406
Non-TIA	1,229 (1.22)	99,562 (98.78)	1	1	
TIA	2 (1.52)	130 (98.48)	1.25 (0.31–5.04)	0.69 (0.17–2.84)	0.608
Non-PUD	775 (0.86)	88,923 (99.14)	1	1	
PUD	456 (4.06)	10,769 (95.94)	4.86 (4.32–5.46)	3.72 (3.28–4.21)	<0.0001
Non-UAG	1,143 (1.21)	93,075 (98.79)	1	1	
UAG	88 (1.31)	6,617 (98.69)	1.08 (0.87–1.35)	0.62 (0.49–0.77)	<0.0001
Non-VD	1,218 (1.22)	98,383 (98.78)	1	1	
VD	13 (0.98)	1,309 (99.02)	0.80 (0.46–1.39)	0.57 (0.33–0.99)	0.049

ESCC, oesophageal squamous-cell carcinoma; OR, odds ratio; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; COX2I, cyclooxygenase-2 inhibitor; PPI, proton pump inhibitor; Af, atrial fibrillation; AIDS, acquired immunodeficiency syndrome; AT, arterial thrombosis; CD, carotid disease; CVD, cerebrovascular disease; CHF, chronic heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; COMP, complications; DVT, deep-vein thrombosis; GERD, gastro-oesophageal reflux disease; HTN, hypertension; HL, hyperlipidaemia; LD, liver disorder; PE, pulmonary embolism; PVD, peripheral vascular diseases; PD, pulmonary disease; RD, rheumatic diseases; TIA, transient ischaemic attack; PUD, peptic ulcer disease; UAG, unstable angina diseases; VD, valvular diseases. [†]OR adjusted for age >70 years, sex, GERD, and Charlson comorbidity index (except for the variable analysed).

(aOR 0.26, 95% CI 0.19–0.34), COX2I (aOR 0.51, 95% CI 0.36–0.72), steroids (aOR 0.26, 95% CI 0.20–0.35), statin (aOR 0.31, 95% CI 0.24–0.41), and metformin (aOR 0.32, 95% CI 0.18–0.57) were associated with a lower risk of ESCC than that in PPI without these medications. A combination of PPI and aspirin (aOR 0.27, 95% CI 0.11–0.68) was associated with a lower risk of EAC compared with PPI without aspirin.

Discussion

In this multicentre retrospective cohort study, we found that the use of PPI, aspirin, COX2I, steroid, statin, and metformin was associated with a lower risk of ESCC,

while aspirin and steroids were associated with a lower risk of EAC.

In line with the previous studies, being male is one of the main risk factors of both ESCC and EAC. One likely reason for this is that male patients tend to have more tobacco and alcohol consumption than female patients, both of which are clear risk factors of ESCC and EAC. Moreover, female hormones are reported to be preventive for ESCC and EAC in several previous studies [11–13]. Indeed, subgroup analysis according to age classes showed that the OR of male compared to female for EAC steadily decreased with ageing, while that for ESCC continuously increased (online suppl. Table 4). Furthermore, menopausal hormone drugs tended to be associated with a lower risk of both ESCC and EAC for female patients

Table 4. Clinical factors associated with EAC (*n* = 306,682)

Factor	EAC (<i>n</i> = 195)	No EAC (<i>n</i> = 306,687)	Crude OR (95% CI)	Adjusted OR [†] (95% CI)	<i>p</i> value
Female	35 (0.02)	157,226 (99.98)	1	1	
Male	160 (0.11)	149,461 (98.89)	4.81 (3.34–6.93)	3.46 (2.36–5.07)	<0.0001
Age ≤70	115 (0.06)	191,559 (99.94)	1	1	
Age >70	80 (0.07)	115,128 (99.93)	1.16 (0.87–1.54)	0.87 (0.65–1.16)	0.336
Non-smoking	77 (0.04)	206,995 (99.96)	1	1	
Smoking	118 (0.12)	99,692 (98.78)	3.18 (2.39–4.24)	1.91 (1.41–2.59)	<0.0001
No PPI	166 (0.06)	279,408 (99.94)	1	1	
PPI	29 (0.11)	27,279 (99.89)	1.79 (1.21–2.66)	0.66 (0.42–1.04)	0.072
No NSAIDs	118 (0.06)	199,750 (99.94)	1	1	
NSAIDs	77 (0.07)	106,937 (99.94)	1.22 (0.92–1.62)	0.91 (0.68–1.23)	0.554
No aspirin	185 (0.07)	280,979 (99.93)	1	1	
Aspirin	10 (0.04)	25,708 (99.96)	0.59 (0.31–1.12)	0.33 (0.17–0.62)	0.0006
No COX2I	184 (0.06)	289,950 (99.94)	1	1	
COX2I	11 (0.07)	16,737 (99.93)	1.04 (0.56–1.90)	0.82 (0.44–1.53)	0.536
No steroid	178 (0.06)	279,624 (99.94)	1	1	
Steroid	17 (0.06)	27,063 (99.94)	0.99 (0.60–1.62)	0.54 (0.32–0.91)	0.022
No statin	167 (0.06)	272,652 (99.94)	1	1	
Statin	28 (0.08)	34,035 (99.92)	1.34 (0.90–2.01)	0.93 (0.62–1.40)	0.716
No strong statin	170 (0.06)	277,718 (99.94)	1	1	
Strong statin	25 (0.09)	28,969 (99.91)	1.41 (0.93–2.15)	0.92 (0.60–1.41)	0.705
No fibrate	192 (0.06)	304,191 (99.94)	1	1	
Fibrate	3 (0.12)	2,496 (98.88)	1.91 (0.61–5.96)	1.21 (0.39–3.79)	0.747
No other lipid-lowering agent	190 (0.06)	302,740 (99.94)	1	1	
Other lipid-lowering agents	5 (0.13)	3,947 (99.87)	2.02 (0.83–4.91)	1.31 (0.54–3.21)	0.548
No metformin	186 (0.06)	298,839 (99.94)	1	1	
Metformin	9 (0.11)	7,848 (99.89)	1.84 (0.94–3.60)	1.10 (0.56–2.16)	0.779
Non-Af	193 (0.06)	304,030 (99.94)	1	1	
Af	2 (0.08)	2,657 (98.92)	1.19 (0.29–4.78)	0.66 (0.16–2.68)	0.560
Non-AIDS	195 (0.06)	306,574 (99.94)	1	1	
AIDS	0 (0)	113 (100)	NA	NA	–
Non-AT	194 (0.06)	305,244 (99.94)	1	1	
AT	1 (0.07)	1,443 (98.93)	1.10 (0.15–7.79)	0.58 (0.081–4.18)	0.592
Non-CD	194 (0.06)	305,825 (99.94)	1	1	
CD	1 (0.12)	862 (99.88)	1.83 (0.26–13.06)	0.82 (0.11–5.88)	0.841
Non-CVD	189 (0.06)	293,966 (99.94)	1	1	
CVD	6 (0.05)	12,721 (99.95)	0.73 (0.33–1.66)	0.39 (0.17–0.89)	0.025
Non-CHF	188 (0.07)	286,948 (99.93)	1	1	
CHF	7 (0.04)	19,739 (99.96)	0.54 (0.26–1.15)	0.27 (0.12–0.57)	0.0007
Non-CKD <stage 5	188 (0.06)	299,092 (99.94)	1	1	
CKD <stage 5	7 (0.09)	7,595 (99.91)	1.47 (0.69–3.12)	0.82 (0.38–1.76)	0.606
Non-CKD stage 5	194 (0.06)	305,817 (99.94)	1	1	
CKD stage 5	1 (0.11)	870 (99.89)	1.81 (0.25–12.94)	0.60 (0.083–4.32)	0.610
Non-dementia	195 (0.06)	299,977 (99.94)	1	1	
Dementia	0 (0.00)	6,710 (100.00)	NA	NA	–
Non-DM (COMP–)	156 (0.06)	272,124 (99.94)	1	1	
DM (COMP–)	39 (0.11)	34,563 (99.89)	1.97 (1.39–2.80)	1.48 (0.61–3.60)	0.392
Non-DM (COMP+)	191 (0.06)	297,891 (99.94)	1	1	
DM (COMP+)	4 (0.05)	8,796 (99.95)	0.71 (0.26–1.91)	0.29 (0.11–0.78)	0.015
Non-DVT	193 (0.06)	304,149 (99.94)	1	1	
DVT	2 (0.08)	2,538 (99.92)	1.24 (0.31–5.00)	0.86 (0.21–3.51)	0.837
Non-GERD	145 (0.05)	282,868 (99.95)	1	1	
GERD	50 (0.21)	23,819 (99.79)	4.10 (2.97–5.65)	2.67 (1.89–3.77)	<0.0001
Non-hemiplegia	195 (0.06)	305,979 (99.94)	1	1	
Hemiplegia	0 (0.00)	708 (100.00)	NA	NA	–

Table 4 (continued)

Factor	EAC (n = 195)	No EAC (n = 306,687)	Crude OR (95% CI)	Adjusted OR [†] (95% CI)	p value
Non-HTN	155 (0.06)	249,226 (99.94)	1	1	
HTN	40 (0.07)	57,461 (99.93)	1.12 (0.79–1.59)	0.59 (0.40–0.85)	0.005
Non-HL	180 (0.07)	289,950 (99.93)	1	1	
HL	15 (0.05)	30,666 (99.95)	0.75 (0.44–1.27)	0.42 (0.25–0.72)	0.002
Non-IHD	195 (0.06)	302,875 (99.94)	1	1	
IHD	0 (0.00)	3,812 (100.00)	NA	NA	–
Non-mild LD	183 (0.06)	296,360 (99.94)	1	1	
Mild LD	12 (0.12)	10,327 (99.88)	1.88 (1.05–3.38)	0.91 (0.50–1.67)	0.765
Non-severe LD	195 (0.06)	305,432 (99.94)	1	1	
Severe LD	0 (0.00)	1,255 (100.00)	NA	NA	–
Non-malignancy (metastasis–)	140 (0.05)	286,900 (99.95)	1	1	
Malignancy (metastasis–)	55 (0.28)	19,787 (97.72)	5.70 (4.17–7.78)	3.73 (2.44–5.70)	<0.0001
Non-malignancy (metastasis+)	177 (0.06)	297,056 (99.94)	1	1	
Malignancy (metastasis+)	18 (0.19)	9,631 (99.81)	3.14 (1.93–5.10)	0.55 (0.25–1.20)	0.134
Non-PVD	193 (0.06)	301,388 (99.94)	1	1	
PVD	2 (0.04)	5,299 (99.96)	0.59 (0.15–2.37)	0.26 (0.063–1.04)	0.057
Non-PD	184 (0.06)	292,240 (99.94)	1	1	
PD	11 (0.08)	14,447 (99.92)	1.21 (0.66–2.22)	0.68 (0.36–1.26)	0.218
Non-RD	193 (0.06)	305,207 (99.94)	1	1	
RD	2 (0.13)	1,480 (99.87)	2.14 (0.53–8.62)	1.84 (0.45–7.46)	0.396
Non-TIA	195 (0.06)	306,402 (99.94)	1	1	
TIA	0 (0.00)	285 (100.00)	NA	NA	–
Non-PUD	121 (0.04)	282,541 (99.96)	1	1	
PUD	74 (0.31)	24,146 (99.69)	7.16 (5.36–9.56)	4.92 (3.59–6.73)	<0.0001
Non-UAG	176 (0.06)	292,426 (99.94)	1	1	
UAG	19 (0.13)	14,261 (99.87)	2.21 (1.38–3.56)	1.18 (0.72–1.93)	0.508
Non-VD	189 (0.06)	302,919 (99.94)	1	1	
VD	6 (0.16)	3,768 (99.84)	2.55 (1.13–5.76)	1.95 (0.86–4.43)	0.111

EAC, oesophageal adenocarcinoma; OR, odds ratio; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; COX2I, cyclooxygenase-2 inhibitor; PPI, proton pump inhibitor; Af, atrial fibrillation; AIDS, acquired immunodeficiency syndrome; AT, arterial thrombosis; CD, carotid disease; CVD, cerebrovascular disease; CHF, chronic heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; COMP, complications; DVT, deep-vein thrombosis; GERD, gastro-oesophageal reflux disease; HTN, hypertension; HL, hyperlipidaemia; LD, liver disorder; PE, pulmonary embolism; PVD, peripheral vascular diseases; PD, pulmonary disease; RD, rheumatic diseases; TIA, transient ischaemic attack; PUD, peptic ulcer disease; UAG, unstable angina diseases; VD, valvular diseases. [†]OR adjusted for age >70 years, sex, smoking, GERD, and Charlson comorbidity index (except for the variable analysed).

with age >50 in our cohort (online suppl. Table 5). Therefore, female hormones may be preventive for oesophageal cancers, particularly for EAC.

In our study, PPI use was associated with a lower risk of ESCC but not with EAC. Since PPIs are often used for GERD patients and GERD is likely a confounder for EAC risk, we performed subgroup analyses (online suppl. Table 6). Interestingly, PPI use was associated with a lower risk of both ESCC and EAC in patients with GERD. These results are compatible with those of a previous study that showed that the PPI was chemopreventive against EAC in patients with Barrett's oesophagus [6]. PPIs strongly reduce gastric acid reflux [14] and may contribute to re-

ducing acid reflux-related carcinogenesis in patients with GERD and Barrett's oesophagus.

Although the PPI was shown to be associated with lower risk of both ESCC and EAC, several adverse effects by long-term PPI use should be noted. The recent study showed that long-term PPI use was associated with a higher risk of gastric cancer [15, 16], potentially due to the worsened gastric atrophy by PPIs [17, 18]. Moreover, long-term PPI use causes consequently a high level of serum gastrin, which may increase gastric carcinoid development [19]. Indeed, overexpression of amidated gastrin and/or long-term PPI treatment promote epithelial proliferation and tumorigenesis in the stomach and even the oesopha-

Table 5. Clinical factors associated with EAC in smoking patients (*n* = 99,810)

Factor	EAC (<i>n</i> = 118)	No EAC (<i>n</i> = 99,692)	Crude OR (95% CI)	Adjusted OR [†] (95% CI)	<i>p</i> value
Female	7 (0.03)	27,331 (99.97)	1	1	
Male	111 (0.15)	72,361 (99.85)	5.99 (2.79–12.85)	5.61 (2.61–12.08)	<0.0001
Age ≤70	80 (0.13)	60,042 (99.87)	1	1	
Age >70	38 (0.10)	39,650 (99.90)	0.72 (0.49–1.06)	0.55 (0.37–0.81)	0.0026
No PPI	97 (0.11)	89,424 (99.89)	1	1	
PPI	21 (0.20)	10,268 (99.80)	1.89 (1.18–3.02)	0.82 (0.48–1.41)	0.477
No NSAIDs	75 (0.12)	63,900 (99.88)	1	1	
NSAIDs	43 (0.12)	35,792 (99.88)	1.02 (0.70–1.49)	0.74 (0.50–1.09)	0.129
No aspirin	112 (0.13)	89,488 (99.87)	1	1	
Aspirin	6 (0.06)	10,204 (99.94)	0.47 (0.21–1.07)	0.30 (0.13–0.70)	0.0049
No COX2I	111 (0.12)	94,787 (99.88)	1	1	
COX2I	7 (0.14)	4,905 (99.86)	1.22 (0.57–2.62)	0.90 (0.41–1.96)	0.789
No steroid	107 (0.12)	90,781 (99.88)	1	1	
Steroid	11 (0.12)	8,911 (99.88)	1.05 (0.56–1.95)	0.57 (0.29–1.09)	0.091
No statin	100 (0.11)	87,144 (99.89)	1	1	
Statin	18 (0.14)	12,548 (99.86)	1.25 (0.76–2.07)	0.92 (0.55–1.53)	0.749
No strong statin	102 (0.12)	88,546 (99.88)	1	1	
Strong statin	16 (0.14)	11,146 (99.86)	1.25 (0.74–2.11)	0.90 (0.53–1.53)	0.691
No fibrate	118 (0.12)	98,567 (99.88)	1	1	
Fibrate	0 (0.00)	1,125 (100.00)	NA	NA	–
No other lipid-lowering agent	115 (0.12)	98,157 (99.88)	1	1	
Other lipid-lowering agents	3 (0.20)	1,535 (99.80)	1.67 (0.53–5.26)	1.15 (0.36–3.64)	0.810
No metformin	114 (0.12)	96,325 (99.88)	1	1	
Metformin	4 (0.12)	3,367 (99.88)	1.00 (0.37–2.72)	0.68 (0.25–1.86)	0.454
Non-Af	116 (0.12)	98,528 (99.88)	1	1	
Af	2 (0.17)	1,164 (99.93)	1.46 (0.36–5.91)	1.06 (0.26–4.31)	0.941
Non-AIDS	118 (0.12)	99,632 (99.88)	1	1	
AIDS	0 (0.00)	60 (100.00)	NA	NA	–
Non-AT	117 (0.12)	99,084 (99.88)	1	1	
AT	1 (0.16)	608 (99.84)	1.40 (0.20–9.99)	0.93 (0.13–6.73)	0.944
Non-CD	118 (0.12)	99,233 (99.88)	1	1	
CD	0 (0.00)	459 (100.00)	NA	NA	–
Non-CVD	116 (0.12)	94,480 (99.88)	1	1	
CVD	2 (0.04)	5,212 (99.96)	0.31 (0.077–1.27)	0.21 (0.052–0.86)	0.030
Non-CHF	114 (0.12)	91,829 (99.88)	1	1	
CHF	4 (0.05)	7,863 (99.95)	0.41 (0.13–1.11)	0.24 (0.088–0.66)	0.0057
Non-CKD <stage 5	113 (0.12)	96,584 (99.88)	1	1	
CKD <stage 5	5 (0.16)	3,108 (99.84)	1.38 (0.56–3.37)	0.95 (0.38–2.35)	0.912
Non-CKD stage 5	117 (0.12)	99,310 (99.88)	1	1	
CKD stage 5	1 (0.26)	382 (99.74)	2.23 (0.31–15.95)	0.93 (0.13–6.84)	0.946
Non-dementia	118 (0.12)	97,916 (99.88)	1	1	
Dementia	0 (0.00)	1,776 (100.00)	NA	NA	–
Non-DM (COMP–)	93 (0.11)	84,328 (99.89)	1	1	
DM (COMP–)	25 (0.16)	15,364 (99.84)	1.48 (0.95–2.30)	0.91 (0.57–1.45)	0.677
Non-DM (COMP+)	116 (0.12)	96,053 (99.88)	1	1	
DM (COMP+)	2 (0.05)	3,639 (99.05)	0.46 (0.11–1.84)	0.23 (0.055–0.93)	0.039
Non-DVT	116 (0.12)	98,801 (99.88)	1	1	
DVT	2 (0.22)	891 (99.78)	1.91 (0.47–7.75)	1.46 (0.36–5.98)	0.599
Non-GERD	84 (0.09)	89,832 (99.91)	1	1	
GERD	34 (0.34)	9,860 (99.66)	3.69 (2.38–5.50)	2.76 (1.81–4.23)	<0.0001
Non-hemiplegia	118 (0.12)	99,443 (99.88)	1	1	
Hemiplegia	0 (0.00)	249 (100.00)	NA	NA	–
Non-HTN	100 (0.13)	75,984 (99.87)	1	1	
HTN	18 (0.08)	23,708 (99.92)	0.58 (0.35–0.95)	0.35 (0.21–0.59)	<0.0001

Table 5 (continued)

Factor	EAC (n = 118)	No EAC (n = 99,692)	Crude OR (95% CI)	Adjusted OR [†] (95% CI)	p value
Non-HL	109 (0.13)	86,478 (99.87)	1	1	
HL	9 (0.07)	13,214 (99.03)	0.54 (0.27–1.07)	0.36 (0.18–0.71)	0.0035
Non-IHD	118 (0.12)	97,678 (99.88)	1	1	
IHD	0 (0.00)	2,014 (100.00)	NA	NA	–
Non-mild LD	109 (0.11)	95,357 (99.89)	1	1	
Mild LD	9 (0.21)	4,335 (99.79)	1.82 (0.92–3.59)	1.05 (0.52–2.11)	0.8975
Non-severe LD	118 (0.12)	99,128 (99.88)	1	1	
Severe LD	0 (0.00)	564 (100.00)	NA	NA	–
Non-malignancy (metastasis–)	83 (0.09)	91,314 (99.91)	1	1	
Malignancy (metastasis–)	35 (0.42)	8,378 (99.58)	4.60 (3.09–6.83)	3.91 (2.30–6.64)	<0.0001
Non-malignancy (metastasis+)	105 (0.11)	95,448 (99.89)	1	1	
Malignancy (metastasis+)	13 (0.31)	4,244 (99.79)	2.79 (1.56–4.96)	0.76 (0.28–2.01)	0.573
Non-PVD	117 (0.12)	96,969 (99.88)	1	1	
PVD	1 (0.04)	2,723 (99.96)	0.30 (0.043–2.18)	0.19 (0.026–1.34)	0.095
Non-PD	109 (0.12)	93,924 (99.88)	1	1	
PD	9 (0.16)	5,768 (99.84)	1.34 (0.68–2.66)	0.90 (0.45–1.83)	0.774
Non-RD	118 (0.12)	99,283 (99.88)	1	1	
RD	0 (0.00)	409 (100.00)	NA	NA	–
Non-TIA	118 (0.12)	99,562 (99.88)	1	1	
TIA	0 (0.00)	130 (100.00)	NA	NA	–
Non-PUD	76 (0.09)	88,923 (99.91)	1	1	
PUD	42 (0.39)	10,769 (99.61)	4.56 (3.13–6.66)	3.54 (2.37–5.28)	<0.0001
Non-UAG	108 (0.12)	93,075 (99.88)	1	1	
UAG	10 (0.15)	6,617 (99.85)	1.30 (0.68–2.49)	0.90 (0.46–1.74)	0.752
Non-VD	113 (0.11)	98,383 (99.89)	1	1	
VD	5 (0.38)	1,309 (99.62)	3.33 (1.36–8.16)	2.86 (1.16–7.07)	0.023

EAC, oesophageal adenocarcinoma; OR, odds ratio; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; COX2I, cyclooxygenase-2 inhibitor; PPI, proton pump inhibitor; Af, atrial fibrillation; AIDS, acquired immunodeficiency syndrome; AT, arterial thrombosis; CD, carotid disease; CVD, cerebrovascular disease; CHF, chronic heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; COMP, complications; DVT, deep-vein thrombosis; GERD, gastro-oesophageal reflux disease; HTN, hypertension; HL, hyperlipidaemia; LD, liver disorder; PE, pulmonary embolism; PVD, peripheral vascular diseases; PD, pulmonary disease; RD, rheumatic diseases; TIA, transient ischaemic attack; PUD, peptic ulcer disease; UAG, unstable angina diseases; VD, valvular diseases. [†] OR adjusted for age >70 years, sex, GERD, and Charlson comorbidity index (except for the variable analysed).

gus in mice [20–23]. PPIs also cause gut dysbiosis by suppressing acid secretion, which may affect the development of gastrointestinal cancers and other diseases [24]. Given that the study period in our study was relatively short, we might underestimate the risk for PPI use. Further study is needed to confirm the recommended duration of PPI use for the chemoprevention of ESCC and EAC.

In our study, the use of aspirin, a COX2I, and steroids was associated with a lower risk of ESCC. Aspirin and steroids were also associated with a lower risk of EAC, and COX2Is tend to be related to a lower risk of EAC, but the difference was not statistically significant. Such differences in the results between ESCC and EAC might be due to the sample size of cancer patients as EAC cases accounted for only 10% of all cancer patients in the present study.

Oesophageal tumorigenesis was induced by chronic inflammation resulting from various factors, mainly including smoking, alcohol, and GERD, through interleukin-6/STAT3, nuclear factor-kappaB, and COX2 pathway [25]. Therefore, these anti-inflammatory reagents may suppress chronic inflammation, mainly through downregulation of COX2, which results in decreased cancer risk [26].

In our study, statin use was also associated with a lower risk of ESCC but not with EAC. Several previous studies have shown the chemopreventive effect of statins against EAC [8, 27]. This discrepancy might be due to the small sample size of the EAC in our study. Moreover, the use of metformin was associated with a lower risk of ESCC but not EAC. This result is compatible with those of previous studies [9, 28]. The different effects of metformin on ESCC

Table 6. Drug combination model for ESCC and EAC

Drug combination	ESCC adjusted OR [†] (95% CI)	<i>p</i> value	EAC adjusted OR [†] (95% CI)	<i>p</i> value
PPI	1		1	
PPI and aspirin	0.26 (0.19–0.34)	<0.0001	0.27 (0.11–0.68)	0.006
PPI	1		1	
PPI and COX2I	0.51 (0.36–0.72)	0.0001	0.14 (0.02–1.04)	0.055
PPI	1		1	
PPI and steroid	0.26 (0.20–0.35)	<0.0001	0.49 (0.24–1.03)	0.061
PPI	1		1	
PPI and statin	0.31 (0.24–0.41)	<0.0001	0.65 (0.33–1.27)	0.209
PPI	1		1	
PPI and metformin	0.32 (0.18–0.57)	0.0001	0.26 (0.04–1.89)	0.183

ESCC, oesophageal squamous-cell carcinoma; EAC, oesophageal adenocarcinoma; OR, odds ratio; CI, confidence interval; NSAID, non-steroidal anti-inflammatory drug; COX2I, cyclooxygenase-2 inhibitor; PPI, proton pump inhibitor. [†]OR adjusted for age >70 years, sex, smoking, GERD, and Charlson comorbidity index.

and EAC may suggest the presence of distinct molecular pathways in these cancer variants, but further studies are required to understand the exact biology.

The effect of drug exposure in a subgroup of smoking patients using other logistic models was estimated (Tables 3, 5). In both ESCC and EAC, the effect of drug exposure on cancer was similar in all patient groups. These drugs have potential anti-carcinogenic effects even in patients at high risk of oesophageal cancer. Furthermore, our additional analyses using other logistic models showed that drug combinations of PPI with several drugs were associated with a lower risk of ESCC and EAC (Table 6).

Our study had several strengths. Firstly, we evaluated associations between the use of various drugs and oesophageal cancer in a large number of patients, including both ESCC and EAC. Secondly, this study had multicentre cohort data. Nevertheless, the study has several limitations. Firstly, this was a retrospective study. Secondly, information on risk factors, including diet, body mass index, and family history, was limited to our database. Thirdly, drugs prescribed outside the study centre, including over-the-counter ones, could not be evaluated. Fourthly, the selection bias was concerned as our population was high-volume centre patients in Japan. We speculated that our population had potentially higher comorbidities than in general Japanese population and that risk assessment might be overestimated for healthy population. In addition, smoking exposure and alcohol consumption and alcohol-degrading enzyme activity might differ between Asian population including Japanese and Western country population. Therefore, our results might

reduce generalizability for healthy population and Western country population. Finally, unknown confounders and misclassification might not be arranged precisely due to the study design. Similar studies with detailed database were desirable in the future.

Conclusion

The use of PPI, aspirin, COX2Is, steroids, statins, and metformin was associated with a lower risk of ESCC, even in the smoking population. Aspirin and steroids were also associated with a lower risk of EAC. PPI use was associated with a lower risk of both ESCC and EAC in patients with GERD. These drugs may be potential candidates for the prevention of oesophageal cancer, while long-term effects by these drugs should be carefully assessed in larger and longer cohorts in future.

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Statement of Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki and received ethics approval from the institutional review boards of the University of Tokyo (ID: 2058-[2]). Written informed consent was obtained from the patients.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

J.A., R.N., and Y.H. contributed to the study design. J.A. wrote the initial draft of the manuscript. J.A., R.N., and T.K.1 analysed the data. T.H., K.H., N.Y., T.N., T.S., S.K., T.I., M.A., N.S., Y.T., A.Y., T.K.2, and K.K. provided guidance regarding the study design and contributed to manuscript editing.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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