Is metformin use associated with a reduced risk of oesophageal cancer? A systematic review and meta-analysis

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ABSTRACT

Objectives Studies on the association between metformin use and the risk of oesophageal cancer (OC) have generated controversial findings. This updated meta-analysis was conducted to reassess the effects of metformin on OC.

Methods A comprehensive search strategy was conducted to select relevant studies from origination to February 2021. Heterogeneity was evaluated through the *Q* test and I^2 statistics. HRs and 95% CIs were pooled through either random-effect or fixed-effect models. Meta-regression, subgroup analyses, sensitivity analysis and publication bias diagnosis were also performed.

Results Seven studies with 5 426 343 subjects were included. Metformin use was associated with reduced risk of OC (HR=0.69, 95% CI 0.54 to 0.87, p<0.001). Sensitivity analysis suggested that the results were relatively stable.

Conclusion Metformin is associated with a reduced risk of OC. More well-designed studies are still needed to further elaborate on these associations.

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INTRODUCTION

Oesophageal cancer (OC), an aggressive malignancy with a poor prognosis, has the seventh highest incidence of all cancers, with more than 604 000 people diagnosed with OC worldwide each year.[1] OC is prone to developing metastasis and has an extremely high mortality rate, ranking sixth among all cancers.[1] In 2020, 544 000 deaths of patients with OC were reported.[1] Considering the rapid development of OC, risk of metastasis and high mortality, early prevention or intervention is especially critical. Thus, multiple medications that may have the potential to reduce the OC risk have been investigated. Previous studies have indicated that proton pump inhibitors[2] and statins[3] might reduce the incidence of OC in the general population.

Given that recent studies have revealed that people with type 2 diabetes might be at greater risk of developing OC and other cancers.[4] The underlying mechanisms of cancer may be closely linked to hyperinsulinemia. Hyperinsulinemia and increased secretion of insulin growth factor have a stimulating effect on cell proliferation.[5] Therefore, treating diabetes may be the key to reducing the incidence and mortality of such cancers. In this respect, the use of antidiabetic medications seems to be essential, so that more studies have been investigating the protective effects of antidiabetic medications. Metformin has been considered the first-line antidiabetic oral agent in treating type two diabetes worldwide.[6] Recent studies suggested its potential protective effects against multiple cancers, including OC.[7–9] Wang *et al* found that metformin exhibited antiproliferative ability and proapoptotic effects in the OC cell line KYSE450, and no significant toxic effects were observed.[10] Several clinical studies[11 12] showed protective effects of metformin, but this remains controversial as Oh and Song[13] did not find a statistically significant protective effect. A previous meta-analysis[14] suggested that metformin was not associated with a reduction in oesophageal carcinogenesis. However, several studies have been published since the publication of the meta-analysis with contrasting results.[15–17] Therefore, it is essential to perform an updated meta-analysis to reassess the effect of metformin on OC.

METHODS

This meta-analysis was performed and reported by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[18] and has been registered on the International Prospective Register of Systematic Reviews.

Search strategy

We performed a systematic literature search to identify eligible studies in Embase, Cochrane Library, PubMed, Web of Science, CBM (China Biomedical Database), CNKI (China National Knowledge Infrastructure), Wanfang (Chinese) Data, and the VIP (Chinese) Database from origination to February 2021. The search terms were as follows: (malignancy OR carcinoma OR adenocarcinoma OR squamous carcinoma OR neoplasm OR tumor OR cancer) AND (esophageal OR esophagus OR oesophageal OR oesophagus) AND (metformin OR dimethylguanylguanidine OR dimethylbiguanidine OR glucophage OR hydrochloride, metformin OR metformin hydrochloride OR HCl, metformin OR metformin HCl). In the Chinese database, the corresponding Chinese phrase would replace the English words.

Inclusion and exclusion criteria

Studies were considered eligible if they fulfilled the following conditions: (1) the research type was

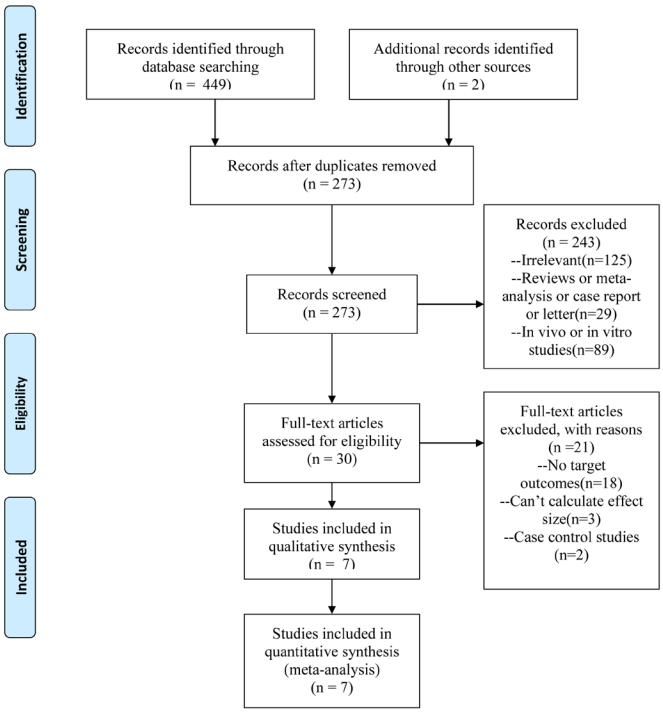

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart.

a cohort study; (2) the ending indicator was the incidence of OC; (3) the experimental group was the use of metformin; (4) HRs, ORs or relative risks with 95% CIs or sufficient data were provided to calculate the effect size. Articles with the following characteristics were excluded: (1) reviews, meta-analysis, case report, in vivo and in vitro studies; (2) insufficient data; (3) duplicate or identical data.

Data extraction and quality assessment

Data extraction and quality assessment were performed independently by two investigators (YC and LH). In case of discrepancy in the process, a third reviewer (CS) was consulted. Data extracted from studies included author, year, study design, comparison (metformin vs non-metformin or metformin vs sulfonylurea), participants' characteristics, HRs with 95% CIs, adjusted confounders and Newcastle-Ottawa Scale (NOS) scores.

The NOS scale was used to evaluate the quality of studies. It consists of three dimensions (group selection, groups comparability and exposures), eight items and a maximum score of 9. Scores of 9–6, 5–4 and 3–0 were rated as high, moderate and low quality, respectively.[19]

Statistical analysis

The association between metformin use and OC outcome was assessed by the pooled HRs with 95% CIs. The method was inverse variance using the logarithm HRs and their estimated variance. Q test and I^2 statistics were used to evaluate the extent of heterogeneity across the studies.[20] If significant heterogeneity (I^2 statistic >50% or Q test <0.1) was observed, then a random-effects model was used, otherwise a fixed-effects model was applied for combined HRs.[21] Sensitivity analysis was performed by switching between fixed and random effects models, for testing the stability of the study results.[22–24] Meta-regression analyses were performed based on the characteristics of the included literature and subgroup analyses were performed according to the results of meta-regression. P value <0.1 suggested that the covariate had a significant effect on heterogeneity.[25] Publication bias was then determined quantitatively by Begg's and Egger's tests.[26 27] The difference was considered statistically significant when the two-sided p value was less than 0.05. All statistical analyses were performed using STATA V.15.0 statistical software (Stata, College Station, Texas).

RESULTS

Study characteristics

The initial search yielded 451 publications and 273 remained after removing duplicates. The irrelevant literature was excluded by reading the titles and abstracts. Then, 30 articles were carefully examined in full text to determine whether they met the inclusion criteria. A total of seven[11–13 15 17 28 29] articles were finally included in this meta-analysis (figure 1).

The studies were published between 2011 and 2020 and detailed summaries are shown in table 1. Four studies were conducted in Asia, three in Western countries. The population sizes of the included studies ranged from 4070 to 4527633. Assessment method for OC was reported in all articles, and all literature possessed high quality.

Overall meta-analysis

HR estimated with its 95% CI was combined using a random-effect model due to the relatively high heterogeneity among the included studies. (I^2=67.6%, $P_{heterogeneity}$=0.005). The pooled HR showed that metformin use was associated with decreased risk of progression to OC (HR=0.69, 95% CI 0.54 to 0.87, p<0.001; figure 2).

Meta-regression and subgroup analyses

We conducted meta-regression analyses on some common covariates, and the results showed that geographic location and comparison contributed more to source of heterogeneity, and sample size did not. Based on the results of meta-regression, subgroup analyses were performed. In the subgroup analysis by comparison of different controls, statistically significant associations were observed whether the comparison was non-metformin or sulfonylurea (HR=0.61, 95% CI 0.50 to 0.74, p<0.001 for non-metformin group; HR=0.90, 95% CI 0.83 to 0.97, p=0.007 for sulfonylurea group). In the case of geographic locations, we found that metformin provided a protective effect in Asia, and the significant effect was also demonstrated in Western countries (HR=0.44, 95% CI 0.30 to 0.65, p<0.001 for Asian countries; HR=0.82, 95% CI 0.69 to 0.98, p=0.026 for Western countries). All these results are represented in table 2.

Sensitivity analyses and publication bias

We conducted a sensitivity analysis by changing the random/fixed effects model, which indicated that our results were relatively stable. In addition, Begg's test showed Z=0.3, p=0.764 and Egger's test showed t = –3.70, p=0.014.

DISCUSSION

Meta-analysis is considered as an important tool to assess the effects of treatment or risk factors for disease more precisely.[30 31] Therefore, we conducted this updated meta-analysis, which identified a 0.69-fold decrease in the risk of developing OC in patients who take metformin (HR=0.69, 95% CI 0.54 to 0.87, p<0.001). This is different from the findings of the previous meta-analysis,[14] which found no statistically significant association between metformin use and OC risk. This difference is

Table 1 Characteristics of the included studies

Author (year)	Study design	Comparison	Region	Sample size (men/women)	Age	Assessment method	Estimate effect (95% CI)	NOS scores	Adjustment factors
Lee *et al* 2011[28]	Cohort	Metformin vs non-metformin	Asia	Exp: 11 212 (–) Con: 4193 (–)	≥20	ICD	HR: 0.44 (0.07 to 2.61)	7	Adjusted*
Ruiter *et al* 2011[11]	Cohort	Metformin vs sulfonylurea	Europe	Exp: 52 698 (24 432/28 266) Con: 32 591 (15 699/16 892)	≥18	ICD-9	HR: 0.90 (0.82 to 0.97)	6	Adjusted†
Tseng 2017[12]	Cohort	Metformin vs non-Metformin	Asia	Exp: 288 013 (155 140/132 873) Con: 16 216 (9293/6923)	Exp: 56.62±10.24 Con: 59.14±10.39	ICD-9-CM	HR: 0.56 (0.33 to 0.94)	8	Adjusted‡
Murff *et al* 2018[29]	Cohort	Metformin vs sulfonylurea	North America	Exp: 88 581 (84 267/4314) Con: 49 282 (48 056/1226)	Exp: 62 (56–71) Con: 67 (58–76)	ICD-9-CM	HR: 0.85 (0.65 to 1.11)	7	Adjusted§
Oh and Song 2019[13]	Cohort	Metformin vs non-metformin	Asia	Exp: 29 974 (–) Con: 36 653 (–)	≥18	ICD-10	HR: 0.38 (0.13 to 1.13)	8	Adjusted¶
Wang *et al* 2019[17]	Cohort	Metformin vs non-metformin	Europe	Exp: 411 603 (239 360/172 243) Con: 4 116 030 (2 393 600/1 722 430)	Exp:59.0 (±13.7) Con:59.0 (±13.7)	ICD-10 and ICD-0–3	HR: 0.68 (0.54 to 0.85)	8	Adjusted**
Sung *et al* 2020[15]	Cohort	Metformin vs non-metformin/asprin	Asia	Exp: 11 365 (5285/6080) Con: 277 932 (148 276/129 656)	≥18	ICD-9/10	HR: 0.27 (0.12 to 0.59)	8	Adjusted††

*Adjusted for age, gender, other oral anti-hyperglycemic medication, Charlson comorbidity index score and duration of metformin exposure.
†Adjusted for age at first OGLD prescription, sex, year in which the first OGLD prescription was dispensed, number of unique drugs used in the year and number of hospitalisations in the year before the start of the OGLD.
‡Adjusted for age, sex, occupation, living region, hypertension, dyslipidaemia, obesity, nephropathy, eye disease, stroke, ischaemic heart disease, peripheral arterial disease, chronic obstructive pulmonary disease, tobacco abuse, alcohol-related diagnoses, HP infection, EBV-related diagnoses, HBV infection, HCV infection, ACEI/ARB, calcium channel blocker, statin, fibrate, aspirin, NSAID.
§Adjusted for age, sex, race, date of cohort entry, body mass index, blood pressure, glomerular filtration rate, haemoglobin A1c, low-density lipoprotein levels, smoking status, select medications, comorbid illnesses number of medications and number of outpatient visits.
¶Adjusted for age, sex, income level, residence, hypertension, coronary artery disease, cerebrovascular disease, psychobehavioral disorder, musculoskeletal disorders, chronic kidney disease, dyslipidaemia, anaemia, chronic obstructive pulmonary disease, arrhythmia, liver cirrhosis, surgery in 2010, hospital visit days in 2010, other antidiabetic medications use.
**Adjusted for age, sex, calendar year, residence, smoking, and alcohol overconsumption, nonsteroidal anti-inflammatory drugs/aspirin and statin use.
††Adjusted for age, sex, comorbidities and other medications.
ACEI/ARB, Angiotensin-converting enzyme inhibitor/Angiotensin receptor blocker; Con, Control group; EBV, Epstein-Barr virus; Exp, Experimental group; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HP, Helicobacter pylori; ICD, Classification of Diseases; NOS, Newcastle-Ottawa Scale; NSAID, non-steroidal anti-inflammatory drugs; OGLD, Oral glucose-lowering drug.

likely because more studies have been included in this meta-analysis. The increased number of included studies and subsequent larger pool size yielded greater statistical power and allowed us to render a more convincing result. Sensitivity analysis also confirmed the relative stability of our results.

Subgroup analysis showed that metformin use was associated with a 56% reduction in OC incidence in Asian countries, and 18% reduction in Western countries. It appeared that metform could be associated with a greater reduction in OC incidence in Asian countries compared with Western countries. This

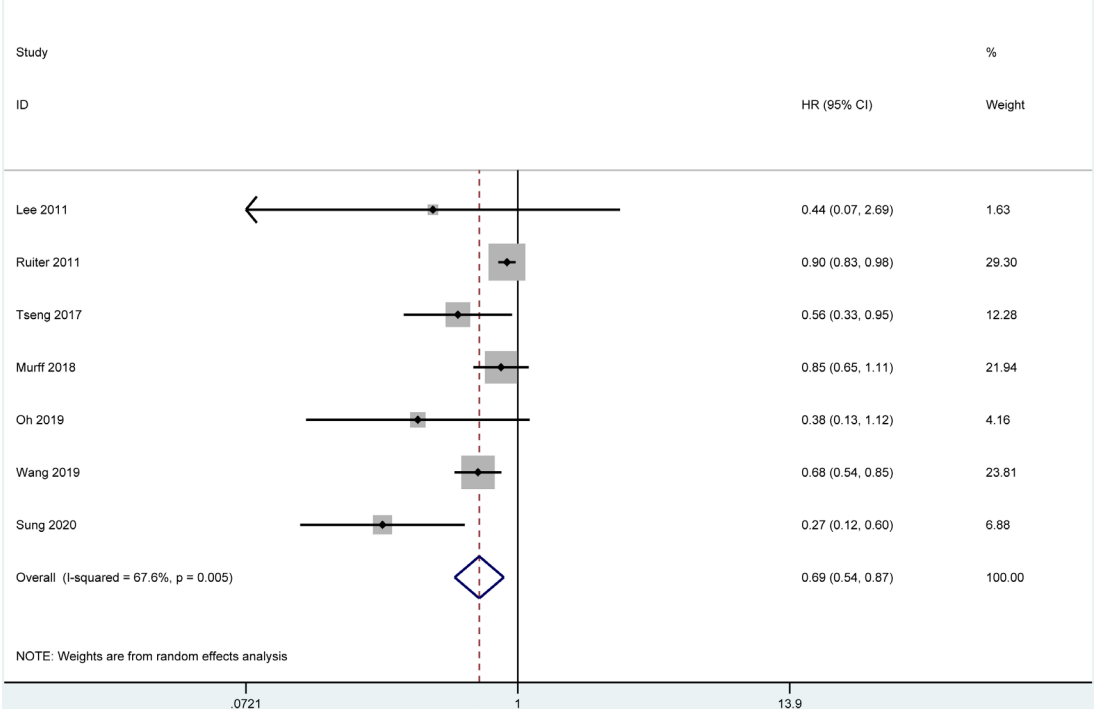

Figure 2 Forrest plot: association between metformin use and the risk of oesophageal cancer.

Table 2 Summary of pooled RRs with CI in the meta-analysis

Analysis	Meta-regression		Number of studies	HR (95% CI)	Heterogeneity		Significant		Model
	β	P			P	I^2(%)	Z	P	
Overall			7	0.69 (0.54 to 0.87)	0.005	67.6	4.36	<0.001	Random
Comparison	0.610	0.007							
Metformin vs non-metformin			5	0.61 (0.50 to 0.74)	0.209	31.8	4.92	<0.001	Fixed
Metformin vs sulfonylurea			2	0.90 (0.83 to 0.97)	0.507	0.0	2.70	0.007	Fixed
Geographic locations	0.432	0.012							
Western			3	0.82 (0.69 to 0.98)	0.075	61.4	2.23	0.026	Random
Asian			4	0.44 (0.30 to 0.65)	0.507	0.0	4.08	<0.001	Fixed

might be explained by discrepancies in prevalence of various subtypes of OC between Asian and Western countries. OC is formed when normal epithelial cells of the oesophageal mucosa are stimulated by various factors inside and outside the body to gradually become cancerous. According to its pathological classification, OC can be divided into squamous carcinoma and adenocarcinoma. Statistics indicate that in Asia, squamous OC accounts for 90% of OCs, while Western populations are more likely to develop oesophageal adenocarcinoma.[1] The risk factors for oesophageal squamous carcinoma and oesophageal adenocarcinoma are not the same. For instance, betel nut chewing, consumption of pickled vegetables, hot drinks and hot food are risk factors for oesophageal squamous carcinoma,[32] while the risk of oesophageal adenocarcinoma is increased with obesity, Barrett's oesophagus and gastro-oesophageal reflux disease.[32] Therefore, it would be reasonable to infer that metformin might have different efficacy on OC with different histopathological aetiologies. However, due to the lack of raw data, subgroups analysis in this regard was not performed. The essential variations in study designs may account for the difference in results obtained from cohort and case–control studies. Recall and selection bias are inherent in case–control studies, and the order of exposure and disease is difficult to ascertain.

Previous studies investigating the mechanism of protective effects of metformin on cancer provided multiple possible explanations for these study's findings. Hardie and colleagues demonstrated that metformin inhibited cancers by activating the Liver kinase b1 (LKB1) -AMP-activated protein kinase (APMK) - mammalian target-of-rapamycin (mTOR) signalling pathway.[33] In mitochondria, metformin uncouples the electron transport chain of complex 1, leading to impaired mitochondrial function and reduced ATP synthesis, followed by activation of AMP-activated protein kinase (AMPK) through LKB1 phosphorylation. AMPK undergoes phosphorylation and activates the tumour suppressor tuberous sclerosis complexes 1,2 by inhibiting Ras homologs negatively mediate mTOR activity. This results in restricted mRNA translation and reduced protein synthesis, which in turn inhibits tumour cell proliferation.[34] As for OC, Kobayashi *et al* suggested an alternative mechanism for cancer proliferation: metformin acts on cell cycle proteins to prevent the G1 phase from entering the S phase normally, eventually bringing cells to a standstill in the G0/G1 phase and inducing apoptosis.[35] Furthermore, Wang *et al* discovered that metformin could enhance the sensitivity of cisplatin chemotherapy in OC.[10]

Several limitations of this meta-analysis should be mentioned. First of all, subgroup analysis of oesophageal adenocarcinoma and oesophageal squamous carcinoma could not be performed due to insufficient data of included original studies; therefore, the correlation between metformin use and specific pathologic types of OC could not be established. Second, it is difficult to determine the exact causation as all the included studies were observational. Finally, considerable heterogeneity was discovered; however, we conducted meta-regression and subgroup analyses to investigate the impact.

Despite these limitations, our meta-analysis had some notable advantages. First, sensitivity analysis suggested that the study result was relatively stable. Second, compared with the previous meta-analysis, more studies were enrolled, which resulted in a relatively enhanced statistical power, and more comprehensive subgroup analyses were performed in this study.

In conclusion, metformin use is associated with reduced risk of OC. Metformin is a widely used and generally well-tolerated medication for diabetes. Given the high prevalence

Main messages

⇒ This meta-analysis estimates the risk of oesophageal cancer (OC) in patients taking metformin. Overall, metformin use is associated with decreased risk of OC.
⇒ More well-designed studies focusing on metformin use and the risk of OC in different geographic locations are warranted.

Current research questions

⇒ The use of metformin may have a potential protective impact against OC. But the effect of metformin still remain controversial.

What is already known on the subject

⇒ Oesophageal cancer (OC) has the seventh highest incidence of all cancers, with more than 604 000 people diagnosed with OC worldwide each year and has an extremely high mortality rate.
⇒ Recent studies have revealed that people with type 2 diabetes might be at greater risk of developing OC and other cancers.
⇒ More studies have been investigating the protective effects of antidiabetic medications, like metformin. It has been found to have potential protective effects against multiple cancers, including OC.

of diabetes and the increased risk of OC among diabetic patients, metformin's effect on OC in our study is promising. However, more well-designed studies are warranted to further elaborate on these associations.

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Contributors CS designed the study, performed literature search, collected the data, performed statistical analysis, interpret data and wrote the manuscript. YC performed literature search, collected the data, statistical analysis, interpret data and wrote the manuscript. LH and XC performed literature search, collected the data, statistical analysis and wrote the manuscript. YW performed literature search, statistical analysis, interpret data, revised the manuscript and provided critical opinion. NHK, SK and FQ provided critical opinion and revised the manuscript. CB and KYK revised the manuscript. RM, CCD and QZ provided critical opinion, participated in literature search and revised the manuscript. All authors approved the final manuscript.

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