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ORIGINAL PAPER

Case–control analysis on metformin and cancer of the esophagus

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Abstract
Purpose Metformin use has been associated with decreased cancer risks, though data on esophageal cancer are scarce. We explored the relation between use of metformin or other anti-diabetic drugs and the risk of esophageal cancer.
Methods We conducted a case–control analysis in the UK-based general practice research database (GPRD, now clinical practice research datalink, CPRD). Cases were individuals with an incident diagnosis of esophageal cancer between 1994 and 2010 at age 40–89 years. Ten controls per case were matched on age, sex, calendar time, general practice, and number of years of active history in the GPRD prior to the index date. Various potential confounders including diabetes mellitus, gastro-esophageal reflux, and use of proton-pump inhibitors were evaluated in univariate models, and the final results were adjusted for BMI and smoking. Results are presented as odds ratios (ORs) with 95 % confidence intervals (CI).
Results Long-term use (≥30 prescriptions) of metformin was not associated with a materially altered risk of esophageal cancer (adj. OR 1.23, 95 % CI 0.92–1.65), nor was long-term use of sulfonylureas (adj. OR 0.93, 95 % CI 0.70–1.23), insulin (adj. OR 0.87, 95 % CI 0.60–1.25), or of thiazolidinediones (adj. OR 0.71, 95 % CI 0.37–1.36).
Conclusion In our population-based study, use of metformin was not associated with an altered risk of esophageal cancer.

Keywords Esophageal cancer · Anti-diabetic drugs · Epidemiology · Case–control analysis · Metformin

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Introduction

Worldwide, more than 400,000 incident esophageal cancer cases and almost as many deaths occurred in 2008 [1]. Within the last decades, a sharp increase in the incidence of esophageal adenocarcinoma has been reported in the US [2] as well as in several European countries [3–5]. At the same time, the prevalence of obesity and diabetes has been increasing [6–9]. Obesity has been identified as a major risk factor for adenocarcinoma of the esophagus [10, 11]. Additionally, diabetes has been associated with an increased risk for several cancer entities [12]. However, data for esophageal cancer risk in diabetes patients have been inconsistent. In a recent study, men with diabetes mellitus had a statistically significantly decreased risk for cancer of the esophagus (relative risk, RR, 0.77, 95 % CI 0.72–0.82) [13]. The decrease was mainly driven by the effect in black men (RR 0.54, 95 % CI 0.48–0.60). In an earlier study, diabetes was associated with an increased risk of esophageal adenocarcinoma (adj. OR 1.59, 95 % CI 1.04–2.43), though the risk was attenuated after further adjusting for body mass

index (BMI) (adj. OR 1.32, 95 % CI 0.85–2.05) [14]. Another study analyzing cases of esophageal adenocarcinoma which was based on interview-derived information on comorbid medical conditions found a nonsignificantly increased risk associated with a previous diabetes diagnosis with no trend for diabetes duration [15]. Furthermore, a case–control study found the risk of esophageal cancer to be unaffected by a previous diabetes diagnosis (OR 1.1, 95 % CI 0.8–1.5) [16]. In a recent meta-analysis encompassing 17 studies, the summary relative risk (SRR) for esophageal cancer was 1.30 (95 % CI 1.12–1.50) in diabetic individuals, and the SRR for esophageal adenocarcinoma specifically was 2.12 (95 % CI 1.01–4.46) [17].

Anti-diabetic drugs have also been shown to affect cancer risk, and long-term metformin use has been associated with reduced risks for some cancer types and for cancer overall [18–21]. So far, the association between metformin use and esophageal carcinoma in particular has only been explored in one recent observational study [22]. In this study, results varied according to the covariates included in the model, and only 27 patients with cancer of the esophagus were studied. In a study of patients with esophageal adenocarcinoma where all patients were receiving neoadjuvant chemoradiation therapy, additional metformin use was associated with an increased response rate compared to nonusers of metformin [23]. The pathologic complete response rate was significantly higher in patients with $\geq$150 mg of metformin per day compared to patients taking <150 mg/day. Metformin also inhibited the growth of three esophageal cancer cell lines in an in vitro study [24].

The potential mechanisms by which metformin may exert anti-proliferative activities are not fully understood. Metformin decreases insulin resistance and lowers circulating insulin levels by activating AMP-activated protein kinase (AMPK), leading to decreased hepatic gluconeogenesis and increased uptake of glucose in muscle [25]. Since some cancer entities seem to proliferate more aggressively in a high insulin environment, metformin could be beneficial in slowing down cancer growth [26]. Additionally, metformin has been shown to act as a direct tumor growth inhibitor, at least in part by up-regulation of AMPK activity and by downstream suppression of signaling through the mammalian target of rapamycin (mTOR) [27].

The objective of our study was to assess esophageal cancer risk in users of anti-diabetic drugs and compare them to individuals with no exposure to these drugs.

Methods

Data source

We performed a retrospective case–control analysis using data from the general practice research database (GPRD, since March 2012 part of the data services provision from clinical practice research datalink, CPRD [28]). The GPRD provides health care information on some seven million patients in the UK and has been previously described in detail [29, 30]. General practitioners (GPs) record information on demographics, diagnoses, and drug prescriptions as well as patient referrals and hospital admissions in the GPRD, using standard coding systems. The GPs generate prescriptions directly with the computer, and this information is automatically transcribed into the individual computerized patient profiles. Additionally, the GPRD holds information regarding lifestyle variables such as body mass index (BMI) and smoking. Recorded information on drug exposure and diagnoses has been validated repeatedly and has proven to be of high quality [31–33]. Patients enrolled in the GPRD are representative of the UK with regard to age, gender, and geographic distribution, currently covering about 7 % of the UK population. GPRD is managed by the medicines and healthcare products regulatory agency (MHRA) in the UK. The study protocol was reviewed and approved by the Independent Scientific Advisory Committee for MHRA database research (ISAC). The investigators had only access to anonymized information.

Study population

The study base population included all patients in the GPRD between 40 and 89 years of age from 1 January 1994 to 31 October 2010. Cases were all persons in the study base population who had an incident diagnosis of esophageal cancer recorded during the study period. The date of this first recorded diagnosis for esophageal cancer will be referred to as "index date." We excluded all patients with a recorded diagnosis of HIV, alcoholism, or any malignancy prior to the index date. All cases were required to have a minimum of 3 years of medical history in the GPRD computer record prior to the index date. From the base population, up to 10 controls without any evidence of esophageal cancer were identified at random for each case with esophageal cancer, matched on calendar time (same index date), age, sex, general practice, and number of years of active history in the GPRD prior to the index date. The same exclusion criteria were applied to controls as to cases.

Exposure to metformin or other anti-diabetic agents

We identified from the computer records all prescriptions for insulin and oral anti-diabetic drugs (metformin, sulfonylureas, thiazolidinediones, glinides, and glucosidase inhibitors) prior to the index date. We defined several exposure levels based on the recorded number of prescriptions prior to the index date and classified patients by type of anti-diabetic treatment and by duration of use: short-term

(1–14 prescriptions), medium-term (15–29 prescriptions), or long-term (≥30 prescriptions) use. Additionally, we looked at time since first prescription of an anti-diabetic drug. Glucosidase inhibitors and prandial glucose regulators (glinides) were not included in the final multivariate model, because exposure to these drugs was low.

We compared use of anti-diabetic drugs to nonuse, and use of more than one anti-diabetic drug was possible. We then adjusted for sequential or concurrent use of various anti-diabetic drugs in the multivariate models.

Statistical analysis

We conducted conditional logistic regression analyses using the SAS statistical software version 9.3 (SAS Institute Inc, Cary, NC) to calculate relative risk estimates as ORs with 95 % confidence intervals (CIs) and considered a 2-sided p value of <0.05 as statistically significant. In the main analysis, the index date was shifted back by 2 years in time both for cases and controls (i.e., we assessed all exposure and covariate information from the day 2 years immediately preceding the index date). This was done to take into account the latency of the disease. We controlled for the potential confounders age, sex, general practice, calendar time, and years of recorded history in the database by matching, and for smoking status (never, ex-smoker, current, or unknown) and BMI (<25, 25–29.9, $\geq$ 30 kg/m^2) in the multivariate model. Additionally, we explored the association between various potential confounders and the risk of esophageal cancer in univariate analyses including alcohol consumption, comorbidities such as diabetes mellitus, gastro-esophageal reflux disease (GERD), congestive heart failure, ischemic heart disease, ischemic or hemorrhagic stroke, arterial hypertension, and dyslipidemia and exposure to antacid drugs, nonsteroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, estrogens, and bisphosphonates. Since these variables did not alter the relative risk estimates for the association between use of anti-diabetic drugs and the risk of esophageal cancer by more than 10 %, they were not included in the final multivariate analyses. Metformin has been associated with an increased risk of lactic acidosis in patients with certain cardiovascular comorbid conditions as well as renal disease. This could, in theory, have led to channeled prescribing of metformin to only those patients without the mentioned comorbidities. We therefore compared metformin use in cases and controls with and without these conditions. However, metformin was not less prescribed in patients with comorbid cardiovascular conditions.

In pre-specified sensitivity analyses, we only included cases with esophageal cancer followed by codes for radiotherapy, chemotherapy, surgery for esophageal carcinoma, or specific oncology codes, in order to reduce the risk of potential misclassification of cancer cases. As diabetes has been shown to be associated with an increased cancer risk in several previous studies, we assessed the risk of esophageal cancer in association with anti-diabetic drug use in a population sample restricted to diabetic patients and controls. For this sensitivity analysis, we additionally analyzed time since diabetes diagnosis and HbA_{1c} level (as a proxy of diabetes control).

Furthermore, as certain risk factors have been shown to have a different effect on the risk of esophageal cancer depending on the histology (adenocarcinoma vs squamous cell carcinoma), we searched the patient records for information about the histology of the diagnosed tumor and attempted to perform stratified analyses according to the histological type of esophageal cancer.

Results

We identified a total of 3,819 cases with incident cancer of the esophagus and 38,190 matched controls. Almost two-thirds of cases were men (64.5 %). The mean (± SD) age of cases and controls was 69.1 (± 11.0) years at the index date. Detailed characteristics of cases and controls are displayed in Table 1. The duration of history recorded in the GPRD before the cancer diagnosis ranged from 5–21.8 years in cases and 3–21.9 years in controls, the median of 11.6 years did not differ between cases and controls. A record of radiotherapy or chemotherapy, an oncology code, or esophagus-related surgery was available for 74.3 % of the cancer cases after the cancer diagnosis. The risk for esophageal cancer was increased for current smokers compared with nonsmokers (crude OR 1.89, 95 % CI 1.72–2.07). Obesity (BMI of $\geq$ 30 kg/m^2) was associated with a slightly increased risk for esophageal cancer in the subgroup with a recorded histology for adenocarcinoma (crude OR 1.43, 95 % CI 1.08–1.91) but not in the subgroup with squamous cell carcinoma (crude OR 0.64, 95 % CI 0.38–1.06).

Exposure to some drug groups was associated with a slightly altered esophageal cancer risk in univariate analyses (Table 1), but did not affect the results of the multivariate analyses. A diagnosis of diabetes was associated with a marginally increased risk of esophageal cancer (crude OR 1.13, 95 % CI 1.01–1.27). A long-lasting diabetes history of $>$ 10 years yielded a crude OR of 1.23 (95 % CI 0.90–1.67), compared to patients who had diabetes for less than 2 years. The time since the first diagnosis of diabetes was similar for cases and controls in the three categories of metformin exposure. High HbA_{1c} levels within the last 3 years before the index date were also associated with a slightly, but statistically not significantly increased risk for esophageal cancer (crude OR 1.36, 95 %

Table 1 Characteristics of patients with esophageal cancer and controls

	Cases (%) (n = 3,819)	Controls (%) (n = 38,190)	Crude OR (95 % CI)	p value
Age (years)				
40–59	810 (21.2)	8,133 (21.3)	–	
60–69	1,000 (26.2)	9,914 (26.0)	–	
70–79	1,263 (33.1)	12,770 (33.4)	–	
≥ 80	746 (19.5)	7,373 (19.3)	–	
Sex				
Male	2,463 (64.5)	24,630 (64.5)	–	
Female	1,356 (35.5)	13,560 (35.5)	–	
Smoking				
Nonsmoker	1,335 (35.0)	16,393 (42.9)	1.00 (referent)	
Current	849 (22.2)	5,709 (15.0)	1.89 (1.72–2.07)	<.0001
Past	1,067 (27.9)	9,800 (25.7)	1.38 (1.26–1.51)	<.0001
Unknown	568 (14.9)	6,288 (16.5)	1.10 (0.98–1.22)	0.1046
BMI				
<25	1,071 (28.0)	10,853 (28.4)	1.00 (referent)	
25–29.9	1,170 (30.6)	12,301 (32.2)	0.96 (0.88–1.05)	0.4145
≥30	624 (16.3)	5,471 (14.3)	1.16 (1.04–1.29)	0.0058
Unknown	954 (25.0)	9,565 (25.1)	1.01 (0.92–1.11)	0.8549
Alcohol use				
Never	570 (14.9)	5,328 (14.0)	1.00 (referent)	
Current	2,338 (61.2)	23,307 (61.0)	0.93 (0.84–1.03)	0.1785
Past	43 (1.1)	444 (1.2)	0.90 (0.65–1.26)	0.5477
Unknown	868 (22.7)	9,111 (23.9)	0.88 (0.78–0.99)	0.0291
Comorbidities				
CHF	174 (4.6)	1,402 (3.7)	1.27 (1.07–1.50)	0.0050
IHD	585 (15.3)	5,864 (15.4)	1.00 (0.91–1.10)	0.9504
Hypertension	1,335 (35.0)	13,458 (35.2)	0.99 (0.92–1.06)	0.7134
Stroke/TIA	260 (6.8)	2,661 (7.0)	0.98 (0.85–1.12)	0.7090
Dyslipidemia	445 (11.7)	4,961 (13.0)	0.87 (0.78–0.97)	0.0134
Diabetes	370 (9.7)	3,325 (8.7)	1.13 (1.01–1.27)	0.0390
GERD	557 (14.6)	4,316 (11.3)	1.36 (1.24–1.50)	<.0001
Barrett's esophagus	107 (2.8)	162 (0.4)	6.85 (5.34–8.78)	<.0001
Achalasia	12 (0.3)	19 (0.05)	6.49 (3.12–13.49)	<.0001
Hiatus hernia	312 (8.2)	2,066 (5.4)	1.58 (1.39–1.79)	<.0001
NSAIDs				
No prior use	1,756 (46.0)	16,837 (44.1)	1.00 (ref)	
1–4 Rx	1,164 (30.5)	11,885 (31.1)	0.93 (0.86–1.01)	0.0818
≥5 Rx	899 (23.5)	9,468 (24.8)	0.90 (0.82–0.98)	0.0188
Estrogens (women only)				
No prior use	1,157 (85.3)	11,296 (83.3)	1.00 (ref)	
1–9 Rx	90 (6.6)	1,050 (7.7)	0.81 (0.64–1.02)	0.0746
≥10 Rx	109 (8.0)	1,214 (9.0)	0.84 (0.67–1.05)	0.1260
Bisphosphonates				
No prior use	3,659 (95.8)	36,955 (96.8)	1.00 (ref)	
1–9 Rx	63 (1.7)	581 (1.5)	1.12 (0.86–1.46)	0.4140
≥10 Rx	97 (2.5)	654 (1.7)	1.54 (1.23–1.93)	<.0001
PPIs				
No prior use	2,913 (76.3)	30,599 (80.1)	1.00 (ref)	

Table 1 continued

	Cases (%) (n = 3,819)	Controls (%) (n = 38,190)	Crude OR (95 % CI)	p value
1–14 Rx	510 (13.4)	5,052 (13.2)	1.08 (0.98–1.20)	0.1226
≥15 Rx	396 (10.4)	2,539 (6.7)	1.71 (1.52–1.92)	<.0001
H_2-antihistaminergic drugs				
No prior use	3,011 (78.8)	30,916 (81.0)	1.00 (ref)	
1–14 Rx	577 (15.1)	5,288 (13.9)	1.13 (1.03–1.24)	0.0133
≥15 Rx	231 (6.1)	1,986 (5.2)	1.21 (1.05–1.39)	0.0105

CHF Congestive heart failure, *CI* Confidence interval, *GERD* Gastro-esophageal reflux disease, *IHD* Ischemic heart disease, *OR* Odds ratio, *TIA* Transient ischemic attack, *NSAID* Nonsteroidal anti-inflammatory drugs, *PPIs* Proton-pump inhibitors

CI 0.95–1.95). We included the variables "time since first diagnosis of diabetes mellitus" and "HbA_{1c} level" in the multivariate model, which was restricted to diabetic patients only.

Long-term use of metformin (≥ 30 prescriptions) was not associated with a materially altered risk of esophageal cancer in the main analysis (adj. OR 1.23, 95 % CI 0.92–1.65) or in the analysis restricted to diabetic patients (adj. OR 1.31, 95 % CI 0.93–1.85) (Table 2). When we restricted the analysis to cases with recorded radiotherapy, chemotherapy, oncology codes, or surgery after the cancer diagnosis, the finding for long-term users of metformin was closely similar to the result from the main analysis (adj. OR 1.31, 95 % CI 0.94–1.82). Analyses stratified according to age or sex did not reveal differing relative cancer risks for metformin users (p value for effect modification >0.05). Furthermore, the analysis according to time since first prescription for an anti-diabetic drug yielded similar results compared to the main analysis (adj. OR for metformin use with a first prescription > 5 years before the cancer diagnosis compared with no metformin use was 1.11, 95 % CI 0.79–1.54).

Neither use of sulfonylureas, insulin, or thiazolidinediones was associated with an altered risk of esophageal cancer in the main analysis or in the analysis restricted to diabetic patients (Table 2).

Only very few codes indicating adenocarcinoma (13 % of the cancer cases) or squamous cell carcinoma (4.7 % of the cancer cases) were found in the patient records. Consequently, exposure to antidiabetic drugs within patients with available information on cancer histology was too low to report any meaningful results.

Discussion

This population-based study on the risk of esophageal cancer and use of anti-diabetic drugs did not provide evidence for an association between metformin and the risk of esophageal cancer. The results were similar in various subgroups of patients and in predefined sensitivity analyses. To our knowledge, to date, there is only one study in the literature that has reported an association between use of metformin and esophageal cancer [22]. In this cohort study, ever use of metformin compared with use of other oral anti-diabetic drugs yielded an adjusted hazard ratio of 0.44 (95 % CI 0.07–2.61) in one statistical model, based on only 21 exposed cases and 6 exposed controls. Of note, in additional analyses, HRs markedly differed according to the covariates included in the model (HRs of 1.15, 95 % CI 0.46–2.84 and 1.27, 95 % CI 0.51–3.16, respectively, for esophageal cancer in metformin users). Additionally, the patient population of this study consisted mainly of Asians while we predominantly studied Caucasians.

Our results are in line with observations from previous studies on the risk factors for esophageal cancer. We report an increased risk of esophageal cancer in current smokers, and smoking was reported to increase the risk of both adenocarcinoma and squamous cell carcinoma in a recent analysis of pooled data from 12 case–control studies [34]. Our observation on the increased cancer risk associated with obesity in cases of adenocarcinoma of the esophagus is also consistent with earlier findings [35, 36]. Furthermore, the risk of esophageal cancer in patients from our study with ten or more prescriptions of a bisphosphonate (1.54, 95 % CI 1.23–1.93) lies within the confidence limits of both previous studies, investigating bisphosphonate use and esophageal cancer risk with GPRD data [37, 38].

Several limitations to our study need to be acknowledged. First, misclassification of cancer diagnoses may be present to some degree as we did not review original medical records for esophageal cancer cases. However, esophageal cancer is a reliable diagnosis in the GPRD, as shown by a recent study including chart review of 895 female esophageal cancer patients [39]. In that sample, 92 % of the cases with a recorded diagnosis of esophageal cancer were shown to have a valid diagnosis. We were not able to adjust for socioeconomic status (SES) or diet, two potential risk factors common to both cancer and diabetes [12]. However, by matching on general practice and

Table 2 Risk of cancer of the esophagus and number of prescriptions for anti-diabetic drug in cases and controls

Drugs and No. prescriptions	All patients				Diabetic patients only			
	Cases (%) (n = 3,819)	Controls (%) (n = 38,190)	Adjusted OR[a] (95 % CI)	p value	Cases (%) (n = 370)	Controls (%) (n = 3,700)	Adjusted OR[b] (95 % CI)	p value
Metformin								
No prior use	3,621 (94.8)	36,505 (95.6)	1.00 (referent)		173 (46.8)	1,857 (50.2)	1.00 (referent)	
1–14	63 (1.7)	561 (1.5)	0.99 (0.74–1.33)	0.9482	62 (16.8)	668 (18.1)	0.95 (0.68–1.33)	0.7678
15–29	43 (1.1)	385 (1.0)	1.01 (0.71–1.43)	0.9768	43 (11.6)	433 (11.7)	1.02 (0.69–1.50)	0.9317
≥30	92 (2.4)	739 (1.9)	1.23 (0.92–1.65)	0.1634	92 (24.9)	742 (20.1)	1.31 (0.93–1.85)	0.1280
Sulfonylureas								
No prior use	3,618 (94.7)	36,471 (95.5)	1.00 (referent)		171 (46.2)	1,915 (51.8)	1.00 (referent)	
1–14	59 (1.5)	430 (1.1)	1.33 (0.99–1.80)	0.0623	58 (15.7)	460 (12.4)	1.31 (0.94–1.83)	0.1074
15–29	47 (1.2)	375 (1.0)	1.16 (0.83–1.64)	0.3810	46 (12.4)	363 (9.8)	1.29 (0.89–1.87)	0.1847
≥30	95 (2.5)	914 (2.4)	0.93 (0.70–1.23)	0.6064	95 (25.7)	962 (26.0)	0.86 (0.62–1.21)	0.3873
Insulin								
No prior use	3,752 (98.3)	37,585 (98.4)	1.00 (referent)		303 (81.9)	3,033 (82.0)	1.00 (referent)	
1–14	18 (0.5)	145 (0.4)	1.04 (0.62–1.73)	0.8841	18 (4.9)	147 (4.0)	1.05 (0.62–1.76)	0.8674
15–29	14 (0.4)	110 (0.3)	1.09 (0.61–1.94)	0.7683	14 (3.8)	131 (3.5)	0.90 (0.50–1.62)	0.7139
≥30	35 (0.9)	350 (0.9)	0.87 (0.60–1.25)	0.4475	35 (9.5)	389 (10.5)	0.71 (0.47–1.08)	0.1133
TZD								
No prior use	3,783 (99.1)	37,902 (99.3)	1.00 (referent)		335 (90.5)	3,397 (91.8)	1.00 (referent)	
1–14	25 (0.7)	158 (0.4)	1.38 (0.88–2.18)	0.1627	24 (6.5)	185 (5.0)	1.19 (0.74–1.92)	0.4813
≥15	11 (0.3)	130 (0.3)	0.71 (0.37–1.36)	0.3019	11 (3.0)	118 (3.2)	0.82 (0.42–1.60)	0.5592

OR Odds ratio, *CI* Confidence interval, *TZD* Thiazolidinediones

[a] all patients adjusted for all other medications in this table, BMI, and smoking

[b] diabetic patients only; adjusted for each other, BMI, smoking, diabetes duration, and HbA_{1c} level

thereby on community, we aimed at minimizing potential confounding by SES and by related variables. Moreover, a recent study from Scotland did not show an association between socioeconomic inequalities and esophageal cancer risk [40]. Furthermore, we were not able to differentiate between cases with different cancer histology in the majority of our patient sample, and the number of individuals with known histology who were exposed to anti-diabetic drugs was too small to confer any meaningful interpretation regarding esophageal cancer risk for histological subgroups. Finally, we might have missed a protective effect of metformin due to limited exposure duration of roughly 5 years in patients with ≥30 prescriptions of metformin. However, since we did not observe any trend toward a decreased risk of esophageal cancer among prescription categories of metformin in this study, such an effect seems to be rather unlikely.

There are several strengths of our study. First, we were able to study a large number of patients with a recorded diagnosis of esophageal cancer in a well-established primary care database of high quality and completeness. All information on drug use and disease diagnoses was recorded prospectively, eliminating the possibility of recall bias. Additionally, we were able to evaluate in our analyses several potential confounders such as BMI, smoking habits, as well as comorbid conditions and prescriptions of other drugs. Furthermore, by excluding all patients with less than 3 years of recorded history in the database before the index date, we reduced the risk of including prevalent rather than incident cancer cases. Cases and controls had a comparable duration of diabetes in each metformin exposure category. This speaks against the presence of different time windows of exposure opportunity (time-window bias) in cases and controls. At last, shifting the index date by 2 years backwards in time increased the likelihood that exposure to anti-diabetic drugs preceded the development of esophageal cancer, thus avoiding any protopathic bias (a drug being prescribed for an early manifestation of a disease that has not yet been diagnosed); it also accounted for the latency period of clinically detectable esophageal cancer.

In conclusion, in our population-based study, we did not find evidence for an altered risk of esophageal cancer in association with use of metformin or other anti-diabetic drugs.

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Conflict of interest The authors declare that they have no conflict of interest.

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