Prognostic role of anti-diabetic drugs in pancreatic cancer: A systematic review and meta-analysis

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ABSTRACT

Anti-diabetic drugs (ADDs) have been reported to modify the risk and survival of several malignancies, but whether ADDs affect the prognostic outcomes for pancreatic cancer (PC) patients remains unclear. A systematic literature search was performed for studies published until September 2016 investigating the associations between ADD use and PC survival. Pooled hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using the random-effects model. Overall survival (OS) and progression-free survival (PFS) were set as the main outcomes. Twelve cohorts and two randomized controlled trials (RCTs) for a total of 12,6158 subjects were identified for this meta-analysis. Pooled analysis of cohorts suggested that metformin use was significantly associated with improved OS in PC patients ($n = 11$ studies; pooled HR 0.77, 95% CI 0.68 to 0.87), with no increased OS for insulin, sulfonylureas (SU) or thiazolidinedione (TZD) (all P values > 0.05). For OS of PC patient using metformin, this effect remained constant by subgroup analyses and sensitivity analysis by trim and filled method. Meta-analysis of RCTs did not show survival benefits for PC patients ($n = 2$; pooled HR 1.20, 95% CI 0.84 to 1.72). We also did not find significant association between metformin use and PFS in PC patients for cohort studies ($n = 2$; pooled HR 1.22, 95% CI 0.76 to 1.95). Our findings provide evidence in cohort studies that metformin, not other ADDs is associated with improved OS in PC patients; however, due to limited number of studies investigating other ADDs except metformin, further large-scale studies are warranted to determine this associations.

INTRODUCTION

Pancreatic cancer (PC) remains the tenth most frequent cancer and the third leading cause of cancer-related death in developed countries [1, 2]. Moreover, most patients survive less than one year after diagnosis. Besides some known factors such as smoking, disease stage, alcohol consumption, chronic pancreatitis, family history, few prognostic factors have been identified [3–6].

Numerous observational studies have reported an obvious protective effect of metformin, a commonly used anti-diabetic drug (ADD) for type 2 diabetes, against risk of several malignancies [7–9]. Moreover,

diabetic patients with cancer tend to have worse survival, and some ADDs, such as metformin, have been shown to decrease the mortality among diabetics with cancer [10–12]. Although the mechanism of carcinostasis has not been fully understood, hyperinsulinemia, caused by insulin resistance, may lead to up-regulation of insulin-like growth factor-I (IGF-I) signaling pathway, thus inducing proliferation and invasion of cancer cells and decrease apoptosis [13, 14].

The aim of our study was to investigate whether ADD use affected prognostic outcomes of patients with known diabetes through systematic review and meta-analysis.

RESULTS

Description of the included studies

The initial database search yielded a total of 3326 references for eligibility. After excluding the duplicates and screening the remaining title and abstract, 42 potentially relevant studies were identified for further review. After selection, a total of 14 publications met our inclusion criteria (Figure 1) [10–12, 15–25]. The clinical features of included studies were summarized in Table 1. In summary, 13 studies involving 39261 patients investigated the survival outcomes for patients of metformin use, five for insulin use, two for sulfonylureas (SU) use and two for or thiazolidinedione (TZD) use. The median follow-up time ranged from 0.77 to 12 years. Five studies were carried out in USA, three in Europe and two in Asia. Several cohorts were adjusted for some conventional influential factors, including age, sex, disease stage. Six studies involved PC patients with I–IV disease stages, and two with stage IV. Assessment of methodological quality for cohort studies yielded a score range of 7 to 9, and 7 of 12 studies had a score of 8 or above (Supplementary Table 3).

Metformin use and PC survival

The combined hazard ratio (HR) for the overall survival (OS) comparing metformin use versus non-use was 0.77 (95% CI 0.68 to 0.87; $I^2 = 52.9\%$) with moderate inter-study heterogeneity ($I^2 = 52.9\%$) (Figure 2) for cohort studies. No significant progression-free survival (PFS) benefit was found for cohort studies (HR 1.22; 95% CI 0.76 to 1.95). We also did not find significant survival benefit for randomized controlled trials (RCTs) (HR 1.2, 95% CI 0.84 to 1.72).

We summarized the subgroup analyses for OS in Table 2 to further test potential sources of heterogeneity among certain major clinical characteristics of the included studies. The pooled HRs for the majority of the subgroups did not change significantly stratified by some major study characteristics, including the study design and setting, study country, the number of hospitals, sample size, adjusted variables or Newcastle-Ottawa quality assessment scale. A possible interaction was found in two features (sample size and study country). Results of analyses limited to studies with some of the main variable adjusted (age, sex and tumor stage) are presented in Table 2. For studies with

Figure 1: Flow diagram of the study selection.

Table 1: Characteristics of the included studies on survival outcomes for PC patients taking ADDs

Authors (Year)	Country	Study design	Setting	No. of hospitals involved	Inclusion Year	Exposure ascertainment	Outcome	Metformin user/ non-user	Sample size	Types of ADD	Disease stage	F/U (months)	Survival endpoints	Adjusted variables
Reni, 2016	Italy	Open Label, Randomized Phase II Trial	Hospital-based	Single	2010-2014	RCT	Adverse event review	31/29	60	metformin	IV	NR	OS, PFS	NR
Lee, 2016	Korea	Retrospective cohort	Hospital-based	Single	2005-2013	self-reported medical records	Medical record review	117/120	1339	Metformin TZDs SU Insulin	I-IV	Median 10.3	OS	Serum CA19-9 levels, tumor size, tail involvement, performance status, cancer stage, use of DDP4 inhibitors
Kozak, 2016	USA	Retrospective cohort	Hospital-based	Single	1998-2013	electronic medical record	Medical record review	18/153	201	metformin	I-IV	Median 11.23	OS, DFS	Age, sex, type of surgery, tumor stage, lymph node metastases, tumor grade, perineural invasion, angiolymphatic invasion, adjuvant chemotherapy, gemcitabine as first-line treatment, radiation treatment, smoking status, number of pack years, statin use
Choi, 2016	Korea	Retrospective cohort	Hospital-based	Single	2003-2010	electronic medical record	NR	56/127	349	Metformin SU Insulin	I-IV	Median 10.2	OS	Performance status, DM status, cancer extent, and weight loss during first-line therapy
Chaitrenkij, 2016	USA	Retrospective cohort	Hospital-based	Single	2000-2011	electronic medical record	NR	366/614	2,964	metformin	I-IV	Median 16.5	OS	Age, Sex, Region, Charlson comorbidity index, Treatment regimen
Cerull, 2016	USA	Retrospective cohort	Population-based	Multiple	2010-2012	Electronic medical record	patient records	456/2937	3393	metformin	I-IV	Median 16.5	OS	Age,Sex,Region,Charlson comorbidity index,Treatment regimen
Ambe, 2016	USA	Prospective cohort	Hospital-based	Single	1986-2013	electronic medical record	medical record review of the social security death index	19/25	44	metformin	I-II	Median 19	OS	Margin status, regional nodes examined, number of regional nodes positive, age at diagnosis, BMI, type of surgery, diabetes duration, CA199 grade, stage
Mathews, 2015	Netherlands	RCT	Hospital-based	Multiple	2010-2014	RCT	Adverse event review	61/60	121	metformin	IV	Median 28.1	OS, PFS	Age, Sex, WHO performance status, Line of treatment of study drug, Disease stage, Primary tumour location, Previous surgery, Diabetes, Fasting concentrations of serum markers,CA199
Tseng, 2013	Taiwan	Retrospective cohort	Population-based	Multiple	1995-2006	structured questionnaire interview	The national death certificate	5927/80970	86897	insulin	I-IV	Up to 12 years	OS	Age, sex, diabetes duration, body mass index, smoking, insulin use, area of residence
Hwang,2013	United Kingdom	Retrospective cohort	Population-based	Multiple	2003-2010	electronic medical record	the exact date of death in the THIN database.	247/269	516	metformin	I-IV	NR	OS	Age, sex, duration of diabetes, presence of diabetic complications, history of pancreatitis, Charlson index, BMI, GFR, smoking at diagnosis, history of insulin use, Time of diagnosis, history of insulin use, history of sulfonylurea use, history of thiazolidinedione use, and HbA1c.
Sadeghi, 2012	USA	Retrospective cohort	Hospital-based	Single	2000-2009	personal interviews, medical record review.	NR	117/185	302	metformin	I-IV	Median 11.4	OS	Disease stage, serum CA-199 level,tumor size, tumor site, performance status, metformin use
Amin, 2015	USA	Retrospective cohort	Population-based	Multiple	2007-2011	NR	NR	589/258	847	metformin	I-IV	NR	OS	Demographic factors, stage, median income, diabetic complications, severity, Charlson comorbidity score, other DM medications, treatment
Jang, 2016	Korea	Prospective cohort	Population-based	Multiple	2005-2011	prescription information	NR	530/234	28862	metformin	I-IV	NR	OS	NR
Jeon, 2014	USA	Retrospective cohort	Population-based	Multiple	2008-2009	NR	NR	132/131	263	insulin / sulfonylurea; metformin/TZD	I-IV	NR	OS	Age, sex, race, stage at diagnosis and chemotherapy

Abbreviations: ADDs, anti-diabetic drugs; PC, pancreatic cancer; CS, cancer-specific survival; DFS, disease-free survival; F/U, follow-up period; N, no; NR, not reported; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; Y, yes.

these three variables adjusted, a null prognostic association of metformin use was noted. Nevertheless, further studies should be conducted to examine the true survival benefit of metformin in PC patients due to the small number of studies involved in these subgroups.

Sensitivity analysis by omitting one single study each time and pooling the others indicated that the pooled HRs were not significantly altered. Funnel plot for publication bias did not show asymmetry (Figure 3). Further Egger’s test ($P = 0.135$) or Begg’s test ($P = 0.436$) also did not found a certain degree publication bias.

Insulin and other ADD use and PC survival

Five studies investigated the impact of insulin use and PC survival and there was no significant association between insulin use and PC survival (HR 1.18, 95% CI 0.83 to 1.69). We also did not find significant association between Su (HR 1.03, 95% CI 0.81 to 1.30) or TZD (HR 0.84, 95% CI 0.58 to 1.22) use and PC survival.

DISCUSSION

This meta-analysis aimed to investigate the association between ADD (metformin, insulin, SU and TZD) use and survival of PC. We found metformin use was associated with significantly favorable OS of PC patients (HR 0.77, 95% CI 0.68 to 0.87) in cohort studies, but was not associated with significantly PFS (HR 1.22;

95% CI 0.76 to 1.95) or for RCTs. We also found no survival benefits of other ADDs such as insulin, SU or TZD for PC patients.

Several potential mechanisms may explain the associations for the fact that conventional ADMs may alter the risk of multiple malignancies. It was reported that metformin plays an important anticancer role in multiple ways including insulin-dependent or independent manners [26]. A recent study found that sulfonylureas can induce cell proliferation and have an effect of carcinogenesis by promoting insulin secretion [27]. Moreover, previous *in vitro* studies showed that thiazolidinediones have an impact on cell growth arrest and apoptosis and the inhibition of cancer cell invasion [28].

Several important strengths of this meta-analysis should be addressed. Firstly, to the best of our knowledge, this is the first systematic review regarding the associations between the use of ADMs and prognosis of PCs. Secondly, a comprehensive and reproducible search strategies were developed to identify all relevant studies or trials in the major databases without language limitations. Thirdly, we included the most commonly used ADDs including metformin, Su, TZDs and insulin for analysis and involved both RCTs and cohort studies. Fourthly, more than 120000 participants were included to quantitatively assess the association between ADDs use and PC prognosis, which was the most comprehensive synthesis of the evidence on this topic ever today. Finally, several subgroup analyses were carried out for some of the important variables,

Table 2: Subgroup analyses of the associations between *ADD use* and survival for PC patients

Metformin/OS	HR	95%CI	Degree of heterogeneity (I ² statistics; %)	No. of included Studies	P for interaction
Total	0.77	0.68 to 0.87	52.9	11	NA
Study design					0.534
Prospective cohort	0.72	0.61 to 0.86	0	2	
Retrospective cohort	0.78	0.67 to 0.90	58.9	9	
Study setting					0.111
Hospital based	0.67	0.53 to 0.85	64.5	6	
Population based	0.84	0.73 to 0.96	33.6	5	
Study region					0.0257
USA	0.78	0.67 to 0.92	47.2	7	
Europe	1.09	0.80 to 1.48		1	
Asia	0.69	0.60 to 0.79	0	3	
Hospital number					0.111
Single	0.67	0.53 to 0.85	64.5	6	
Multiple	0.84	0.73 to 0.96	33.6	5	
Sample size					0.036
≥ 500	0.83	0.72 to 0.95	59.1	6	
< 500	0.64	0.53 to 0.78	0	5	
Main variable adjusted*					0.276
Yes	0.83	0.68 to 1.03	57.8	5	
No	0.73	0.64 to 0.83	30.8	6	
NOS scale					0.359
≥ 8	0.73	0.59 to 0.90	59.4	6	
< 8	0.82	0.71 to 0.94	36.2	5	
OS	HR	95%CI	Degree of heterogeneity (I ² statistics; %)	No. of included Studies	
Insulin	1.18	0.83 to 1.69	69	5	
Su	1.03	0.81 to 1.30	17.9	2	
TZD	0.84	0.58 to 1.22	0	2	
RCT-metformin	1.2	0.84 to 1.72	15.3	2	
PFS-metformin	1.22	0.76 to 1.95	52.8	3	

Abbreviations: ADDs, anti-diabetic drugs; PC, pancreatic cancer; CI, confidence interval; het, heterogeneity; HR, hazard ratio; NA, not available; SU, sulfonylureas; TZD, thiazolidinedione.

such as study design and setting, research region, number of research hospital, main variable adjusted and quality score. The results showed consistency across subgroups.

Still there are limitations in our systematic review. Firstly, the number of studies for each medication involved in this meta-analysis was relatively small except for metformin, and thus it is difficult to draw definite conclusions for the limited statistical power in Su, TZDs or insulin subset. Secondly, we did not assess dose or

duration-response relationship in our meta-analysis as most of the included studies had no dose or duration information for abstraction, so it is impossible for us to perform this kind of analysis. Therefore, further study should be focused on this aspect. Thirdly, although some known major confounders including age, sex and disease stage were identified and adjusted for some of the included studies, some other variables (such as tumor size, body mass index or chemotherapy) could influence our exploration

of associations between ADDs and PC survival. We also noted that two of the included studies provided only unadjusted HRs using univariate analysis [15, 18], which would to some extent influence the results though the sensitivity analysis did not show the change in the pooled

estimates. Moreover, although we did not find significant publication bias for metformin subset in cohort studies, we could not totally exclude potential impact of unpublished studies on the pooled results, which might have resulted in reporting bias. And the adjusted estimates of the results

Figure 2: Association between metformin intake and overall survival for pancreatic cancer patients.

Figure 3: Funnel plot for meta-analysis of the association between metformin intake and overall survival for pancreatic cancer patients.

using the trim and fill methods remained unchanged, indicating the stable of our analysis. Finally, as rare studies included data regarding prediagnosis or postdiagnosis ADD use, the included studies generally defined ADD exposure as use of ADDs during the peridiagnosis period regardless of the prediagnosis and postdiagnosis exposure. So it is impossible for us to perform this kind of analysis. However, two studies reported that the initiation of metformin after cancer diagnosis did not improve survival for patients with PC [11, 19].

The survival benefit of metformin was seen mainly in cohort studies, which accounted for most of the included studies (12/14) and sample size (12,037/12,6158). As for study design, the patients included in RCTs were likely to have a low risk of cancer mortality or progression which were both performed in the Western countries (Italy and Netherlands). Moreover, the survival impact of metformin in cohort studies might also represent an overestimate of its true effect in that cohort studies would not have the random allocation process to examine exposure-outcome hypotheses optimally. Despite adjusting for potential covariates, there remained to be numerous potential residual confounders. For example, diabetic patients of these studies usually used multiple ADDs simultaneously. Therefore, other ADDs may also have a cancer-modifying effect on patient survival, which may overestimate the survival effect of metformin.

The current meta-analysis provides evidence that metformin reduces the risk of all-cause mortality for PC patients and therefore reinforces previous concerns regarding the real world survival effect of metformin for type 2 diabetes. Based on the findings of this study, we suggest the following avenues for further study. The first is to investigate the pragmatic real world effectiveness of metformin intervention for PC patients through controlled clinical trials or RCTs. The second avenue for further study is to conduct the population level meta-analysis based on large-scale population based cohort studies.

To sum up, the results from this meta-analysis revealed that in cohort studies, metformin, not other ADDs is associated with improved OS in PC patients; however, due to limited number of studies investigating other ADDs except metformin, further large-scale studies are warranted to determine this associations.

MATERIALS AND METHODS

Literature search and study selection

Based on the PRISMA statement [29], we performed a comprehensive literature search in PUBMED and EMBASE databases up to September 2016 for relevant citations without language restrictions. We used the search strategies (Supplementary Tables 1–2) that included Medical Subject Headings and Emtree headings combined key words relating to the prognostic effect of

ADDs among PC patients. We also manually scanned the reference lists from the extracted relevant research papers, previous reviews and meta-analysis for additional possible publications. Unpublished studies or data were not included due to insufficient information obtained.

We included published studies providing aggregate data if they met the following criteria: (1) evaluated any prognostic information in PC patients comparing ADDs users with non-users, (2) reported a summary statistic of HRs with 95% CIs or provided data for calculation as described by Parmar et al.[30]. We defined ADD exposure as use of ADDs during the peridiagnosis period regardless of the prediagnosis and postdiagnosis exposure. RCTs or observational studies were eligible for this meta-analysis. If there were more than one studies from the same cohort, we selected the most detailed or recent one for analysis. All the studies reporting prognostic information, including OS, and PFS, were selected in the main analyses. Two independent investigators (L.Z. and S.Y.) conducted study selection from eligible studies.

Data extraction and quality assessment

Two independent investigators (L.Z. and S.Y.) selected articles and extracted data from eligible studies, evaluated the quality of each study and any discrepancies were resolved by a consensus discussion with a third investigator (H.B.). The characteristics recorded were the study author, study publication year, research country, study design and setting, involved centers, enrolled period of study, information source for exposure ascertainment and outcome assessment, sample size in exposed and non-exposed group, sample size, type of ADDs, tumor stage, mean follow-up period, survival endpoints and adjustment variables. The methodological quality of each study was evaluated using the Newcastle-Ottawa quality assessment scale [31], in which three domains including cohort selection, comparability, and outcome were evaluated with a score range from 0 to 9, with 9 representing the highest quality and 0 the lowest.

Statistical analyses

STATA software (version 12.0, StataCorp LP, College Station, TX) was used to perform the meta-analysis. Survival estimates with full adjustments for known confounders of included studies were abstracted. Summary data reporting HRs with corresponding 95% CIs estimated from Cox proportional hazards models were pooled with random-effects model [32]. The data regarding the association of ADDs (use vs. no use) with survival outcomes were pooled separately. We used the Cochrane Q statistic (with a *P* value less than 0.10 considering statistically significant) and the *I*² statistic (with an *I*² exceeding 50% indicating significant heterogeneity) to test for between-study heterogeneity [33]. OS for metformin

was explored as the primary outcome measure. Other outcome measure such as progression-free survival (PFS) was also evaluated. We performed sensitivity analyses to explore the reasons for statistical heterogeneity. The risk of publication bias was assessed visually by inspecting of a funnel plot and statistically by using Egger's or Begg's regression model [34, 35]. We further ascertained the number of missing studies using Duval and Tweedie's trim and fill method to adjust the summary hazard ratio based on all the studies including the hypothesized missing ones [36]. All statistical analyses were two-sided and a *P* value less than 0.05 was considered significant.

CONFLICTS OF INTEREST

The authors declare no potential conflicts of interest.

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REFERENCES

1. Ferlay J, Partensky C, Bray F. More deaths from pancreatic cancer than breast cancer in the EU by 2017. *Acta oncologica* (Stockholm, Sweden). 2016; 55:1158–1160.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA: a cancer journal for clinicians*. 2012; 62:10–29.
3. Hidalgo M. Pancreatic cancer. *The New England journal of medicine*. 2010; 362:1605–1617.
4. Raimondi S, Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an overview. *Nature reviews Gastroenterology & hepatology*. 2009; 6:699–708.
5. Hassan MM, Bondy ML, Wolff RA, Abbruzzese JL, Vauthey JN, Pisters PW, Evans DB, Khan R, Chou TH, Lenzi R, Jiao L, Li D. Risk factors for pancreatic cancer: case-control study. *The American journal of gastroenterology*. 2007; 102:2696–2707.
6. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, Zhang H, Li Z. Diabetes mellitus and risk of pancreatic cancer: A meta-analysis of cohort studies. *European journal of cancer* (Oxford, England : 1990). 2011; 47:1928–1937.
7. Grouven U, Hemkens LG, Bender R, Sawicki PT. Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues. Reply to Nagel JM, Mansmann U, Wegscheider K et al. [letter] and Simon D [letter]. *Diabetologia*. 2010; 53:209–211.
8. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes care*. 2009; 32:1620–1625.
9. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia*. 2009; 52:1766–1777.
10. Choi Y, Kim TY, Oh DY, Lee KH, Han SW, Im SA, Kim TY, Bang YJ. The Impact of Diabetes Mellitus and Metformin Treatment on Survival of Patients with Advanced Pancreatic Cancer Undergoing Chemotherapy. *Cancer research and treatment : official journal of Korean Cancer Association*. 2016; 48:171–179.
11. Cerullo M, Gani F, Chen SY, Canner J, Pawlik TM. Metformin Use Is Associated with Improved Survival in Patients Undergoing Resection for Pancreatic Cancer. *Journal of gastrointestinal surgery*. 2016; 20:1572–1580.
12. Ambe CM, Mahipal A, Fulp J, Chen L, Malafa MP. Effect of Metformin Use on Survival in Resectable Pancreatic Cancer: A Single-Institution Experience and Review of the Literature. *PloS one*. 2016; 11:e0151632.
13. Kuuselo R, Savinainen K, Azorsa DO, Basu GD, Karhu R, Tuzmen S, Mousses S, Kallioniemi A. Intersex-like (IXL) is a cell survival regulator in pancreatic cancer with 19q13 amplification. *Cancer research*. 2007; 67:1943–1949.
14. Asano T, Yao Y, Shin S, McCubrey J, Abbruzzese JL, Reddy SA. Insulin receptor substrate is a mediator of phosphoinositide 3-kinase activation in quiescent pancreatic cancer cells. *Cancer research*. 2005; 65:9164–9168.
15. Reni M, Dugnani E, Cereda S, Belli C, Balzano G, Nicoletti R, Liberati D, Pasquale V, Scavini M, Maggiora P, Sordi V, Lampasona V, Ceraulo D, et al. (Ir)relevance of Metformin Treatment in Patients with Metastatic Pancreatic Cancer: An Open-Label, Randomized Phase II Trial. *Clinical cancer research*. 2016; 22:1076–1085.
16. Lee SH, Yoon SH, Lee HS, Chung MJ, Park JY, Park SW, Song SY, Chung JB, Bang S. Can metformin change the prognosis of pancreatic cancer? Retrospective study for pancreatic cancer patients with pre-existing diabetes mellitus type 2. *Digestive and liver disease*. 2016; 48:435–440.
17. Kozak MM, Anderson EM, von Eyben R, Pai JS, Poultides GA, Visser BC, Norton JA, Koong AC, Chang DT. Statin and Metformin Use Prolongs Survival in Patients With Resectable Pancreatic Cancer. *Pancreas*. 2016; 45:64–70.
18. Jang WI, Kim MS, Kang SH, Jo AJ, Kim YJ, Tchoe HJ, Park CM, Kim HJ, Choi JA, Choi HJ, Paik EK, Seo YS, Yoo HJ, et al. Association between metformin use and mortality in patients receiving curative resection for pancreatic cancer: A nationwide population-based study. *Liver Cancer*. 2016; 5:75.
19. Chaiteerakij R, Petersen GM, Bamlet WR, Chaffee KG, Zhen DB, Burch PA, Leof ER, Roberts LR, Oberg AL. Metformin Use and Survival of Patients With Pancreatic Cancer: A Cautionary Lesson. *Journal of clinical oncology*. 2016; 34:1898–1904.
20. Mathews CE, Kordes S, Pollak MN, Zwiderman AH, Mathot RA, Weterman MJ, Beeker A, Punt CJ, Richel DJ, Wilmink JW. Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *American journal of physiology Regulatory, integrative and comparative physiology*. 2015; 16:839–847.

21. Amin S, Mhango G, Lin J, Boffetta P, Wisnivesky J, Lucas A. Metformin use does not improve survival among diabetics with pancreatic adenocarcinoma: A population-based analysis. *American Journal of Gastroenterology*. 2015; 110:S17.
22. Jeon CY, Pandol SJ, Goodman MT. Survival time in pancreatic cancer patients with metabolic syndrome varies by use of insulin and statins. *Cancer research*. 2014; 74.
23. Tseng CH. Diabetes, insulin use, smoking, and pancreatic cancer mortality in Taiwan. *Acta diabetologica*. 2013; 50:879–886.
24. Hwang AL, Haynes K, Hwang WT, Yang YX. Metformin and survival in pancreatic cancer: a retrospective cohort study. *Pancreas*. 2013; 42:1054–1059.
25. Sadeghi N, Abbruzzese JL, Yeung SC, Hassan M, Li D. Metformin use is associated with better survival of diabetic patients with pancreatic cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2012; 18:2905–2912.
26. Gallagher EJ, LeRoith D. Diabetes, cancer, and metformin: connections of metabolism and cell proliferation. *Annals of the New York Academy of Sciences*. 2011; 1243:54–68.
27. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *Diabetes care*. 2006; 29:254–258.
28. Okumura T. Mechanisms by which thiazolidinediones induce anti-cancer effects in cancers in digestive organs. *Journal of gastroenterology*. 2010; 45:1097–1102.
29. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Annals of internal medicine*. 2009; 151:W65–94.
30. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in medicine*. 1998; 17:2815–2834.
31. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010; 25:603–605.
32. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials*. 1986; 7:177–188.
33. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine*. 2002; 21:1539–1558.
34. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed)*. 1997; 315:629–634.
35. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994; 50:1088–1101.
36. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000; 56:455–463.