Effects of metformin on survival outcomes of pancreatic cancer patients with diabetes: A meta-analysis

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Abstract. Pancreatic cancer risk is reduced by metformin treatment in patients with diabetes. However, the effect of metformin on pancreatic cancer overall survival is unclear. The aim of the present study was to determine the association between metformin and clinical outcomes of pancreatic cancer patients with diabetes. An electronic and manual search was conducted using PubMed, Web of Science, Medline-Ovid and Cochrane Library databases between the beginning and March 31, 2017. A total of 8 studies consisting of 4,293 patients with pancreatic cancer with diabetes were included, comprising 2,033 patients who had received metformin and 2,260 patients who had not. The meta-analysis showed that metformin was associated with a relative survival benefit in pancreatic cancer patients [hazard ratio (HR), 0.81; 95% confidence interval (CI), 0.70-0.93]. These associations were also observed in subgroups of Asian countries 0.64 (95% CI, 0.52-0.80) and Western countries 0.88 (95% CI, 0.82-0.95), as well as diabetes (no indication of diabetes type). Excluding the studies considered as be prone to immortal time bias resulted in HRs (95% CIs) of 0.86 (0.69-1.07). The results of this study support the notion that the use of metformin may improve the overall survival of patients with pancreatic cancer with concurrent diabetes. However, the proposed beneficial effect of metformin on pancreatic cancer survival may be based on immortal time bias. Further carefully designed studies with high quality are warranted to confirm this efficacy.

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Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in both men and women in Western countries (1,2). Despite the recent advances in surgical techniques and adjuvant therapies, prognosis for patients with pancreatic cancer remains poor. The 5-year survival rate is only 24% even in patients with early disease and margin-negative resection. For patients with pancreatic cancer present with unresectable disease, the 5-year survival rate is worse at just 2% (3). More effective treatment strategies are urgently needed for the management of pancreatic cancer.

Metformin, a medication in the biguanide class, is used as an oral glucose-lowing agent in the treatment of type 2 diabetes mellitus (T2DM). It has been reported that metformin treatment reduces hepatic gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase (4). Metformin were reported to play a potential anticancer effect through molecular mechanisms of the mammalian target of rapamycin (mTOR)-signaling pathway and ATM/LKB1/AMPK axis (5-7). Preclinical work has also added to the evidence that metformin have antineoplastic activity in pancreatic cancer cell lines (8). Considering all the results above, it is natural to regard metformin as a well-tolerated and promising agent for prevention and treatment of pancreatic cancer.

So far, there is a growing interest in investigating the role of metformin for its anticancer effect in different cancer types. Three systematic reviews assessed the effects of metformin on clinical outcomes of any type of cancer and reported that metformin was associated with a reduction in overall mortality and cancer-specific mortality (9-11). However, the results vary in the associations between different cancer types and mortality risk with metformin exposure. For example, results of several systematic reviews suggest that treatment with metformin is associated with reduced cancer mortality compared with other glucose-lowering therapies in colorectal (12), breast (13), ovarian and endometrial cancer (14), while was not associated with the reduction of mortality in prostate cancer (15).

Also, several recent observational studies have explored the association between use of metformin and clinical outcomes of pancreatic cancer. Lee *et al* (16) supported that metformin

exposure was associated with improved clinical outcomes of pancreatic cancer patients. However, Hwang *et al* (17), Reni *et al* (18) and Kordes *et al* (19) found that metformin exposure was not associated with survival benefit in subjects with advanced pancreatic cancer. Based on these studies, the relationship between metformin use and the prognosis of pancreatic cancer in diabetic patients is still controversial. Therefore, we performed a systemic review and meta-analysis to assess the effect of metformin usage on survival outcome of patients with concurrent diabetes and pancreatic cancer.

Data collection methods

The meta-analysis was conducted in accordance with the PRISMA guidelines (19), STROBE Statement (20) as well as Cochrane Collaboration guidelines (21).

Search strategy. We searched the PubMed, Web of Science, Medline-Ovid, and Cochrane Library databases for relevant studies up to 31th March 2017, which was performed by two study investigators independently. The keywords combined with corresponding Mesh terms used for searching included (metformin or biguanide or dimethylbiguanidine) and (neoplasms or tumor or cancer or carcinoma or malignancy) and (pancreas or pancreatic). In addition, references cited in the identified studies, recent review articles, meta-analyses and other relevant studies were also scrutinized to identify potentially pertinent articles which possibly missed in the original search.

Eligibility criteria. Inclusion criteria were: (1) patients with a pathologically confirmed diagnosis of pancreatic adenocarcinoma; (2) original articles reported time to event data [hazard ratios (HRs) with 95% confidence interval (CI)] belong to association between metformin use and survival of pancreatic cancer, and (3) study design: Randomized controlled trials, cohort studies, or case-control studies. Additionally, considering that diagnosis of diabetes was regarded as an important confounder of the relationship between metformin exposure and prognosis of pancreatic cancer, we restricted this meta-analysis to studies that included only pancreatic patients pre-existing with diabetes based on medical or pathology reports. We excluded small sample size studies with no time to event data provided or low study quality. No language restriction was performed. When more than one publication reported on the same study, only the publication with most complete dataset or reported recently was included.

Data extraction. Data extraction was performed in duplicate by two independent reviewers based on the inclusion criteria listed above. Any disagreements were reconciled through group discussion. The following information was extracted from eligible articles: Publication data (study title, the first author's last name, study country), study design (clinic-based or population-based cohort studies, RCT or case-control studies), data source, cancer stage, cancer subtypes, sample size, length of follow-up, outcomes, risk estimates with their corresponding CIs, the matching variables in the multivariable model, financial disclosure documentation, and industry sponsorship.

Quality assessment. To ascertain the validity of the eligible studies, the quality of nonrandomized observational studies was evaluated in reference to the Newcastle Ottawa Scale (NOS) by two investigators (22). In this 'star system', included studies were judged on three aspects: Selection of study groups, comparability of studies groups, and the ascertainment of exposure or outcome. Based on this tool, the quality of observational studies, with nine stars at most, was categorized as low quality (less than 4 points), medium quality (a score of 5 or 6), or high quality (a score of 7 or higher).

Statistical analysis. Pooled HRs with 95% CI was analyzed. Heterogeneity across included studies was analyzed by I^2 statistics and Q test (23). I^2 values of >50% or Q test of P-values less than 0.01 represented significant heterogeneity. Publication bias for observational studies was evaluated using Begg's funnel plot and Egger's test ($P<0.05$ indicated the presence of publication bias) (24-26). A DerSimonian-Laird (D-L) random-effect model (27) was selected to calculate the pooled HRs for overall survival (OS). Otherwise, an inverse-variance fixed-effect meta-analysis model (28) was chosen. The subgroup analyses stratified by the potentially important factors, such as study region, diabetes type, cancer stage as well as immortal time bias, were further carried out to examine the source of possible heterogeneity. Forest plot were distinguished according to the author's surname and year of publication to illuminate the HRs with 95% CI. All main statistical analyses were conducted using Review Manager Version 5.3 software package (Oxford, United Kingdom), while publication bias and sensitivity analysis were performed using Stata software (Stata Corp, College Station, TX, USA).

Results

Literature search. We retrieved a total of 2,121 citations through electronic and manual search. After excluding 315 duplicate and 1,778 irrelevant articles based on titles or abstracts, we finally included 28 citations seemed to meet the inclusion criteria for detailed evaluation. After reading the full text, 20 were excluded because article overlapping, no survival information, not diabetic patients and no sufficient data. At last, 8 full articles (16,17,29-34) matched our inclusion criteria and included in this meta-analysis. The process of study selection is shown in a flow diagram (Fig. 1).

Characteristics of included studies and study quality. Data on first author, publication year, country, study design, study period, population, age, cancer treatment, adjusting variables and follow-up time are presented in Table I. The eight observational studies in the meta-analysis of overall survival included 4,293 pancreatic cancer patients with diabetes, including 2,033 patients who took metformin and 2,260 who did not. These studies were all published in recent years (2012 to 2017), and six studies were published in 2016. Five studies were conducted in the United States (29,31-34), two in Korea (16,30), one in UK (17). These eight eligible papers are all retrospective cohort studies. Sample sizes ranged from 44 to 1916 patients. The percentage of metformin users in pancreatic cancer patients ranged from 11 to 57%. Four studies (17,31,34,35) explicitly mentioned exclusion of patients

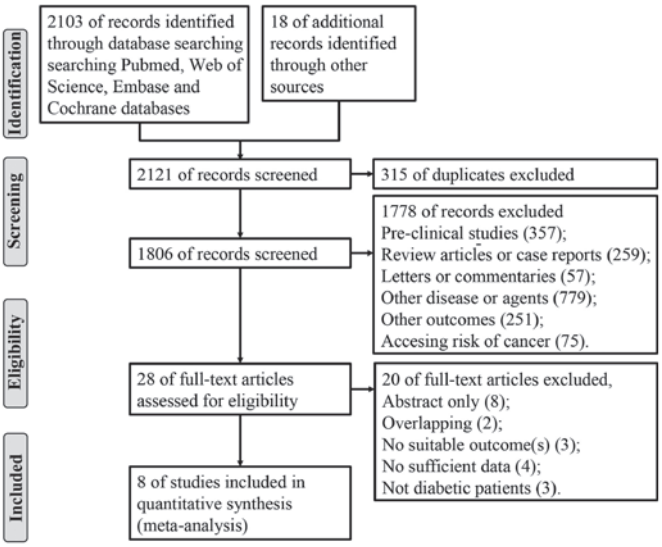

Figure 1. Flow diagram for study selection.

with type 1 diabetes mellitus. In all the 8 studies, all estimates were adjusted for potential confounders using multivariate analysis, though the variables involved were not exactly the same among them. The quality of the 8 included studies was appraised according to the NOS, and NOS scores for each study are shown in Table I. All the 8 included studies are cohort studies. Of the 8 included studies, 3 studies scored 8 and 5 studies scored 7, which showed a high quality of all the included studies.

Quantitative synthesis. The study-specific and pooled HRs for OS associated with metformin in pancreatic cancer patients are shown in Fig. 2. All the eligible studies reported the HR for OS when compared the overall survival of metformin with non-metformin use groups. In a total of 8 studies, 4 studies reported a statistically decreased risk of death from all causes in pancreatic cancer patients with diabetes by multivariate analysis (16,30,32,33). However, no statistically significant differences were observed in the other 4 studies (17,29,31,34). Considering the presence of significant heterogeneity among all the included studies (P=0.01; I^2=64%), we used the random-effects models to conduct the pooled analysis. The pooled results demonstrated that metformin administration to patients with pancreatic cancer and diabetes was associated with a 19% reduced risk for overall mortality compared with those who did not receive metformin (HR: 0.81; 95% CI: 0.70-0.93 by random effect).

In a fixed model analysis stratified by study region (Asian or Western countries), we found that metformin exposure was associated with a significantly reduced risk for death in Asian countries (HR: 0.64; 95% CI: 0.52-0.80 by fixed effect; P=0.57 for heterogeneity; I^2=0%). In the subgroup of Western countries, the meta-analysis demonstrated that the HR of OS was 0.88 (95% CI: 0.82-0.95 by fixed effect; P=0.08 for heterogeneity; I^2=50%) (Table II). We next performed subgroup analyses by diabetes type (diabetes or T2DM). In the subgroup of patients with diabetes (no indication of diabetes type), metformin was still associated with reduced death risk (HR: 0.85; 95% CI: 0.78-0.92 by fixed

Table I. Characteristics of the 8 studies included in the meta-analysis.

Author, year	Country	Range	Sample size (M/N-M)	Age (years)	DM	Cancer stage	Survival analysis	Follow-up	NOS score	(Refs.)
Lee *et al*, 2016	Korea	2005-2013	237 (117/120)	66	T2DM	Resectable LAPC MPC	Multivariate	10.3 months	8	(16)
Hwang *et al*, 2013	UK	2003-2011	516 (247/269)	72.5	T2DM	APC	Multivariate	NR	7	(17)
Ambe *et al*, 2016	USA	1986-2013	44 (19/25)	68	DM	I, II	Multivariate	19 months	8	(30)
Choi *et al*, 2016	Korea	2003-2010	183 (56/134)	59.6	DM	APC	Multivariate	10.2 months	7	(31)
Kozak *et al*, 2016	USA	1998-2013	115 (13/102)	69	T2DM	I, II, III, IV	Multivariate	11.23 months	8	(32)
Sadeghi *et al*, 2012	USA	2000-2009	302 (117/185)	64	DM	Resectable Unresectable Metastatic Nonmetastatic	Multivariate	11.4 months	7	(33)
Amin *et al*, 2016	USA	2007-2011	1916 (1098/818)	76.9	DM	I, II, III, IV	Multivariate	NR	7	(34)
Chaiteerakij *et al*, 2016	USA	2000-2011	980 (366/614)	67.4	T2DM	Resectable LAPC MPC	Multivariate	9.26 months	7	(35)

APC, advanced pancreatic cancer; DM, diabetes mellitus; LAPC, locally advanced pancreatic cancer; M, metformin group; MPC, metastatic pancreatic cancer; N-M, non-metformin group, patients treated with other hypoglycemic drugs but not metformin; NOS, Newcastle-Ottawa Scale; NR, not reported; T2DM, type 2 diabetes mellitus.

Table II. Associations between metformin and overall survival.

Criteria	N	Pooled HR		Heterogeneity	
		Fixed (95% CI)	Random (95% CI)	I^2 (%)	P-value
Main effect	8	0.86 [0.80, 0.92]	0.81 [0.70, 0.93]	60	0.01
Region					
Asian country	2	0.64 [0.52, 0.80]	0.64 [0.52, 0.80]	0	0.57
Western country	6	0.88 [0.82, 0.95]	0.87 [0.76, 1.00]	50	0.08
Diabetes type					
Diabetes	4	0.85 [0.78, 0.92]	0.76 [0.62, 0.94]	50	0.11
T2DM	4	0.88 [0.78, 0.99]	0.84 [0.64, 1.10]	73	0.01
Cancer stage					
Early	1	0.54 [0.16, 1.86]	-	-	-
Advances	2	0.97 [0.81, 1.17]	0.89 [0.56, 1.42]	81	0.02
All stage	5	0.84 [0.78, 0.90]	0.78 [0.67, 0.91]	60	0.04
Immortal time bias					
With	4	0.79 [0.69, 0.89]	0.73 [0.59, 0.92]	49	0.12
Without	4	0.88 [0.82, 0.96]	0.86 [0.69, 1.07]	68	0.03

CI, confidence interval; HRs, Hazard ratios; N, number. of studies; T2DM, type 2 diabetes mellitus.

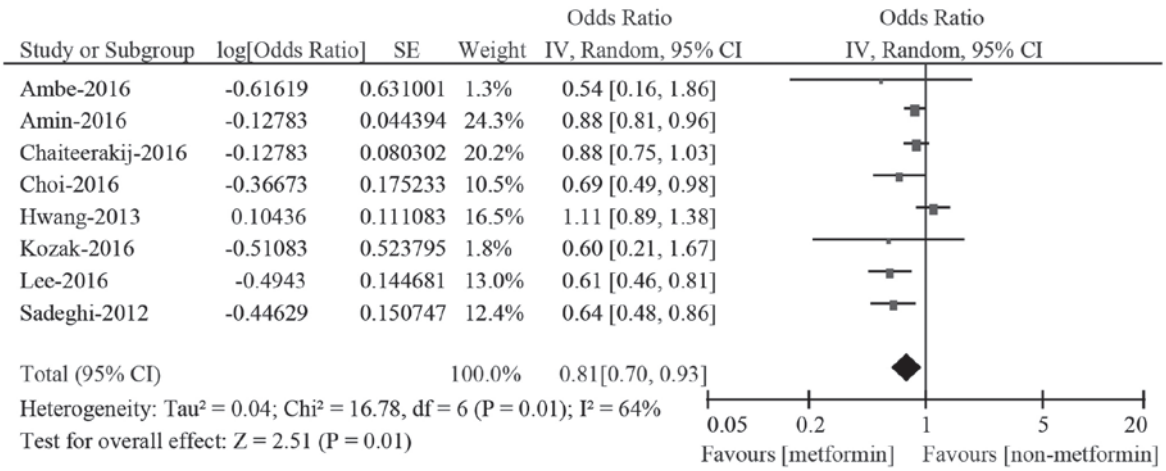

Figure 2. HRs for overall survival associated with metformin exposure vs. non-use. HRs, hazard ratios; CI, confidence interval; df, degrees of freedom.

effect; P=0.11 for heterogeneity; I^2=50%). In the subgroup of patients with T2DM, the relative survival benefit associated with metformin reversed (HR: 0.84; 95% CI: 0.64-1.10 by random effect; P=0.01 for heterogeneity; I^2=73%) (Table II). Analyses on cancer stage did not show beneficial associations besides overall survival among advanced pancreatic cancer patients (HR: 0.89; 95% CI: 0.56-1.42 by random effect; P=0.02 for heterogeneity; I^2=81%). Details of exposure assessment were not presented in studies by Ambe *et al* (30), Chaiteerakij *et al* (35) and Choi *et al* (31), and metformin use with more than 1 month after cancer diagnosis in the study by Lee *et al* (16), perhaps these studies were prone to immortal time bias. Excluding the studies considered as be prone to immortal time bias resulted in HRs (95% CIs) of 0.86 (0.69-1.07).

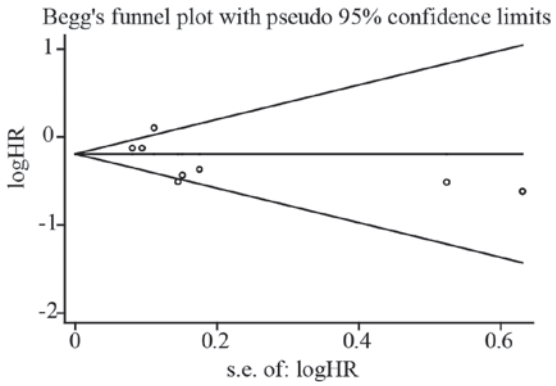

Figure 3. Begg's funnel plot of the included studies for publication bias test on the association of metformin exposure with survival outcomes of pancreatic cancer patients with diabetes.

Sensitivity analysis and publication bias. Taking into account the large variations in the covariates of the included studies, we conducted a sensitivity analysis. Sensitivity analysis was performed by sequential omission of any individual studies to investigate the influence of single data set on the overall meta-analysis. Sensitivity analysis indicated that removal of each study from the meta-analysis did not overthrow the result of the present pooled analysis. However, results in heterogeneity was reduced when remove the study by Hwang *et al* (17). Presence of publication bias evaluated using Begg's funnel plot (P=0.458 for metformin on OS) and Egger's linear regression test (P=0.195 for metformin on OS) showed no obvious publication bias (Fig. 3).

Discussion

Our meta-analysis assessed the effects of metformin exposure on overall survival of pancreatic cancer patients with diabetes mellitus. In fact, our meta-analysis including 4,293 participants from eight cohort studies revealed that diabetic patients with pancreatic cancer using metformin achieved an estimated survival benefit of 19% compared with non-metformin users. In sub-group analysis, metformin administration significantly associated with a good prognosis in patients from Asian. As shown in Western, metformin exposure may also associate with a good prognosis in these patients but the effect was modest.

As a well-accepted anti-diabetes drug, the potential anti-cancer effects of metformin have not been fully elucidated. Metformin modulates several signal pathways crucial to cancer progression. It inhibits lipogenic pathways and activates AMP-activated kinase (AMPK) (36-38), an inhibitor of cellular proliferation via the mammalian target of rapamycin (mTOR) pathway (39,40) to decrease cell metabolism status and reduce serum concentrations of insulin and insulin growth factor I (IGF-I) (41,42). Although experimental evidences have confirmed the anti-tumor effect of metformin, results of clinical and epidemiological researches are complex and inconsistent. Our meta-analysis are inconsistent with a previous meta-analysis of overall survival in pancreatic cancer patients with concurrent diabetes, which included two observational studies and found that metformin use was associated with a survival benefit (HR: 0.668; 95% CI: 0.397-1.125) in patients with resected pancreatic cancer, but no statistically significant difference was found (29).

A number of potential limitations need to be considered in this meta-analysis. First, the included studies are mainly retrospective cohort studies. No randomized controlled trials or prospective studies were included, which reduced the reliability of evidence. Second, high I^2 indicated high heterogeneity between studies, which were actualized in a mixture of populations with different treatment background and diverse inclusion criteria, study population, and adjustment. Third, the included studies didn't show the impact of diabetes type, data of diabetes onset, the concentration or duration of metformin exposure. Thus, the observed benefit from concentration or duration of metformin treatment cannot be clearly defined. Fourth, the impact of other hypoglycemic agents such as insulin, sulfonylureas and thiazolidinedione were only adjusted in one study (17), which might inversely affect clinical outcomes of pancreatic cancer. Finally, after excluding studies prone to have immortal time bias, meta-analysis of existing studies does not support a survival benefit (HR: 0.86, 95% CI: 0.69-1.07, I^2=68%), which suggest that the proposed beneficial effect of metformin on cancer survival might be based on immortal time bias.

There are also several strengths in this meta-analysis. First, one strength of this current meta-analysis was a comprehensive search strategy and inclusion criteria to extract as much information from the literature as possible, including information from any publication type and any language. Second, we performed sensitivity analysis to investigate whether any single study changed the results, and the results showed the robustness of the conclusions. Third, based on the NOS scores, all the eligible studies in the meta-analysis were of high quality with stars ranged from 7-8. At last, both qualitative analysis by Begg's test and Egger's test showed no major publication bias.

In summary, our finding suggests that metformin usage in pancreatic cancer patients with concurrent diabetes seem to have an improved survival outcome. However, the proposed beneficial effect of metformin on pancreatic cancer survival may be based on immortal time bias. Methodological challenges of pharmacoepidemiologic studies have to be taken into account in observational studies of metformin in pancreatic cancer. Further carefully designed observational studies and potentially RCTs should be designed to improve the study quality, as well as taking several confounding factors into consideration, including date of diabetes onset, intensity and duration of metformin exposure as well as other clinical characteristics.

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