Metformin in Esophageal Cancer

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Esophageal cancer (EC), ranking sixth in global cancer mortality, comprises two distinct diseases: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). EAC is linked to Barrett's esophagus (BE), influenced by factors like gastroesophageal reflux disease (GERD) and obesity, while ESSC arises from squamous cells, with tobacco and alcohol as notable risks.

Keywords: esophageal cancer (EC) ; esophageal adenocarcinoma (EAC) ; esophageal squamous cell carcinoma (ESCC)

1. Introduction

The role of metformin in the context of esophageal cancer (EC) is currently under in-depth clinical investigation, aimed at unraveling its significance and therapeutic potential. Research on metformin's role in esophageal cancer has yielded mixed results, revealing a complex connection. Some studies suggest a potential reduction in cancer risk and improved efficacy in anti-cancer treatments. Ongoing clinical investigations are crucial for elucidating the role of metformin in EC [1]. However, the existing body of evidence remains inconclusive, emphasizing the need for further comprehensive research to establish the precise clinical significance of metformin.

2. Metformin for Esophageal Cancer Risk Reduction

Lee et al. utilized data from the Taiwanese National Health Insurance (NHI) organization to conduct a prospective cohort analysis involving 800,000 individuals [2]. They found that metformin use was associated with a reduced risk of esophageal cancer development. This protective effect remained significant after adjusting for various factors, including age, gender, comorbidity score, duration of metformin use, and the use of other anti-hyperglycemic medications. Furthermore, the study examined different doses of metformin and observed gender-specific effects. Female metformin users had a significantly lower risk of EC, while the risk reduction in male users was not statistically significant. In summary, the findings suggest a potential protective effect of metformin against EC, emphasizing its role in reducing the risk of this specific type of cancer [2]. Tseng et al. investigated the impact of metformin on EC risk among Taiwanese patients with type 2 diabetes mellitus (T2DM). They documented that the incidence of EC was significantly lower in metformin users (25.03 per 100,000 person-years) compared to never users (50.87 per 100,000 person-years), with an overall hazard ratio (HR) of 0.487 (95% confidence intervals: 0.347–0.684). The HR based on cumulative duration of metformin use demonstrated a decreasing trend, suggesting a protective effect with longer use [3]. Becker et al. conducted a case-control analysis investigating the relationship between the use of metformin and other anti-diabetic drugs and the risk of EC. They used data from the UK-based General Practice Research Database (GPRD) and identified cases of individuals aged 40–89 years who were diagnosed with esophageal cancer between 1994 and 2010, and selected ten controls for each case. The controls were matched based on age, sex, calendar time, and the number of years of active history. They found that long-term use (over 30 prescriptions) of metformin did not show a significant association with an altered risk of EC, with an adjusted OR of 1.23 and a 95% CI of 0.92–1.65 [4]. Wang et al. aimed to investigate the relationship between metformin use and the risk of developing esophageal squamous cell carcinoma (ESCC). They conducted a population-based cohort study in Sweden from 2005 to 2015, involving 8.4 million participants. Among them, 411,603 were metformin users, and they were compared to 4,116,030 nonusers. They found that metformin users had a decreased risk of ESCC compared to nonusers, with a more significant reduction in risk among new metformin users and individuals aged 60–69 years. This suggests that metformin may have a protective effect against the development of ESCC [5]. Finally, Loomans-Kropp et al. investigated the impact of common drugs, including metformin, on reducing the risk of EAC. They suggested that the use of proton pump inhibitors (PPIs), statins, non-steroidal anti-inflammatory (NSAIDs) drugs, or metformin may reduce the risk of EAC. Metformin use was associated with reduced odds of EAC, with an odds ratio (OR) of 0.76 (95% CI, 0.62–0.93). This indicates that metformin was associated with a 24% reduction in the odds of developing EAC [6].

Data from two recent meta-analyses present contradictory findings [7][8]. Chen et al. examined the association between metformin use and the risk of EC. The study included seven research papers with a total of 5,426,343 subjects. Their findings indicate that metformin use is associated with a reduced risk of OC, with a pooled HR of 0.69 and a 95% confidence interval (CI) of 0.54 to 0.87 ($p < 0.001$), suggesting that metformin may have a protective effect against EC, emphasizing the need for further well-designed studies to provide additional insights into this association [7]. Conversely, Wu et al. assessed the effect of metformin on esophageal cancer risk in patients with T2DM through a systematic review and meta-analysis. They indicated that metformin did not significantly reduce the risk of EC in patients with T2DM (HR 0.88, 95% CI 0.60–1.28, $p > 0.05$). However, subgroup analyses by geographic location revealed a significant reduction in esophageal cancer risk associated with metformin in Asian patients with T2DM (HR 0.59, 95% CI 0.39–0.91, $p = 0.02$), with no heterogeneity between studies [8]. In conclusion, while metformin did not show a notable reduction in EC risk in T2DM patients overall, a significant risk reduction was observed in Asian populations, although further clarification is needed. The above are summarized in **Table 1**.

Table 1. Table summarizes the studies regarding EC risk reduction. Abbreviations: EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; GC, gastric cancer; CRC, colorectal cancer; HCC, hepatocellular cancer; PC, pancreatic cancer; T2DM, type 2 diabetes mellitus; HR, hazard ratio; OR, odds ratio; CI, confidence interval.

Author/Year	Type of Cancer	Population	Concentration/Duration of Metformin Treatment	Results	Ref.
Lee et al. (2011)	EC, GC, CRC, HCC, PC	480,984 adult Taiwanese participants with T2DM vs. 417,844 non-DM controls	Mean metformin dosage was expressed in daily 500 mg units	↓ CRC and HCC incidences, depending on gender and cancer type (CRC in women, HCC in men), metformin HRs (95% CI): total 0.12 (0.08–0.19), CRC 0.36 (0.13–0.98), HCC 0.06 (0.02–0.16), PC 0.15 (0.03–0.79)], metformin dosage for a significant decrease in cancer incidence was ≤500 mg/day.	[2]
Tseng et al. (2017)	EC	288,013 metformin-treated T2DM Taiwanese adults vs. 16,216 other antidiabetic-drug-treated T2DM Taiwanese adults	Duration of metformin ≥ 2 years	↓ EC [HR (95% CI) 0.487 (0.347–0.684)]	[3]
Becker et al. (2013)	EC	All EC-T2DM patients in the GPRD (40–89 years of age, from1994–2010) vs. EC-free T2DM controls (up to 10 controls for each case)	Long-term (≥30 prescriptions) use	Not associated with a materially altered risk of esophageal cancer (adj. OR 1.23, 95% CI 0.92–1.65)	[4]
Wang et al. (2020)	ESCC Swedish	411,603 T2DM adults vs. 4,116,030 non-T2DM controls	Long-term or 1-year use	↓ ESCC [HR 0.68, 95% CI 0.54–0.85], especially in new-metformin users	[5]
Loomans-Kropp et al. (2021)	EAC	1943 EAC cases vs. 19,430 controls	≥2 prescriptions in the same drug category on different days and drug use must have occurred prior to study selection	Metformin use alone showed significant ↓ EAC risk among all participants [OR 0.65; 95% CI 0.50, 0.82)] and those without BE [OR 0.99; 95% CI 0.28, 3.46]	[6]
Chen et al. (2020)	EC	Meta-analysis of 7 studies with 5,426,343 subjects	NA	↓ EC [HR = 0.69, 95% CI 0.54 to 0.87, $p < 0.001$]	[7]
Wu et al. (2020)	EC	Meta-analysis of 5 studies	NA	Metformin did not reduce EC risk in T2DM patients (HR 0.88, 95% CI 0.60–1.28, $p > 0.05$). Subgroup analyses by geographic location showed that metformin ↓ EC in Asian patients withT2DM (HR 0.59, 95% CI 0.39–0.91, $p = 0.02$), without heterogeneity between studies ($p = 0.80$ and I2 = 0%).	[8]

3. Metformin's Impact on Esophageal Cancer Survival

Wang et al. investigated the relationship between diabetes, metformin use, and survival in EC patients focusing on all-cause and disease-specific mortality [9]. They suggested that EC patients with diabetes but not using metformin had increased all-cause mortality. In contrast, non-diabetic patients and diabetic patients using metformin showed decreased all-cause mortality. They also found a trend of decreasing all-cause mortality with a higher daily dose of metformin. They did not find associations between mortality outcomes and other antidiabetic medications like sulfonylureas, insulin, or thiazolidinedione [9]. However, more research is needed to determine the specific impact of metformin on survival in EC. Skinner et al. focused on the impact of metformin use on the response to therapy in EAC patients undergoing neoadjuvant chemoradiation [10]. They analyzed data from 285 patients treated with concurrent chemoradiation followed by esophagectomy. Among them, 29 were diabetic and taking metformin, 21 were diabetic but not taking metformin, and 235 were non-diabetic. They found that the pathologic complete response (CR) rate was higher in patients taking metformin (34.5%) compared to diabetic patients not taking metformin (4.8%) and non-diabetic patients (19.6%). The higher metformin dose was associated with a greater CR rate. Metformin use was independently associated with pathologic CR, and it was also linked to decreased loco-regional failure following radiation. The findings suggest that metformin may enhance the response to chemoradiation therapy in esophageal cancer, with a dose-dependent effect [10]. Spierings et al. aimed to explore the impact of metformin use on pathological response, overall survival, and disease-free survival in patients with resectable esophageal cancer undergoing neoadjuvant chemo(radio)therapy with curative intent [11]. The research included 461 patients who underwent esophagectomy between March 1994 and September 2013. Among the patients, 43 had T2DM, with 32 using metformin. The findings revealed that metformin use did not lead to higher pathological response rates compared to non-metformin users. They suggested that, contrary to findings in other tumor types, metformin may not have a beneficial effect on EC [11]. Van De Voorde et al. delved into the potential benefits of metformin in patients treated for EC [12]. They included 196 patients categorized as non-diabetic, diabetic and not taking metformin, or diabetic and taking metformin. Most patients underwent trimodality therapy (surgery, chemotherapy and radiation therapy). They found an overall pathologic CR rate of 26%, with 25% for non-metformin users and 39% for diabetics taking metformin. The two-year OS rate was 59%, and metformin use was associated with significantly better distant metastasis-free survival and OS rates. Multivariate analysis confirmed that metformin treatment significantly prolonged survival. They concluded that, in their population-based investigation, metformin use was linked to improved overall and distant metastasis-free survival in patients with EC [12].

A recent meta-analysis provides a wealth of evidence towards this direction [13]. Sakamoto et al. presented the first meta-analysis investigating the impact of metformin on neoadjuvant chemoradiotherapy (NACRT) in rectal and esophageal/gastroesophageal cancer patients. They reported that the metformin group exhibited an increased pathologic CR rate compared to the non-metformin group. Notably, diabetic patients, who typically face a poorer cancer prognosis, demonstrated an association between metformin use and the pCR rate. The study focused on advanced cancers of grade T3 or higher, with advanced cancers contributing significantly to the observed association between metformin and the pCR rate. The study suggested that metformin's effectiveness may be particularly pronounced in EAC, as no effect was demonstrated in studies including patients with ESCC. The anti-cancer effects of metformin are attributed to mechanisms such as mTOR inhibition and synergistic effects with chemotherapy and radiotherapy. Further research, including randomized controlled trials, is encouraged to elucidate metformin's efficacy, especially in non-diabetic patients. These are briefly mentioned in **Table 2**.

Table 2. The influence of metformin on survival rates of EC. Abbreviations: EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; T2DM, type 2 diabetes mellitus; CRT, chemoradiation therapy; HR, hazard ratio; OR, odds ratio; CI, confidence interval; *n*, number of patients; CR, complete response rate; pCR, pooled complete response rate; NA, non-applicable.

Author/Year	Type of Cancer	Population	Concentration/Duration of Metformin Treatment	Results	Ref.
Wang et al. (2023)	**EC**	**T2DM + no metformin (*n* = 379), no T2DM + no metformin (*n* = 3999), T2DM + metformin (*n* = 473)**	**Any dose**	**↓ all-cause mortality in non-T2DM patients and metformin-T2DM patients, ↓ HRs of all-cause mortality with a higher daily dose of metformin (Ptrend = 0.04)**	**[9]**

Author/Year	Type of Cancer	Population	Concentration/Duration of Metformin Treatment	Results	Ref.
Skinner et al. (2013)	EAC	286 EAC patients treated with concurrent CRT followed by esophagectomy (29 T2DM + metformin patients, 21 T2DM + no metformin patients, 235 non-T2DM)	Any dose	↑ CR rate in T2DM + metformin patients vs. T2DM + no metformin patients (34.5% vs. 4.8%, $p = 0.01$) and vs. non-T2DM (19.6%, $p = 0.05$), ↑ CR rate with ≥ 1500 mg/d metfromin, ↓ in field loco-regional failure following radiation ($p = 0.05$)	[10]
Spierings et al. (2015)	EC	461 EC patients treated with concurrent CRT followed by esophagectomy (32 T2DM + metformin patients)	Any dose	No differences in pathological response rates or overall survival or disease-free survival between meformin to non-metformin users	[11]
Voorde et al. (2015)	EC	196 EC adult patients (19 T2DM + metformin patients, 5 T2DM + no metformin patients, 172 non-T2DM)	Any dose	↑ distant metastasis-free survival rate ($p = 0.040$), ↑ overall survival rate ($p = 0.012$), ↑ survival ($p = 0.043$)	[12]
Sakamoto et al. (2022)	EC, rectal cancer	meta-analysis of 5 studies with 2041 patients	NA	↑ pCR rate (OR= 0.51 [0.34–0.76], $p < 0.01$), a positive correlation of metformin with EAC (coefficient = 0.13 [0.02–0.25], $p = 0.03$) and fluoropyrimidine anticancer drug use (coefficient = 0.01 [0.001–0.02], $p = 0.03$).	[13]

4. Metformin as a Chemopreventive Agent

An accumulating body of evidence strongly suggests that metformin holds promise as a chemopreventive agent. Arai et al. conducted a multicenter retrospective cohort analysis to investigate the chemopreventive effects of commonly used drugs on ESCC and EAC [14]. They showed that the use of PPIs, aspirin, cyclooxygenase-2 inhibitor (COX2I), steroids, statins, and metformin was associated with a lower risk of ESCC compared to non-use. Specifically, the adjusted ORs (aORs) for ESCC were 0.48 for PPIs, 0.32 for aspirin, 0.70 for COX2I, 0.19 for steroids, 0.43 for statins, and 0.42 for metformin. Contrarily, Chak et al. aimed to assess the potential chemopreventive effects of metformin on BE, focusing on its impact on phosphorylated S6 kinase (pS6K1), a biomarker of insulin pathway activation [15]. In a randomized, double-blind, placebo-controlled phase 2 trial with 74 BE subjects, metformin (daily up to 2000 mg for 12 weeks) did not significantly reduce esophageal pS6K1 levels compared to placebo. While metformin did show an almost significant reduction in serum insulin levels and insulin resistance, it did not affect cell proliferation or apoptosis in esophageal tissues. These findings do not support metformin as a chemopreventive agent for BE-associated carcinogenesis. In the same direction, Agrawal et al. aimed to explore the impact of metformin use on the risk of developing esophageal adenocarcinoma in patients with BE [16]. Over a 20-year period, 583 patients with BE or EAC were identified. Age, smoking, and diabetes mellitus were identified as significant risk factors for EC, while statin use showed a protective effect. However, metformin use did not exhibit a statistically significant association, suggesting it did not demonstrate a protective effect against the development of EAC in this research. Notably, Antonowicz et al. focused on the presence of volatile aldehydes in the breath of EAC patients and their potential for early diagnosis improvement [17]. They revealed that EAC patients exhibit an enrichment of volatile aldehydes, particularly short-chain alkanals and medium-chain alkanals, including decanal, in biopsies and adjacent tissues. The identified short-chain alkanals form DNA adducts, indicating genotoxicity and inadequate detoxification in EAC. They suggested that metformin plays a role in enhancing aldehyde detoxification, as evidenced by its ALDH-enhancing and aldehyde-scavenging effects. Aldehyde accumulation in EAC is associated with genotoxicity, and metformin's potential to augment aldehyde detoxification may have implications for chemopreventative strategies in precancerous conditions like Barrett's esophagus. Additionally, the findings underscore the clinical relevance of exhaled aldehydes as potential diagnostic biomarkers for early detection of EAC [17].

Summarizing, metformin's role in EC presents conflicting results, with some studies suggesting a potential for risk reduction and enhanced anti-cancer treatment efficacy. However, the evidence remains inconclusive, warranting further research to determine its precise clinical significance. The above are briefed in **Table 3**.

Table 3. A summary of Metformin's role as a chemopreventive agent. Abbreviations: EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; BE, Barrett's esophagus; T2DM, type 2 diabetes mellitus; CRT, chemoradiation therapy; HR, hazard ratio; OR, odds ratio; aOR, adjusted odds ratio; CI,

confidence interval; *n*, number of patients; CR, complete response rate; pCR, pooled complete response rate; NA, not applicable.

Author/Year	Type of Cancer	Population	Concentration/Duration of Metformin Treatment	Results	Ref.
Arai et al. (2022)	EC	308,793 patients (1911 ESCC, 195 EAC) and 306,687 non-EC patients	Any dose	↓ risk of ESCC (aOR 0.42, $p < 0.0001$)	[14]
Chak et al. (2015)	BE	74 subjects with BE	Randomly assigned to groups given metformin daily (increasing to 2000 mg/day by week 4, $n = 38$) or placebo ($n = 36$) for 12 weeks.	No differences in esophageal levels of pS6K1or epithelial proliferation or apoptosis in esophageal tissues.	[15]
Agrawal et al. (2014)	BE, EC	583 patients (115 EAC, 468 BE)	Any dose	No protective effect of metformin	[16]
Antonowicz et al. (2021)	EAC	Cell lines: FLO-1, OACM5.1, ESO26, KYAE-1, OE33, CPA, CPB, CPD	NA	↑ short-chain alkanals and medium-chain alkanals -> ↓ genotoxicity	[17]

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