Published in final edited form as:

Curr Med Chem. 2018 ; 25(22): 2595–2607. doi:10.2174/0929867324666170412145232.

Effect of Metformin and Statin Use on Survival in Pancreatic Cancer Patients: a Systematic Literature Review and Meta-analysis

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Abstract

Background and Objective—Current epidemiological studies report conflicting results for the effect of statin or metformin on pancreatic cancer overall survival. This literature review and meta-analysis summarize the studies reporting an association between statin or metformin use and overall survival of pancreatic cancer patients.

Methods—We systematically searched for studies about the association between statin or metformin use and pancreatic cancer overall survival in electronic databases (PubMed, ISI Web of Science, MEDLINE, Cochrane, Scopus, Google Scholar). A meta-analysis based on hazard ratios (HRs) and 95% confidence intervals (CIs) was performed using random effect models. Heterogeneity between the studies was examined using I^2 statistics, and sensitivity analyses were conducted to assess the robustness of the findings.

Results—Of 116 statin-related articles identified, 6 retrospective cohort studies representing 12,057 patients were included. There was significant heterogeneity between studies. Statin use was associated with improved survival among pancreatic cancer patients (meta-HR = 0.75; 95% CI:

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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0.59, 0.90; $P < 0.001$). Of 311 metformin-related articles, 8 retrospective cohort studies and 2 randomized clinical trials, representing 3,042 patients were identified. Metformin use was associated with better overall survival among pancreatic cancer patients (meta-HR = 0.79; 95% CI: 0.70, 0.92, $P < 0.001$), and significant heterogeneity was observed between studies.

Conclusion—Our findings suggest that the improved survival time of pancreatic cancer patients are associated with statin or metformin use. Due to the multiple sources of heterogeneity of the original studies, these findings should be considered cautiously, and confirmed with larger prospective individual-level studies.

Keywords

Statin; metformin; pancreatic cancer; overall survival; meta-analysis

INTRODUCTION

Pancreatic cancer is currently the fourth leading cause of cancer related death in US, and it is expected to be the second leading cause by 2020 [1]. Survival rates for this cancer are very low, with the average 1 and 5 year relative survival rates of 27% and 6%, respectively [2]. Even among the minority of patients diagnosed in early stages of pancreatic cancer, the survival rates are still low – the average 5-year survival for stage IA pancreatic cancer is 14% [2]. The currently available drugs to treat pancreatic cancer are expensive, show little increase in overall survival, and are associated with excessive side effects [3]. Furthermore, development of a new drug requires an average of 13 years of intensive research, with typical expenses of US \$1.8 billion from the bench to the patients [4]. To reduce the cost and time involved in anticancer drug development, one possible approach is to explore established non-cancer drugs for anticancer activities, known as ‘drug repurposing’ [5, 6]. Statins and metformin, two old non-cancer drugs with sound safety profiles and that are well tolerated, have shown promising anticancer effects [7, 8]. However their efficacy in the prevention and treatment of pancreatic cancer still remains unclear. This literature review and meta-analysis are conducted to address the possibility of repurposing these two old drugs for potential pancreatic cancer treatment.

Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are prescribed to reduce patients’ serum cholesterol levels and thereby lower morbidity and mortality from cardiovascular disease [9]. However, studies indicate that statins may also inhibit tumor growth and metastasis through a number of mechanisms including [10, 11]: suppressing cell cycle progression and proliferation [12], inducing apoptosis [13], retarding the angiogenic process, and interfering with migration and adhesion of malignant cancer cells [14]. Because of their pleiotropic effects, there has been considerable interest for cancer prevention and treatment of statins for other cancer sites, including liver, breast, and prostate [15–18]. Recent studies have also shown that statins have possible anticancer properties for pancreatic cancer due to the inhibition of post-translational modification of key proteins involved in pancreatic tumor proliferation and metastasis through the mevalonate pathway [19].

Another non-cancer drug, metformin has been widely used to treat Type II diabetes mellitus (DM) for more than 30 years. Extensive preclinical and clinical studies have demonstrated the antitumor properties of this drug over the past decades [20]. Several potential anti-cancer mechanisms of metformin include: a reduction of hyperinsulinemia, growth inhibition by abolishing mTOR activation through AMP-activated protein kinase (AMPK)-dependent or independent mechanism [21–26]; blockage of cell cycle progression [23, 27, 28]; and inhibition of cancer stem cells and alteration of anti-inflammatory properties [29, 30]. Interestingly, metformin has been shown to inhibit pancreatic cancer growth by disrupting the crosstalk between insulin/insulin growth factor 1 (IGF-1) receptor and G protein-coupled receptors (GPCR) [31]. Furthermore, metformin may inhibit pancreatic tumorigenesis by modulating multiple targets in inflammatory pathways [32].

While beneficial effects of statins and metformin in pancreatic cancer treatment are biologically plausible, findings from epidemiological studies assessing the use of these two drugs and survival in pancreatic cancer patients have been inconsistent. Here, we performed a systematic literature review and meta-analysis of retrospective cohort studies and randomized clinical trials to investigate the beneficial effects of statin or metformin on overall survival of pancreatic cancer patients. The results of this study may add to the evidence for repurposing these two established drugs for pancreatic cancer treatment.

METHODS

Literature Search Strategy

This meta-analysis was conducted in accordance with the guidelines for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Observational Studies in Epidemiology (MOOSE) [33, 34]. To identify relevant studies, we searched PubMed, ISI Web of Science (Science Citation Index Expanded), MEDLINE, Cochrane Library, Scopus, Google Scholar, from January 01, 1966 to May 20, 2016. The research terms for statin studies included “Statin” or “Hydroxymethylglutaryl-CoA Reductase Inhibitors” and “Pancreatic Cancer” or “Pancreatic Neoplasm” and “Survival” or “Mortality”. Likewise, the research terms for metformin studies included “Metformin” or “Biguanides” or “Glucophage” and “Pancreatic Cancer” or “Pancreatic Neoplasm” and “Survival” or “Mortality”. Additionally, a manual search was performed for the reference lists of selected articles.

Criteria for Study Selection

Based on a review of the retrieved articles' titles/abstracts and full texts, studies were selected if the study met all of the following criteria: 1) designed as a case-control or cohort study or clinical trial; 2) the population was pancreatic cancer patients, regardless of age; 3) compared the outcomes between patients using metformin or statin and patients not using metformin or statin; 4) provided key information, including hazard ratios (HRs) and 95% confidence intervals (CIs), the size of baseline samples, the total number of cases, and the cofounders adjusted for in final models; and 5) the publication language was English. When two or more studies were not independent (i.e. conducted using the same study subjects), we only included the study with larger sample size and longer follow-up period to avoid giving

double weight to the estimates derived from the same study. Studies were excluded, if it was a literature review, meta-analysis, abstract without full text or letter to the editor. After application of the above inclusion and exclusion criteria, two investigators (JYE, XLT) independently reviewed the articles. Differences between investigators were resolved by discussion. Ultimately, no case-control studies were identified. So we included retrospective cohort studies and clinical trials that reported adjusted HR and 95% CI for the association between pancreatic cancer mortality and use of statin or metformin compared to non-statin or non-metformin use.

Data Extraction

The primary endpoint of this meta-analysis is overall survival among pancreatic cancer patients. Two investigators (JYE, XLT) independently extracted key information from the full text articles using a predefined data extraction sheet; and discordant findings were resolved by discussion. The extracted data included: study characteristics (first author, country of origin, year of publication), study design and study population, enrollment period, comparison group (statin or metformin, alone or in combination with other anticancer treatment, compared with other anticancer treatment other than statin or metformin, or no treatment) and number of patients in each medication group, multivariable-adjusted estimates (HR and 95% CI), as well as main findings derived from the studies (Table 1, Table 2).

Statistical Analysis

The goal of each included study was to identify the independent effect of statin and metformin on overall survival of pancreatic cancer patients, controlling for possible confounders. To summarize the findings of the selected studies, the adjusted HR and 95% CI were evaluated by DerSimonian and Laird random-effects model, with the assumption that included studies were random samples from possible studies [35]. Heterogeneity was assessed by the Cochran's Q test, with $P < 0.05$ indicating significant heterogeneity [36]. The I^2 statistic was used to measure the consistency of effects across studies, with 20–50%, 50–75%, and >75% indicating low, moderate, and high heterogeneity, respectively [37]. Funnel plots and the Egger's test were used to examine the effect of publication bias [38]. Further, we performed sensitivity analyses to assess the robustness of estimates. All statistical analyses were conducted using Stata version 12 (StataCorp, College Station, TX, USA) by using plug-in metan (University of Oxford, UK). The P -values were two sided with significant level $\alpha = 0.05$.

RESULTS

Characteristics of Included Studies

There were 116 potential statin-related studies identified by the literature research (Fig. 1A). After reviewing titles and abstracts, 10 studies were further assessed by reviewing the full text. Four were excluded: two of them had missing hazard ratio information [39, 40], one was an abstract that investigated the same patients presented in another study, and one was an abstract without full text [41]. The six remaining studies included 12,057 pancreatic cancer patients (Table 1). All of the studies were published between 2012 and 2016, and the

three were conducted in the USA. Among the six studies, 3,168 (26.3%) patients were treated with statin or simvastatin alone and remaining 8,889 (73.7%) patients were non-statin users.

There were 311 potential metformin-related studies identified by the literature research (Fig. 1B). Among these, 14 publications were selected after reviewing the titles and abstracts. One was missing hazard ratio [42], one was a meta-analysis [43], and two publications were abstracts without full text [44]. The remaining 10 studies included 3,042 pancreatic cancer patients were all published between 2012 and 2016, and four were conducted in the US and three in South Korea, and one in each of Italy, the Netherlands and the UK (Table 2). Among the 10 studies, 1,142 (37.5%) patients were treated with metformin alone or in combination with other drugs and remaining 1,900 (62.5%) patients were treated with non-metformin agents.

Statin Use and Overall Survival Among Pancreatic Cancer Patients

The use of statin to patients with pancreatic cancer was significantly associated with reduced mortality compared to those without statin treatment (HR = 0.75; 95% CI: 0.59, 0.90; P -value < 0.001 for heterogeneity; I^2 = 81.1%; Fig. 2). The further funnel plot was performed for these studies, indicating that there is a significant publication bias for statin-related studies (Bias = -0.58; 95% CI: -0.91, -0.25; Egger P -value = 0.008; Fig. 3). To assess the heterogeneity in statin-related studies, each single study was excluded one by one. When the study published by *Kozak et al.* [45] was excluded, the result showed moderate heterogeneity (HR = 0.82; 95% CI: 0.69, 0.95; P -value = 0.005 for heterogeneity; I^2 = 73.3%), and there is marginal presence of publication bias (Bias = -0.55; 95% CI: -1.05, -0.04; Egger P -value = 0.041). A sensitivity analysis excluding the study by *Jeon et al.*, which including 64.8% of the total population (7813/12057), shows a more pronounced association (HR = 0.68; 95% CI: 0.46, 0.89; P -value = 0.001 for heterogeneity; I^2 = 79.1%) and there is presence of publication bias (Bias = -0.72; 95% CI: -1.12, -0.32; Egger P -value = 0.011). In addition, another sensitivity analysis restricting four studies that adjusted diabetes, or anti-hyperglycemic medications, showed that statin use was still associated with a reduction of mortality (HR = 0.71; 95% CI: 0.47, 0.95; P -value = 0.001 for heterogeneity; I^2 = 82.4%), and there is presence of publication bias (Bias = -0.55; 95% CI: -0.88, -0.21; Egger P -value = 0.019).

Metformin Use and Overall Survival Among Pancreatic Cancer Patients

The meta-analysis for metformin-related studies demonstrated that the use of metformin was also associated with reduced risk of death from pancreatic cancer compared to without metformin treatment (HR = 0.79; 95% CI: 0.70, 0.92; P -value = 0.036 for heterogeneity; I^2 = 49.7%; Fig. 4). The study by *Chaiteerakij et al.* covers 32.2% of total population (980/3042). The funnel plot suggested that there is no existence of publication bias for metformin-related studies (Bias = -0.07; 95% CI: -0.72, 0.58; Egger P -value = 0.81; Fig. 5). A sensitivity analysis restricting to 8 retrospective cohort studies showed a better survival outcome (HR = 0.76; 95% CI: 0.64, 0.88; P -value = 0.06 for heterogeneity; I^2 = 48.3%), and the funnel plot shows no publication bias (Bias = -0.34; 95% CI: -1.01, 0.33; Egger P -value = 0.26). Furthermore, another sensitivity analysis restricting to 7 studies on pancreatic

cancer patients concurrent with diabetes showed that metformin was still associated with reduction of mortality (HR = 0.77; 95% CI: 0.64, 0.89; P -value = 0.038 for heterogeneity; I^2 = 55.0%), and there is no existence of publication bias (Bias = -0.42; 95% CI: -1.35, 0.52; Egger P -value = 0.30).

DISCUSSION

In this review, we conducted meta-analyses to quantitatively investigate the association between statin or metformin use and overall survival of pancreatic cancer patients. To our knowledge, this is the first meta-analysis to assess the association of statin treatment with pancreatic cancer survival. In these meta-analyses, 6 publications for statin treatment and 10 publications for metformin treatment provided the evidence that both statin and metformin use were associated with improved survival in pancreatic cancer patients.

We found that statin use was statistically significantly associated with improved overall survival with a significant publication bias. This finding was consistent with most, but not all, of the individual study results that were included this meta-analysis. A retrospective study using the Yonsei Tumor Registry database at Severance Hospital in South Korea, that included 1,761 patients newly diagnosed with pancreatic adenocarcinoma found that statin use was associated with a lower risk of overall mortality (HR = 0.78; 95% CI: 0.62, 0.99), especially among simvastatin users (HR = 0.55; 95% CI: 0.31, 0.98) and atorvastatin users (HR = 0.64; 95% CI: 0.44, 0.93) [46]. They observed a duration response effect, with the HRs decreasing with longer duration of statin use compared with non-statin use. The patients who used statin for ≥ 6 months after diagnosis received survival benefits compared with those who did not use statin (< 6 months use: HR = 0.54; 95% CI: 0.35, 0.94) [46]. *Wu et al.* conducted a retrospective cohort study in early-stage pancreatic cancer patients and found that simvastatin use but not lovastatin use was significantly associated with improved survival [median 28.5 months; 95% CI: 20.8–38.4 months for simvastatin vs. median 12.9 months; 95% CI: 9.6–15.5 months for lovastatin] [47]. Furthermore, they observed that active use of moderate-high-dose simvastatin at baseline was associated with improved overall and disease-free survival, compared to patients with low-intensity doses of simvastatin. However, *Kozak et al.* did not observe a dose response effect, among 31 patients with statin dosage information, there was no significant difference on overall survival between statin doses less than 40 mg/day compared with 40 mg/day or more (P -value = 0.17) [45]. These results suggested that the contribution of the variations of specific statins, dosage and duration of statin use to the mortality should be assessed when the association between statin use and overall survival of pancreatic cancer patients is investigated.

Our meta-analysis demonstrated that the use of metformin was also associated with improved overall survival of pancreatic cancer patients compared to without metformin treatment, and the funnel plot suggested that there is no existence of publication bias. Findings from previous epidemiological studies of metformin use and pancreatic cancer survival are inconsistent. In a retrospective cohort study, *Sedeghi et al.* reported that metformin use was significantly associated with improved overall survival (HR = 0.64; 95% CI: 0.48, 0.86) in pancreatic cancer patients with DM [48]. An observational study by *Lee et al.* also found that metformin use was associated with favorable survival outcomes in

pancreatic cancer patients with pre-existing DM (HR = 0.61; 95% CI: 0.46, 0.81), especially in patients with more advanced disease [49]. Two South Korean studies, reported that metformin use was independently associated with improved survival of pancreatic cancer patients suggesting that metformin may be used as an adjunct to the standard of care in the treatment of pancreatic cancer [50, 51]. In contrast, four studies did not report significant associations between metformin use and survival in pancreatic cancer patients [45, 52–54]. A meta-analysis of four publications reported that borderline significant survival benefit for metformin users in pancreatic cancer patients with DM [43]. Our meta-analysis suggested that metformin use was significantly associated with improved survival of pancreatic cancer patients, providing support for repurposing metformin for improving pancreatic cancer survival. However, the majority of metformin users may also take statins, and statin use was not adjusted for in most studies. The survival benefits observed in metformin users may be, in part, due to the statin use. Future studies should investigate the differential effects of metformin and statin use, and whether dual therapy may infer additional benefits on pancreatic cancer survival over statin use alone.

Critical issues in this meta-analysis were the heterogeneity and publication bias. Sources of heterogeneity have included differences in study designs, study population characteristics, duration of follow-up and drug use, as well as different co-variables/confounding factors used to adjust for the drug effects on the outcomes. In metformin-related studies, 8 of 10 studies were retrospective cohort, while 2 of 10 studies were randomized clinical trials. Meta-analysis has limited performance with two studies only [59], however, both randomized clinical trials reported that metformin, in combination with current chemotherapy, did not improve pancreatic cancer patients' survival, compared with patients treated with chemotherapy alone [56, 57]. Metformin treatment may be more beneficial to pancreatic cancer patients diagnosed at a younger age and early cancer stage [60]. The two clinical trials testing metformin effect were conducted among patients with locally advanced or metastatic tumors, which may contribute to their null findings. These two clinical trials are subjective to unavailability of plasma metformin concentration and inadequate sample sizes to detect a small survival benefits or benefits confined to small subset of pancreatic cancer patients. A sensitivity analysis restricting to 8 retrospective cohort studies showed a better survival outcome, and the funnel plot shows no clear evidence of publication bias. We acknowledged that the sample size of our meta-analysis, especially for the statin-related studies, was small, it is possible that any existing bias may not have been detected for either analysis. To assess the heterogeneity in statin-related studies, each single study was excluded one by one. When we excluded the study by *Kozak et al.* [45], we observed moderate heterogeneity, and likely presence of publication bias.

Not accounting for disease stage, an important prognostic factor in pancreatic cancer, may bias the estimates of the effects of statin and metformin on pancreatic cancer survival toward the null hypothesis. A SEER Medicare analysis of 7,813 elderly patients with pancreatic ductal adenocarcinoma (PDAC) showed that statin use after pancreatic cancer diagnosis was associated with enhanced survival in patients with low-grade, resectable PDAC (HR = 0.79; 95% CI: 0.67, 0.93), but not in all PDAC patients (HR = 0.94; 95% CI: 0.89, 1.01) [55]. Two recent randomized clinical trials suggested that metformin offers no survival advantage in patients with metastatic or advanced pancreatic cancer [56, 57] indicating that impact of

metformin on advanced pancreatic cancer may be minimal [58]. We performed a sensitivity analysis by restricting the analysis to three statin-related studies conducted among patients with surgically resectable pancreatic cancer. Our results showed that statin was significantly associated with an improved overall survival (HR = 0.59; 95% CI: 0.34, 0.85; P -value = 0.021 for heterogeneity; $I^2 = 74\%$). Another sensitivity analysis restricting to the three metformin-related retrospective cohort studies conducted among patients with surgically resectable pancreatic cancer patients, suggested that metformin was not associated with a reduction of mortality (HR = 0.77; 95% CI: 0.29, 1.24; P -value = 0.412 for heterogeneity; $I^2 < 0.1\%$). These results are consistent with other studies findings that the stage of cancer is an important effect modifier in the possible relationship between statin and metformin use and overall survival of pancreatic cancer patients. Future studies that evaluate the effects of statin and metformin use on survival should focus on patients with early-stage pancreatic cancer.

In addition, this meta-analysis is limited by methodological shortcomings from the original studies because of other factors, such as diabetes. *Nakai et al.* retrospectively reviewed the medical records of 250 advanced pancreatic cancer patients receiving chemotherapy, and demonstrated that statin use was associated with improved survival among the diabetic patients (HR = 0.40; 95% CI: 0.18, 0.81), but not in patients without diabetes (HR = 1.03; 95% CI: 0.50, 1.91) [61]. To assess the possible effect modification by diabetes, a sensitivity analysis, restricting four studies that adjusted for the presence of diabetes or anti-hyperglycemic drugs yielded similar results when we included six statin-related studies. Seven of 8 metformin-related retrospective cohort studies were conducted among pancreatic cancer patients with diabetes, and only one study [45] included non-diabetic patients. The sensitivity analysis restricted to the 7 retrospective cohort studies with diabetic patients showed similar result to that including all 10 studies. Additionally, the findings could be very different for ever-users vs. new users as demonstrated in a recent study using data from the Women's Health Initiative [62]. However, the existing epidemiological studies on metformin and statin included mostly every user and very few existing studies included the analysis of new users. Future studies should be designed to assess the effects of new use of metformin and statin on pancreatic cancer survival.

It is worth noting that immortal time bias, *i.e.* a span of time in the observation of a cohort being the outcome of interest could not have occurred [63], may have impacted on the selected studies. Immortal time bias arises when study measures "any drug use" despite the initiation of the drug during follow-up. The person-time survival until medication initiation is then erroneously attributed to the medication. However, this bias is often not considered in epidemiological studies regarding drug effects on survival of cancer patients [63–65]. Only one [53] of 8 retrospective cohort studies for metformin considered the immortal time bias, and they showed no benefit of metformin use after patients are diagnosed with PDAC on pancreatic cancer survival. Two [46, 55] of 6 retrospective cohort studies included in this meta-analysis of statin use and pancreatic cancer patient survival considered this bias: one [46] showed an improved benefit; the other did not [55]. Hence, studies in our meta-analysis may have been impacted to this bias, and the results should be interpreted with caution.

In summary, this meta-analysis provided preliminary evidence that statin or metformin use may improve the survival time among pancreatic cancer patients. These two drugs have been

prescribed for other purposes for many years but should be further investigated, both individually and in combination for therapeutic repurposing for pancreatic cancer patient survival. Well-known methodological challenges of ‘drug repurposing’ studies have to be considered in further observational studies of statin or metformin in pancreatic cancer. In the future, a large prospective study or randomized clinical trial, particularly with cancer survival as the primary outcome is needed to validate these findings and to confirm whether statin or metformin improves pancreatic cancer outcomes.

Acknowledgments

This work was supported by grants from the National Cancer Institute at the National Institutes of Health (K07CA190541, P30CA072720), and a grant (Grant No.: 81470132) from the National Natural Science Foundation of China.

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Fig. 1. Flow diagram of study selection. (A) statin-related studies; and (B) metformin-related studies.

Fig. 2.

Forest plot showing the meta hazard ratio for overall survival by statin vs. non-statin exposure. For each study, the estimates of HR and 95% CI were plotted with a box and a horizontal line. Hollow diamond indicates HR and 95% CI. Abbreviations: CI, confidence interval; df, degrees of freedom.

Fig. 3. Funnel plot analysis to detect publication bias for statin-related studies. Each point represents an individual study for the indicated association.

Fig. 4.

Forest plot showing the meta hazard ratio for overall survival by metformin vs. non-metformin exposure. For each study, the estimates of HR and 95% CI were plotted with a box and a horizontal line. Hollow diamond indicates HR and 95% CI. Abbreviations: CI, confidence interval; df, degrees of freedom.

Fig. 5. Funnel plot analysis to detect publication bias for metformin-related studies. Each point represents an individual study for the indicated association.

Table 1
Major characteristics and hazard ratio estimates of included studies for statin use and pancreatic cancer patient survival.

Study author, country, year	Design and population	Enrollment	Comparison groups	No of Participants	Adjusted HR (95% CI)	Co-variables	Main findings
Nielsen, Denmark, 2012 [66]	Retrospective cohort study of pancreatic cancer patients	1995–2007	Statin users vs. non-users	459/1377	0.95 (0.85, 1.09)	Age, sex, birth year, cancer stage, chemotherapy, radiotherapy, cardiovascular disease, diabetes, descent, highest education level, and residential area.	Statin use was not associated with improved survival in pancreatic cancer patients
Nakai, Japan, 2013 [61]	Retrospective cohort study of advanced pancreatic cancer patients	2001–2011	Statin users vs. non-users	30/220	0.62 (0.34, 1.07)	Age, sex, tumor size, metastasis, performance status, chemotherapy, diabetes, sulfonylurea, thiazolidinedione, hypertension, angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB), and Ca-blocker	Statin use was prognostic factor of overall survival in pancreatic cancer patients with diabetes, but not in patients without diabetes.
Jeon, USA, 2015 [55]	Retrospective cohort study of pancreatic cancer patients	2007–2009	Statin users vs. non-users	2456/5357	0.94 (0.89, 1.01)	Age, sex, race, neighborhood income, cancer stage, grade, tumor size, resection, radiation, chemotherapy, obesity, dyslipidemia, diabetes/impaired glucose tolerance, chronic pancreatitis, and chronic obstructive pulmonary disease (COPD).	Statin use after cancer diagnosis was significantly associated with improved survival in patients with low-grade, resectable pancreatic cancer, but not among all pancreatic cancer patients
Wu, USA, 2015 [47]	Retrospective cohort study of stage I-II pancreatic cancer patients undergoing resection	2005–2011	Simvastatin users vs. non-users	71/155	0.56 (0.38, 0.83)	Age, sex, resection, disease stage, chemotherapy, and Charlson index.	Moderate-high dose simvastatin was associated with improved overall and disease-free survival in pancreatic cancer patients undergoing resection
Kozak, USA, 2016 [45]	Retrospective cohort study of pancreatic cancer patients underwent surgical resection	1998–2013	Statin users vs. non-users	34/137	0.33 (0.14, 0.80)	Age, nodes staging, resection, metformin, radiation, and chemotherapy.	Statin use was associated with improved overall survival in pancreatic cancer patients with resectable pancreatic cancer
Lee, South Korea, 2016 [46]	Retrospective cohort study of pancreatic cancer patients	2006–2014	Statin users vs. non-users	118/1643	0.78 (0.62, 0.99)	Age, sex, cancer location, cancer stage, diabetes, hypertension, dyslipidemia, smoking, alcohol use, body mass index and CA 19-9.	Statin use was associated with improved survival in pancreatic cancer patients

Table 2

Major characteristics and hazard ratio estimates of included studies for metformin use and pancreatic cancer patient survival.

Study author, country, year	Design and Population	Enrollment	Comparison Groups	No of participants	Adjusted HR (95% CI)	Co-variables	Main findings
Sadeghi, USA, 2012 [48]	Retrospective cohort study of pancreatic cancer patients with diabetes	2000–2009	Metformin users vs. non-users	117/185	0.64 (0.48, 0.86)	Tumor size, tumor site, cancer stage, CA 19-9, and performance status.	Metformin use was associated with improved survival in pancreatic cancer patients with diabetes
Hwang, UK, 2013 [52]	Retrospective cohort study of pancreatic cancer patients with diabetes	2003–2010	Metformin users vs. non-users	247/269	1.09 (0.80, 1.47)	Age, sex, duration of diabetes, diabetic complications, pancreatitis, Charlson index, body mass index, glomerular filtration rates (GFRs), smoking, insulin, sulfonyleurea, thiazolidinedione, and HbA _{1c}	Metformin use was not associated with improved survival in advanced pancreatic cancer patients with diabetes
Kim, South Korea, 2014 [50]	Retrospective cohort study of pancreatic cancer patients with diabetes	2005–2010	Metformin users vs. non-users	111/317	0.78 (0.62, 0.98)	Performance status, CA 19-9, cancer stage, body mass index, and number of organ involvement.	Metformin use was associated with improved survival in pancreatic cancer patients with diabetes
Kordes, Netherlands, 2015 [56]	Random clinical trial of advanced pancreatic cancer patients	2010–2014	Gemcitabine+ erlotinib+ metformin users vs. Gemcitabine+ erlotinib users	60/61	1.06 (0.72, 1.55)	Age, sex, performance status, line of treatment of study drug, cancer stage, cancer location, previous surgery history, diabetes, and fasting concentration of serum markers.	Adding metformin did not improve survival in advanced pancreatic cancer patients treated with gemcitabine and erlotinib
Ambe, USA, 2016 [54]	Retrospective cohort study of resectable pancreatic cancer patients with diabetes	1986–2013	Metformin users vs. non-users	19/25	0.54 (0.16, 1.86)	Age, body mass index, type of surgery, diabetes duration, CA 19-9, cancer grade, cancer stage, margin status, regional nodes examined, and number of regional nodes positive.	Metformin use was not associated with improved survival in resected pancreatic cancer patients with diabetes
Choi, South Korea, 2016 [51]	Retrospective cohort study of advanced pancreatic cancer patients with diabetes	2003–2010	Metformin users vs. non-users	56/127	0.69 (0.49, 0.98)	Age, sex, performance status, cancer extent, body mass index, weight loss, sulfonyleurea, insulin, CA 19-9, albumin, and chemotherapy	Metformin use was associated with improved survival in advanced pancreatic cancer patients who received palliative chemotherapy.
Chaitteerakij, USA, 2016 [53]	Retrospective cohort study of advanced pancreatic cancer patients with diabetes	2000–2011	Metformin users vs. non-users	366/614	0.92 (0.79, 1.08)	Age, sex, body mass index, cancer stage, and year of diagnosis.	Metformin use was not associated with improved survival in

Study author, country, year	Design and Population	Enrollment	Comparison Groups	No of participants	Adjusted HR (95% CI)	Co-variables	Main findings
							pancreatic cancer patients with diabetes
Kozak, USA, 2016 [45]	Retrospective cohort study of pancreatic cancer patients underwent surgical resection	1998–2013	Metformin users vs. non-users	18/153	0.6 (0.21, 1.68)	Age, nodes staging, resection, statin, radiation, and chemotherapy.	Metformin use was not associated with improved overall survival in pancreatic cancer patients with resectable pancreatic cancer
Reni, Italy, 2016 [57]	Random clinical trial of metastatic pancreatic cancer patients	2010–2014	Cisplatin+ epirubicin+ capecitabine+ gemcitabine + metformin users vs. Cisplatin+ epirubicin+ capecitabine+ gemcitabine users	31/29	1.56 (0.87, 2.8)	Age, CA 19-9, performance status, metastasis, SNP rs11212617, adiponectin, and IL-6	Adding metformin did not improve survival in metastatic pancreatic cancer patients treated with cisplatin, epirubicin, capecitabine and gemcitabine
Lee, South Korea, 2016 [49]	Retrospective cohort study of pancreatic cancer patients with diabetes	2005–2013	Metformin users vs. non-users	117/120	0.61 (0.46, 0.81)	Tumor size, cancer location, CA 19-9, cancer stage, and performance status.	Metformin use was associated with improved survival in pancreatic cancer patients with diabetes, especially among those with advanced cancer stage