RESEARCH ARTICLE

Metformin May Improve the Prognosis of Patients with Pancreatic Cancer

Jia-Wei Zhang*, Qing Sun

Abstract

<u>Background</u>: Pancreatic cancer risk is increased in patients with type 2 diabetes, while being reduced by metformin treatment. However, it is unclear whether metformin could be associated with clinical outcomes of patients with pancreatic cancer and concurrent type 2 diabetes. <u>Materials and Methods</u>: A pooled analysis of 4 publications including 1,429 patients was performed to investigate the association of metformin and overall survival(OS) in patients with pancreatic cancer and concurrent type 2 diabetes. <u>Results</u>: A borderline significant relative survival benefit was found in metformin treated patients compared with non-metformin treated patients (hazard ratio 0.80; 95% CI: 0.62-1.03). <u>Conclusions</u>: These results suggest that further investigation is warranted of whether metformin may benefit the survival of patients with pancreatic cancer and concurrent type 2 diabetes.

Keywords: Pancreatic cancer - metformin - survival - prognosis

Introduction

Pancreatic cancer (PC) is a highly lethal disease with complex etiology involving environmental and genetic factors (Chen et al., 2013; Shen et al., 2013; Shu et al., 2013; Tong et al., 2013). Although cigarette smoking is to explain 25% of cases, recent studies suggest that obesity and long-term type 2 diabetes are also major modifiable risks of PC. Furthermore, obesity and type 2 diabetes seem to affect the clinical outcome of patients with PC. Possible mechanisms for diabetes increasing cancer risk include cellular proliferative effects of hyperinsulinemia, hyperglycemia and abnormalities in insulin/IGF (insulin-like growth factor) receptor pathways. Experimental and epidemiologic data suggests that the antidiabetic drug metformin has antitumor activity in PC.

A hospital-based case-control study which was conducted at M. D. Anderson Cancer Center suggested that in diabetic patients treated with metformin, the risk of pancreatic cancer was significantly lower compared with those not treated with metformin [odds ratio,0.38; 95% confidence interval (95%CI), 0.22-0.69; *p*=0.001] (Li et al., 2009). Drawn from the Taiwanese National Health Insurance data of 2000, a representative sample of 800,000 showed that metformin decreased pancreatic cancer incidence ,hazard ratios (HR) 0.15, 95%CI: 0.03-0.79 (Lee et al., 2011).

Metformin activates AMP kinase (AMPK), which negatively regulates mTORC1[mammalian target of rapamycin (mTOR) complex 1]. Recent results show that metformin induces activation of AMPK ,which disrupts crosstalk between insulin/IGF-1 receptor and GPCR (G protein-coupled receptor) signaling of pancreatic cancer cells and inhibits the growth of these cells in xenograft models (Rozengurt et al., 2010).

Since metformin decreases the risk of pancreatic cancer, we assume it benefits the survival. A meta-analysis was done to explore the association between metformin and the survival of pancreatic cancer patients.

Materials and Methods

Study selection

We searched Medline, PubMed, highwire, biomed, springer, ebsco, sciencedirect, and Cochrane databases for relevant articles published from Jan 2010 to November 2014, in English-language using the following terms: metformin, pancreatic cancer, tumor, adenocarcinoma and survival, further screened references of the retrieved articles for earlier original studies. The inclusion criteria was: pancreatic cancer, cancer pathologically or histologically confirmed, and overall survival (OS) reported in metformin and non-metformin treated patients. Articles not written in English and unpublished reports were excluded.

Data extraction

We extracted the information from each published article as follows: author, year of publication, sample size, country of origin and OS. Adjusted Cox proportional hazard ratios were used for the quantitative analysis. If adjusted HRs were not available, the crude HRs were used. If neither adjusted nor crude HR data was available but Kaplan-Meier curves or appropriate summary statistics

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were provided, HRs and 95% confidence intervals were calculated as relevant effect measures through published methods.
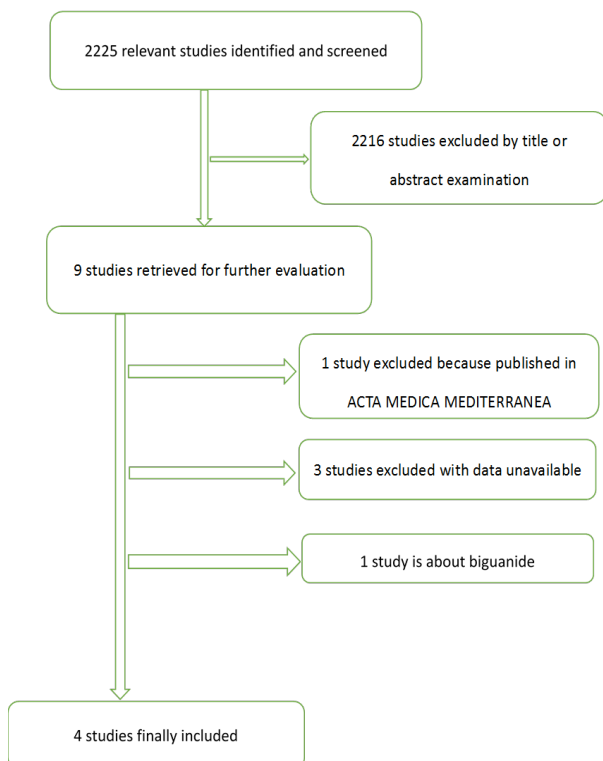
Statistical methods

By pooled Cox proportional HRs, OS was evaluated and 95%CIs were evaluated by published methods, because statistically a meta-analysis of summary results is as efficient as a joint analysis of individual participant result. The between-study heterogeneity was assessed by using the Cochran Q test with a significant level of $p<0.10$. Initial analyses with a fixed-effect model was performed and if there was significant heterogeneity, confirmatory analyses were done with a random-effect model. Funnel plots and the Egger's test was used to examine the effect of publication bias. All P values were two sided, while all analyses were done using the Stata software.

Results

Meta-analysis database

Figure1 shows the study selection flow chart. 2225 related publications were identified by initial screening, of which 9 publications seemed to meet the inclusion criteria. Three studies in which survival information was not obtainable were exclude (Witkowski et al., 2012; Esbah et al., 2013; Wilmink et al., 2014). The study by Nakai et al. because it was about biguanide not metformin and the study by Eren et al. because it was published in ACTA MEDICA MEDITERRANEA were further excluded (Nakai et al., 2013; Eren et al., 2014). As a result, the final result pool consisted of 4 studies, including 1,429 patients with PC and concurrent type 2 diabetes (Table1). Among the 4 studies, OS and HRs information was

available. Among the 1,429 patients, 531 patients treated with metformin alone or in combination with other anti-diabetic drugs and the remaining 898 patients treated with non-metformin regimens such as insulin and sulfonylurea.

Quantitative Analyses

Overall Survival: As summarized in Figure2, Our analysis suggested that the use of metformin to patients with PC and type 2 diabetes was associated with significantly reduced risk of death compared with those in non-metformin treatment (HR=0.80; 95%CI: 0.62-1.03 by random effect; p=0.011 for heterogeneity; I^2=73.1%). The study by Hwang et al. (2013) included 36.1% of the total patients (516/1,429),which dominates the analysis, and therefore, we did sensitivity analyses by excluding one study at a time. After exclusion of the study of Hwang et al. (2013) the pooled HR significantly changed (HR=0.72; 95%CI:0.61-0.84; p=0.565 for heterogeneity; I^2=0.0%). We further performed funnel plot and Egger's test (p=0.176), suggesting none presence of publication bias (Figure 3).

Stratified analyses

2 studies of the 4 enrolled the advanced PC patients, the other 2 did not show the OS of PC patients of all stages. We assumed the survival benefit of metformin was not
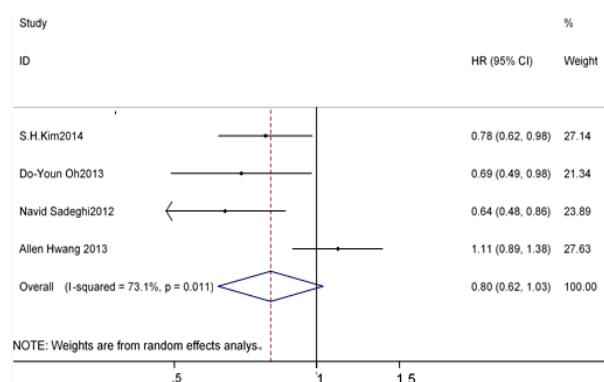
Figure 2. Hazard Ratios(HRs) of Overall Survival by Metformin versus Non-metformin Exposure. For each study, the estimates of HR and 95%CI were plotted with a box and a horizontal line. Hollow diamond indicates pooled HR and 95%CI. Abbreviations: CI, confidence interval; df, degrees of freedom
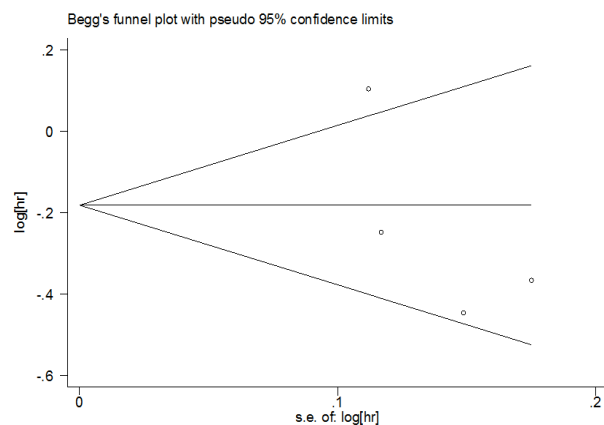
Figure 3. Funnel Plot Analysis to Detect Publication Bias. Each circle represents an individual study for the indicated association. Hollow circles indicate original observation studies. Abbreviation:s.e., standard error

Figure 1. Study Flow Chart for the Process of Selecting the Final 4 Publications

Table 1. Characterstatics of the Studies Included in the Meta-analysis

Study	Year	Country	disease	Population	N (met/non-met)	HR	95%CI
Kim et al., 2014	2014	South Korea	2DM+PC	retrospective cohort	428 (111/317)	0.78	0.62-0.98
Oh et al., 2013	2013	South Korea	2DM+APC	consecutive cohort	183 (56/127)	0.693	0.492-0.977
Sadeghi et al., 2012	2012	USA	2DM+PC	retrospective cohort	302 (117/185)	0.64	0.48-0.86
Hwang et al., 2013	2013	UK	2DM+APC	retrospective cohort	516 (247/269)	1.11	0.89-1.38

CI, confidence interval; 2DM, type 2 diabetes mellitus; PC, pancreatic cancer; APC, advanced pancreatic cancer; N, number; met, metformin; non-met non-metformin

associated with the stage of pancreatic cancer, because in the study of Sadeghi et al. a subgroup of 2DM patients concurrent with non-metastatic PC, HR=0.53, 95%CI: 0.36-0.78(Sadeghi et al., 2012)].The study of Kim et al. showed that after adjusting for cancer stage, metformin still benefited the survival of PC (Kim et al., 2014). But the information is too limited to do a meta-analysis.

Discussion

To our knowledge, it is the first quantitative analysis to explore the association of metformin treatment and clinical outcomes of patients of concurrent pancreatic cancer and type 2 diabetes. In this meta-analysis, 1,429 patients from 4 independently published investigations were included, we provided evidence that metformin treatment was associated with improved OS in patients with concurrent type 2 diabetes and pancreatic cancer.

Metformin is one of the most commonly prescribed drugs for the treatment of type 2 diabetes mellitus. Compared to other antidiabetic medication, metformin was reported more efficient in treating pancreatic cancer, decreasing the incidence and improving survival. The study of Oh et al. showed that antidiabetic medication in general, sulfonylurea, or insulin did not affect while metformin benefit the survival of PC patients (Oh et al., 2013). In another study including insulin, sulfonylurea, biguanide, and thiazolidinedione, none of them had prognostic impact on advanced pancreatic cancer (Nakai, et al., 2013). A study from Taiwan approved that sulfonylurea was associated with increased risk of PC, adjusted HR=2.36, 95%CI 1.21-4.61 (Chiu et al., 2013). A study from Germany showed the cumulative dose exposure of insulin glargine reduced the risk of cancer mortality in general, and of pancreatic cancer in particular (Ioacara et al., 2014). In a study from UK, a total of 62,809 patients were assigned into four groups according to whether they received monotherapy with sulfonylurea or metformin, combined therapy (sulfonylurea plus metformin), or insulin. Monotherapy with metformin carried the lowest risk of cancer. In comparison, the adjusted HR was 1.08 (95% CI 0.96-1.21) for sulfonylurea plus metformin, 1.36 (95% CI 1.19-1.54) for sulfonylurea monotherapy, and 1.42 (95% CI 1.27-1.60) for insulin-based regimens. Adding metformin to insulin regimen reduced progression of cancer (HR 0.54, 95% CI 0.43-0.66). Insulin therapy increased the risk of pancreatic cancer (HR 4.63, 95% CI 2.64-8.10) compared with metformin (Currie et al.,2009). Another study suggested that both sulfonylureas (≥ 30 prescriptions, adjusted OR: 1.90, 95% CI: 1.32-2.74) and of insulin (≥ 40 prescriptions, adjusted OR: 2.29, 95% CI: 1.34-3.92) increased risk of pancreatic cancer (Bodmer

et al., 2012). The association of cancer and antidiabetic medication but metformin seems contradictory and inconclusive.

In this analysis, 1,429 patients with concurrent PC and 2DM were enrolled, 531 patients received metformin treatment and 898 patients received non-metformin treatment. Only the study of Hwang et al. suggested there was no association between metformin and OS. In the study, subjects were classified as exposed if they were prescribed metformin around the time of PC diagnosis(between 6 months prior and 1 month after), while the other three studies did not disclose the information of metformin exposure time and dose. The information is too limited to analyze if the survival benefit was associated with exposure time and dose. The 4 studies were all retrospective, random clinical trials were expected to explore the efficacy of metformin in the treatment of PC.

The existing evidence approved that metformin was efficient in the treatment of pancreatic cancer, which may modify the strategy of cancer treatment in the near future.

Acknowledgements

References

Bodmer M, Becker C, Meier C, Jick SS, Meier CR (2012). Use of antidiabetic agents and the risk of pancreatic cancer: a case-control analysis. *Am J Gastroenterol*, **107**, 620-6.

Chen WQ, Liang D, Zhang SW, et al (2013). Pancreatic cancer incidence and mortality patterns in China, 2009. *Asian Pac J Cancer Prev*, **4**, 7321-4.

Chun-Chih Chiu, Chin-Chou Huang, Yu-Chun Chen, et al (2013). Increased risk of gastrointestinal malignancy in patients with diabetes mellitus and correlations with anti-diabetes drugs: A nationwide population-based study in Taiwan. *Intern Med*, **52**, 939-46.

Currie CJ, Poole CD, Gale EA (2009). The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia*, **52**, 1766-77.

Do-Youn Oh, Younak Choi, Tae-Yong Kim, et al (2013). The impact of diabetes mellitus and metformin on survival of patients with advanced pancreatic cancer receiving chemotherapy. *J Clin Oncol*, **31**, 4044

Esbah O, Oksuzoglu B, Eren T, et al (2013). Metformin in diabetic pancreatic cancer patients: benefit or not - multicenter experience. *J Clin Oncol*, **31**, 15110.

Esbah O Eren, T Helvaci, K Guler, et al (2014). The effect of metformin use on prognosis in pancreatic cancer. *Acta Medica Mediterranea*, **30**, 465-471

Hwang AL, Haynes K, Hwang WT, Yang YX (2013). Metformin and survival in pancreatic cancer a retrospective cohort. *Pancreas*, **42**, 1054-9.

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Kim SH, Kim MH, Kang B, Ahn JB, Choi HJ (2014).Metformin use is associated with improved survival in diabetic pancreatic cancer patients. *Ann Oncol*, **25**, iv238.

Lee MS, Hsu CC, Wahlqvist ML, et al (2011). Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. *BMC Cancer*, **11**, 20.

Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL (2009). Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology*, **137**, 482-8.

Nakai Y, Isayama H, Sasaki T, et al (2013). Clinical outcomes of chemotherapy for diabetic and nondiabetic patients with pancreatic cancer better prognosis with statin use in diabetic Patients. *Pancreas*, **42**, 202-8.

Rozengurt E, Sinnett-Smith J, Kisfalvi K (2010). Crosstalk between insulin/insulin-like growth factor-1 receptors and G protein-coupled receptor signaling systems: a novel target for the antidiabetic drug metformin in pancreatic cancer. *Clin Cancer Res*, **16**, 2505-11.

Sadeghi N, Abbruzzese JL, Yeung S-JJ, Hassan M, Li D (2012). Metformin use is associated with better survival of diabetic patients with pancreatic cancer. *Clin Cancer Res*, **18**, 2905-912.

Shen B, Zheng MQ, Lu JW, et al (2013). CXCL12-CXCR4 promotes proliferation and invasion of pancreatic cancer cells. *Asian Pac J Cancer Prev*, **14**, 5403-8.

Shu J, Li CG, Liu YC, Yan XC, et al (2012). Comparison of serum tumor associated material (TAM) with conventional biomarkers in cancerpatients. *Asian Pac J Cancer Prev*, **13**, 2399-403.

Sorin Ioacara, Cristian Guja, Constantin Ionescu-Tirgoviste, Simona Fica, Michael Roden (2014). Cancer specific mortality in insulin-treated type 2 diabetes patients. *PLoS One*, **9**, 93132.

Tong GX, Geng QQ, Chai J, et al (2014). Association between pancreatitis and subsequent risk of pancreatic cancer: a systematic review of epidemiological studies. *Asian Pac J Cancer Prev*, **15**, 5029-34.

Wilmink J, Kordes S, Zwinderman K, et al (2014). A phase II randomized, placebo controlled study to evaluate the efficacy of the combination of gemcitabine, erlotinib, and metformin in patients with locally advanced or metastatic pancreatic cancer. *J Clin Oncol*, **32**, 4021.

Witkowski ER, Ragulin-Coyne E, Chau Z, et al (2012). Effects of metformin on pancreatic cancer survival among medicare beneficiaries. *J Clin Oncol*, **30**, 14691.