8-1-2017

Differential and Joint Effects of Metformin and Statins on Overall Survival of Elderly Patients with Pancreatic Adenocarcinoma: A Large Population-Based Study.

Jian-Yu E
Rutgers, the State University of New Jersey

Shou-En Lu
Rutgers, the State University of New Jersey

Yong Lin
Rutgers, the State University of New Jersey

Judith M. Graber
Rutgers, the State University of New Jersey

David Rotter
Rutgers, the State University of New Jersey

Differential and joint effects of metformin and statins on overall survival of elderly patients with pancreatic adenocarcinoma: a large population-based study

Jian-Yu E[1, 2], Shou-En Lu[1,3], Yong Lin[1,3], Judith M. Graber[1,2,4], David Rotter[1], Lanjing Zhang[1,5,6], Gloria M. Petersen[7], Kitaw Demissie[1, 2], Grace Lu-Yao[8,9,10], Xiang-Lin Tan[1,2,11*]

[1]Rutgers Cancer Institute of New Jersey, Rutgers, The State University of New Jersey, New Brunswick, NJ

[2]Department of Epidemiology, School of Public Health, Rutgers, The State University of New Jersey, Piscataway, NJ

[3]Department of Biostatistics, School of Public Health, Rutgers, The State University of New Jersey, Piscataway, NJ

[4]Environmental and Occupational Health Sciences Institute, Rutgers, The State University of New Jersey, Piscataway, NJ

[5]Department of Pathology, University Medical Center of Princeton, Plainsboro, NJ

[6]Department of Biological Sciences, Rutgers, The State University of New Jersey, Newark, NJ

[7]Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, MN

[8]Department of Medical Oncology, Sidney Kimmel Cancer Center at Jefferson, Sidney Kimmel Medical College, Philadelphia, PA

[9] Sidney Kimmel Cancer Center at Jefferson, Philadelphia, PA

[10] Jefferson College of Population Health, Philadelphia, PA

[11]Department of Medicine, Robert Wood Johnson Medical School, Rutgers, The State University of New Jersey, New Brunswick, NJ

Running title: Statin use and pancreatic cancer mortality

Key Words: Pancreatic Cancer, Metformin, Statin, Survival, Cox proportional hazards models

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; DCSI, diabetic comorbidity severity index; HMO, health-care maintenance organizations; HR, hazard ratio; IGT, Impaired

Glucose Tolerance; PDAC, pancreatic ductal adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results

Financial Support: X.L. Tan is supported by a grant from the National Cancer Institute at the National Institutes of Health (K07CA190541). This research was in part supported by the Biometrics Shared Resource of the Rutgers Cancer Institute of New Jersey (P30CA072720).

[*]**Corresponding Author**: Dr. Xiang-Lin Tan, Department of Medicine, Division of Population Science, Rutgers Cancer Institute of New Jersey, Rutgers, The State University of New Jersey, 195 Little Albany Street, R5566, New Brunswick, NJ, 08901. Email: tanxi@cinj.rutgers.edu; Phone: 1-732-235-6516; Fax: 1-732-235-8809.

Abstract

Background: Published evidence indicates that individual use of metformin and statin is associated with reduced cancer mortality. However, their differential and joint effects on pancreatic cancer survival are inconclusive.

Methods: We identified a large population-based cohort of 12,572 patients aged 65 years or older with primary pancreatic ductal adenocarcinoma (PDAC) diagnosed between 2008 and 2011 from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Exposure to metformin and statins was ascertained from Medicare Prescription Drug Event files. Cox proportional hazards models with time-varying covariates adjusted for propensity scores were used to assess the association while controlling for potential confounders.

Results: Of 12,572 PDAC patients, 950 (7.56%) had used metformin alone, 4506 (35.84%) had used statin alone, and 2445 (19.45%) were dual users. Statin use was significantly associated with improved overall survival [hazard ratio (HR), 0.94; 95% confidence interval (CI), 0.90−0.98], and survival was more pronounced in post-diagnosis statin users (HR, 0.69; 95% CI, 0.56−0.86). Metformin use was not significantly associated with overall survival (HR, 1.01; 95% CI, 0.94−1.09). No beneficial effect was observed for dual users (HR, 1.00; 95% CI, 0.95−1.05).

Conclusions: Our findings suggest potential benefits of statins on improving survival among elderly PDAC patients; further prospective studies are warranted to corroborate the putative benefit of statin therapy in pancreatic cancer.

Impact: Although more studies are needed to confirm our findings, our data add to the body of evidence on potential anti-cancer effects of statins.

Introduction

Pancreatic cancer poses a high mortality burden in the United States, and current therapies have modestly improved survival (1-6). The impetus for exploring chronic disease medications for use in anticancer approaches is to advance new therapeutic strategies into clinical settings with relatively short regulatory evaluation timelines. Among medications being evaluated, metformin and statins are two frequently prescribed drugs with an established safety profile that show promising anti-cancer effects (7, 8), although their efficacy in pancreatic cancer treatment remains unclear.

Beneficial effects of metformin and statins on pancreatic cancer treatment are biologically plausible (9-13), although findings from epidemiological studies on their therapeutic benefits have been inconsistent. Our recent meta-analysis included ten publications on metformin treatment and six publications on statin treatment and found that each medication was associated with improved overall survival in pancreatic cancer patients (14). However, some critical issues have not been addressed. First, dyslipidemia is more prevalent in diabetic patients, and the majority of metformin users also take lipid-lowering drugs such as statins (15-17). Therefore, the survival benefits observed in metformin users may in part be due to the statin use. Moreover, there are few studies that examined the interactive or potential joint effect of combination treatments of metformin and statins (18, 19). Second, misclassification or disregard of immortal time (period of cohort entry and date of first exposure to a drug during which death or an outcome under study could not occur) may introduce unintended bias, which leads to the overestimation of drug effects (20). Several retrospective cohort studies were likely to have suffered from this bias because use of metformin or statin was dichotomized into ever/never categories without taking into account timing of drug use in relation to cohort entry (18, 21-23). Third, previous studies were unable to distinguish the effects of pre-diagnosis drug use (medications initiated before diagnosis) *versus* post-diagnosis drug use (medications initiated after diagnosis), and which have been demonstrated in recent studies, such as those using data from the Women's Health Initiative (24). Previous

epidemiological studies on metformin and statins include mostly pre-diagnosis users, and very few include post-diagnosis users. To address the "healthy user effect" (25), the pre-diagnosis users should be analyzed separately from post-diagnosis users. Finally, questions regarding how drug initiation and dosages impact on mortality among pancreatic cancer patients remain unanswered. It is therefore important to examine the treatment effect of optimal therapeutic regimens in observational studies.

To inform future trial design and effective clinical practice, these critical issues were examined in a large cohort population with more rigorous approaches. We used a nationally representative cancer database in the United States to determine the differential and joint effects of metformin and statin use on the survival outcomes among elderly pancreatic cancer patients.

Materials and Methods

Study population

After approval by the Institutional Review Board at Rutgers University, this study was performed using the Surveillance, Epidemiology, and End Results (SEER-18) registry linked to Medicare claims. Approximately 97% of US persons aged 65 years or older are eligible for Medicare Part A coverage, which includes hospital, skilled-nursing facility, hospice and some home health care. Ninety-six percent of elderly Part A beneficiaries chose to enroll in Medicare Part B that covers physician and outpatient services. As of 2016, SEER-Medicare Part A and B data were available for patients diagnosed with cancer through 2013, and data on Medicare Part D for outpatient prescription-drug coverage were available from 2007 to 2012. To allow a 1- year window before or after cancer diagnosis for the baseline assessment of comorbidities and use of prescriptions, we selected patients with primary pancreatic ductal adenocarcinoma (PDAC) diagnosed from January 2008 to December 2011. Primary PDAC cases were identified by using the *International Classification of Disease for Oncology, Third Edition* (ICD-O-3) histology codes: 8000, 8010, 8020, 8021, 8022, 8140, 8141, 8211, 8230,

8500, 8521, 8050, 8260, 8441, 8450, 8453, 8470, 8471, 8472, 8473, 8480, 8481, 8503 (https://seer.cancer.gov/icd-o-3/). The detailed patient selection steps are illustrated in Figure 1. Briefly, we excluded patients with non-primary pancreatic cancer or non-adenocarcinoma histology, or patients in HMO (health-care maintenance organizations). Patients diagnosed at autopsy or with missing diagnosis date or death date equal to or less than diagnosis date were also excluded from the study cohort. To include comorbidity characteristics before cancer diagnosis and treatment characteristics present in inpatient and outpatient claim files, we restricted the analysis dataset to patients who were continuously enrolled in Medicare Part A and Part B from 12 months before cancer diagnosis until death or December 30, 2012, the last date of available Medicare claims data. To capture the potential drug effect up to 3 months before cancer diagnosis and the outcomes after cancer diagnosis, we further restricted our dataset to patients who were continuously enrolled in Medicare Part D beginning 3 months before cancer diagnosis to death or the end of follow up.

Sociodemographic and clinical characteristics and comorbidities

Sociodemographic information, including age, sex, race, and neighborhood income, were obtained from the SEER-Medicare linked databases. We controlled the burden of comorbidities, including cardiovascular disease and chronic kidney disease, using the Deyo adaption of Charlson comorbidity index (26-28). The Charlson comorbidity conditions were identified using inpatient and outpatient hospital claims (Medicare Provider Analysis and Review, Outpatient Standard Analytical File) as well as claim files by individual physicians (Carrier File) (28, 29). To avoid overestimating comorbidity related to PDAC diagnosis, we used the claims in the 11 months prior to cancer diagnosis to calculate the Charlson score. The diabetic comorbidity severity index (DCSI) of diabetic or Impaired Glucose Tolerance (IGT) patients was used to adjust for diabetic severity for predicting mortality (30, 31). Due to the lack of smoking information, we used chronic obstructive pulmonary disease (COPD) as a surrogate for smoking-related illness (32). Tumor characteristics, including tumor grade, stage and size, were ascertained from the SEER registry database. Treatment information,

including resection, radiation, and chemotherapy, was identified from the Medicare Claims (Medicare Provider Analysis and Review, Carrier, Outpatient Standard Analytical File) using *the International Classification of Disease, 9th Revision* (ICD-9) and the Healthcare Common Procedure Coding System codes (33).

Metformin and statin regimens

Metformin and statin regimens were extracted from the Medicare Part D Claims file. Daily intensity for metformin was estimated as total milligrams dispensed divided by total days of prescriptions before cancer diagnosis. Statins were categorized based on drug characteristics as: lipophilic (atorvastatin, fluvastatin, lovastatin, and simvastatin); hydrophilic (pravastatin and rosuvastatin); high potency (atorvastatin, rosuvastatin, and simvastatin); or low potency (fluvastatin, lovastatin, and pravastatin) (34). Statin intensity was assessed as an ordinal variable (high, moderate, and low) according to average daily dose lowering of low-density lipoprotein cholesterol (35).

Statistical analysis

Demographic and clinical characteristics, along with comorbid conditions, were compared among four groups: metformin alone, statin alone, dual users and neither users using Chi-square tests. Overall PDAC survival was assessed with survival times calculated as the time from diagnosis to death, or censored at the end of follow-up. Propensity scores (36) were used to estimate the probability of one of the following four exclusive medication use categories: "ever used statin" (p1), 'ever used metformin' (p2), 'ever used both statin and metformin' (p3) and 'none'. They were calculated based on patients' sociodemographic characteristics, and comorbidities (Charlson Comorbidity Score, obesity, chronic pancreatitis, dyslipidemia, and diabetes/IGT) using a general (polytomous) logistic regression model (37). To control pre-treatment imbalances on observed variables, propensity scores p1, p2 and p3 were included as covariates in the statistical models for propensity score adjustment.

We first examined the association using a conventional Cox model with medication use as a non-time-dependent variable. To reduce immortal time bias, we then applied a time-dependent covariate Cox regression analysis by treating the medication use as time-varying covariates. The associations between metformin and/or statin use and overall survival were evaluated by sequentially adding the following variables: 1) demographic characteristics; 2) tumor characteristics; 3) treatment characteristics; 4) comorbidities, and 5) Charlson Comorbidity Score. We developed the final model by adjusting for tumor characteristics, treatment characteristics, and propensity scores, as well as the variables that remained imbalanced after propensity score adjustment (i.e., dyslipidemia, diabetes/IGT, Charlson Comorbidity Score).

To assess the possible effect modification by diabetes/IGT, dyslipidemia or tumor characteristics, we performed stratified analyses by diabetes/IGT and dyslipidemia as well as tumor stage, grade and tumor size. Additionally, we determined the differential effects on survival for pre-diagnosis users *versus* post-diagnosis users, by stratified medication use before and after cancer diagnosis. Furthermore, subset analyses were conducted to assess the effects of metformin use (timing initiation and daily intensity) and statin use (timing initiation, name, type, potency and intensity) among patients who initiated medications before cancer diagnosis. When we assessed the metformin effect on overall survival, statin use was adjusted as a time-varying covariate. Similarly, we adjusted metformin use to assess statin effect. All statistical analyses were performed using SAS Version 9.4 (SAS Institute in Cary. NC).

Results

A total of 12,572 patients with primary PDAC composed the analytic population for the study (Figure 1). Of 12,572 PDAC patients (median age = 76 years), 11,526 (91.77%) patients died before December 30, 2012 with a median follow-up period of 3.80 months (interquartile range: 1.4−10.1 months). Among them, 950

(7.56%) had used metformin without a statin (metformin alone), 4506 (35.84%) had used statin without metformin (statin alone), and 2445 (19.45%) were dual users (Table 1). Compared to Kaplan-Meier median survival of neither users (3.60 months), survival was 3.97, 4.06 and 4.23 months for metformin users, statin users, and dual users, respectively.

Before adjustment using the propensity score, there were significant differences on almost all studied variables among the four groups (Table 1). Metformin alone, statin alone, and dual users were significantly younger than neither users. Statin alone and dual users had a higher proportion of males, lower localized/regional tumor stage and smaller tumor size, compared to neither users. Additionally, metformin alone had higher proportion of chemotherapy and radiation therapy than neither users. Not surprisingly, a higher frequency of patients with dyslipidemia or diabetes/IGT, used either metformin, or statin, or both. After propensity score adjustment, only age, Charlson Comorbidity Score, dyslipidemia, and diabetes/IGT, could not be well-balanced among the four groups (Table 1).

In the conventional Cox model, metformin alone [hazard ratio (HR), 0.91; 95% confidence interval (CI), 0.85−0.98)], statin alone (HR, 0.91; 95% CI, 0.88−0.95) or a combination (HR, 0.90; 95% CI, 0.86−0.95) was significantly associated with improved overall survival (Table 2). The estimated HRs for three groups in the time-varying Cox model were larger, compared to those in the conventional Cox model, indicating that immortal time bias had exaggerated medication benefits for cancer patients in the non-time dependent model. Moreover, only patients on statin alone had significantly reduced overall mortality, and this association remained significant after adjusting for different potential confounders (HR, 0.94; 95% CI, 0.90−0.98). However, the association of overall survival with the exposure to metformin alone or a combination remained non-significant (Table 2). When we restricted our population to patients who had survived for greater than 2 months (N = 8274), we observed a weaker and non-significant association between statin use and overall

survival (HR, 0.96; 95% CI, 0.91−1.01) (Supplementary Table S1), suggesting that the contribution of statins to survival may be mitigated with time.

When stratified by the status of diabetes/IGT or dyslipidemia, we observed similar patterns of results, and no evidence that diabetes/IGT or dyslipidemia modify effects of statins ($P_{\text{interaction}} > 0.05$) (Supplementary Table S2). Additionally, we performed stratified analyses on tumor stage, grade, and size to confirm the statin effect. Statin use showed a significant association with improved overall survival among patients with distant tumor stage or III/IV tumor grade, but no effect modification by tumor size was observed (Supplementary Table S3). When we stratified medication use before and after cancer diagnosis, the median survival among pre- and post-diagnosis statin users were 4.07 and 10.93 months, respectively, compared with 3.67 months in non-statin users (Figure 2). The adjusted HR for post-diagnosis statin users [0.69 (95% CI, 0.56−0.86)] was significantly different from pre-diagnosis statin users [0.94 (95% CI, 0.91−0.98)] ($P < 0.01$) (Table 3).

Compared with non-metformin users, patients who used metformin either > 6 months or ≤ 6 months before diagnosis did not have longer survival, however, using metformin 1,000−1,500 mg/day was significantly associated with an increased overall mortality (HR, 1.10; 95% CI, 1.03−1.17) (Table 4). Compared with non-statin users, survival benefits were observed in patients who started statins > 6 months before diagnosis (HR, 0.95; 95% CI, 0.91−0.98), but not those who started statins ≤ 6 months before diagnosis (HR, 0.96; 95% CI, 0.87−1.07). No significant difference on survival was observed between patients who started statins > 6 months before diagnosis and those who started statins ≤ 6 months before diagnosis ($P = 0.71$). Additionally, compared to non-statin users, patients who used rosuvastatin or hydrophilic or high potency statins had longer survival (Table 4). Patients with low intensity statin survived longest (HR, 0.92; 95% CI, 0.87−0.98), followed by moderate intensity (HR, 0.95; 95% CI, 0.90−1.00), while high intensity statin use did not show significant improvement of survival (HR, 0.96; 95% CI, 0.92−1.01) (Table 4). The trend of HR from low to high statin intensity was borderline significant ($P = 0.07$).

Discussion

To our knowledge, this is the largest US-population based study to examine the differential and joint effects of metformin and statins on survival among pancreatic cancer patients. We found that exposure to statins, rather than metformin, is associated with an improved overall survival of elderly pancreatic cancer patients. In particular, post-diagnosis exposure to statins is associated with a 31% reduction in mortality, and pre-diagnosis exposure to statins with a 6% reduction in mortality. Furthermore, the effect of rosuvastatin (the statin with the longest half-life) is most pronounced. These new insights provide crucial data for planning randomized clinical trials using statins as an adjuvant treatment of pancreatic cancer.

Findings from previous epidemiological studies of metformin use and pancreatic cancer survival are conflicting. Possible explanations include failure to consider diabetic severity and comorbidities (38), statin use (39), and immortal time bias (40). When accounting for these critical issues, we observed that metformin use was not significantly associated with overall survival, either in pre-diagnosis users or in post-diagnosis users. Our results are consistent with a recent retrospective cohort study of 980 PDAC patients with diabetes when the analysis was performed by using time-varying Cox model (41). These results suggested that the metformin exposure variable is better treated as a time-dependent variable rather than a fixed-time variable (42). In this current study, we acknowledge that we may not have had sufficient power to detect smaller effects due to the limited sample sizes in our subgroup analysis: only 497 patients started metformin ≤ 6 months before diagnosis, and 700 patients used less than 1,000 mg/day of metformin.

We observed that statin use was significantly associated with improved overall survival of elderly PDAC patients, and this finding was more pronounced in post-diagnosis statin users. A retrospective study that included 1,761 newly diagnosed PDAC patients found that statin use was significantly associated with a lower mortality using a time-dependent Cox model (HR, 0.78; 95% CI, 0.62−0.99) (43). Our results are comparable

with the results from a recent SEER-Medicare study of 7,813 elderly PDAC patients (34). The limitations of the previous SEER-Medicare study are the failure to control for important comorbidities and metformin use, as well as the limited sample size. Based on previous literature, our recent meta-analysis also suggested that statin use was significantly associated with improved survival of pancreatic cancer patients (HR, 0.75; 95% CI, 0.59−0.90) (14).

Anticancer effects of statins have been demonstrated in various preclinical and mechanistic studies. The main effect of statins is to inhibit cholesterol synthesis through inhibition of the rate-limiting enzyme HMG-CoA reductase (44). In addition, statins have cancer chemotherapeutic properties through various mechanisms: halting cell cycle progression and proliferation (45); increasing radiosensitization in cancer cells (46); promoting apoptosis (47, 48); and impairing metastasis of tumors (49). Based on our current understanding of the diverse molecular pathways of statin action, a protective effect of statins on overall survival of pancreatic cancer patients is biologically plausible. Unexpectedly, the current study did not observe a survival benefit for dual users. This might be explained by a higher Charlson comorbidity score and a higher proportion of obesity and diabetes/IGT in dual users, compare to patients with statin alone. The potential anti-tumor benefits of statins should be carefully further assessed in preclinical and clinical studies to repurpose statins for the treatment of pancreatic cancer.

We observed that that rosuvastatin significantly improved overall survival, while other statins did not. Although the mechanisms are unknown, it is worth noting that the half-life elimination of rosuvastatin is much longer (about 20 hours), compared to a half-life of all other statins (which range from 2 and 3 hours). Interestingly, it has been showed that mice xenotransplanted with pancreatic cancer cells and treated with rosuvastatin had higher survival rates, compared to the mice treated with other commercially available statins (50). In addition, we found that hydrophilic and high potency statins exerted better survival outcomes than

non-statin use. These may be due to many factors such as different chemical structures leading to changes in their bioavailability, pharmacokinetics, and pharmacodynamics (51).

We also found low and moderate intensity of statin use improved survival significantly, but high intensity statin showed a non-significant survival benefit. The marked differences were partially due to lowering LDL-C strengths among different intensities, indicating a contribution of downstream intermediates in cholesterol biosynthesis for growth and viability of pancreatic cells. It is possible that the patients using high intensity statin might have worse hyperlipidemia, and therefore no survival benefit was observed for patients with high intensity statin. Our findings are comparable with those in a recent Kaiser Permanente South California (KPSC) study by Huang *et al.* (52). They reported a 13% and 12% reduction in mortality during study period among any statin users and among pre-diagnosis statin users, respectively. Further, they found that simvastatin and atorvastatin were the only two medications that were independently associated with improved survival. However, the sample size of the KPSC study was too small to evaluate the effect of rosuvastatin and post-diagnosis statin use.

Several limitations inherent with our data must be addressed. First, the study is limited by its retrospective design and is not a randomized clinical trial. Drug exposures are dependent on other factors related to elderly patients' baseline health. To address this issue, we used propensity scores to estimate the likelihood that patients would use metformin and/or statin. The propensity scores controlled for selection bias that could occur as a result of imbalances of comorbidities and sociodemographic factors (36). Second, we have no drug use information prior to age 65, since only patients aged 65 years or older are eligible for Medicare Part D coverage, leading to possible misclassification of ever use of these drugs if prior users did not file medication claims. However, among 3579 identified PDAC patients with diabetes/IGT, 1437 (40.2%) patients (471 of metformin only users plus 966 of dual users) had a history of metformin use and 2142 (59.9%) never used metformin, which is comparable with the proportion of diabetic PDAC patients using metformin in previous

studies (39, 41). Third, we were unable to account for the effect of some established determinants of pancreatic cancer survival, such as cholesterol, triglyceride, glucose level, liver specific metastases, CA 19-9, or CEA. Fourth, we lacked individual-level data on socioeconomic status of cancer patients, which might confound the association of metformin/statin and mortality. Finally, due to data limitations, tumor characteristics such as tumor grade and tumor size were missing on over 20% of the subjects.

Considering these limitations is critical for interpreting the strength of evidence of survival benefit, and future observational studies should focus on addressing the possible effect of timing as well as type and dosage of statin use on pancreatic cancer survival. Further prospective studies with solid rationale for evaluating the use of statin in conjunction with chemotherapy for pancreatic cancer can help determine if statin is an effective treatment for pancreatic cancer.

Acknowledgements

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

References

1. Brown ML, Riley GF, Schussler N, Etzioni R. Estimating health care costs related to cancer treatment from SEER-Medicare data. Med Care. 2002;40:IV-104-17.
2. Chang S, Long SR, Kutikova L, Bowman L, Crown WH, Lyman GH. Burden of pancreatic cancer and disease progression: economic analysis in the US. Oncology. 2006;70:71-80.
3. Du W, Touchette D, Vaitkevicius VK, Peters WP, Shields AF. Cost analysis of pancreatic carcinoma treatment. Cancer. 2000;89:1917-24.
4. Elixhauser A, Halpern MT. Economic evaluations of gastric and pancreatic cancer. Hepatogastroenterology. 1999;46:1206-13.
5. O'Neill CB, Atoria CL, O'Reilly EM, LaFemina J, Henman MC, Elkin EB. Costs and trends in pancreatic cancer treatment. Cancer. 2012;118:5132-9.
6. Wilson LS, Lightwood JM. Pancreatic cancer: total costs and utilization of health services. J Surg Oncol. 1999;71:171-81.
7. Aldasouqi SA, Duick DS. Safety issues on metformin use. Diabetes Care. 2003;26:3356-7.
8. Jacobson TA. NLA Task Force on Statin Safety--2014 update. J Clin Lipidol. 2014;8:S1-4.
9. Issat T, Nowis D, Legat M, Makowski M, Klejman MP, Urbanski J, et al. Potentiated antitumor effects of the combination treatment with statins and pamidronate in vitro and in vivo. Int J Oncol. 2007;30:1413-25.
10. Kusama T, Mukai M, Iwasaki T, Tatsuta M, Matsumoto Y, Akedo H, et al. 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibitors reduce human pancreatic cancer cell invasion and metastasis. Gastroenterology. 2002;122:308-17.
11. Yao CJ, Lai GM, Chan CF, Cheng AL, Yang YY, Chuang SE. Dramatic synergistic anticancer effect of clinically achievable doses of lovastatin and troglitazone. Int J Cancer. 2006;118:773-9.

12. Mistafa O, Stenius U. Statins inhibit Akt/PKB signaling via P2X7 receptor in pancreatic cancer cells. Biochem Pharmacol. 2009;78:1115-26.
13. Yue W, Yang CS, DiPaola RS, Tan XL. Repurposing of metformin and aspirin by targeting AMPK-mTOR and inflammation for pancreatic cancer prevention and treatment. Cancer prevention research. 2014;7:388-97.
14. E JY, Graber JM, Lu SE, Lin Y, Lu-Yao G, Tan XL. Effect of Metformin and Statin Use on Survival in Pancreatic Cancer Patients: a Systematic Literature Review and Meta-analysis. Curr Med Chem. 2017.
15. Brown AS. Lipid management in patients with diabetes mellitus. Am J Cardiol. 2005;96:26E-32E.
16. Dake AW, Sora ND. Diabetic Dyslipidemia Review: An Update on Current Concepts and Management Guidelines of Diabetic Dyslipidemia. Am J Med Sci. 2016;351:361-5.
17. Jaiswal M, Schinske A, Pop-Busui R. Lipids and lipid management in diabetes. Best Pract Res Clin Endocrinol Metab. 2014;28:325-38.
18. Kozak MM, Anderson EM, von Eyben R, Pai JS, Poultsides GA, Visser BC, et al. Statin and Metformin Use Prolongs Survival in Patients With Resectable Pancreatic Cancer. Pancreas. 2016;45:64-70.
19. Amin S, Boffetta P, Lucas AL. The Role of Common Pharmaceutical Agents on the Prevention and Treatment of Pancreatic Cancer. Gut Liver. 2016;10:665-71.
20. Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol. 2008;167:492-9.
21. 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.
22. Nakai Y, Isayama H, Sasaki T, Mizuno S, Sasahira N, Kogure H, et al. Clinical outcomes of chemotherapy for diabetic and nondiabetic patients with pancreatic cancer: better prognosis with statin use in diabetic patients. Pancreas. 2013;42:202-8.
23. Sadeghi N, Abbruzzese JL, Yeung SC, Hassan M, Li D. Metformin use is associated with better survival of diabetic patients with pancreatic cancer. Clin Cancer Res. 2012;18:2905-12.

24. Wang A, Aragaki AK, Tang JY, Kurian AW, Manson JE, Chlebowski RT, et al. Statin use and all-cancer survival: prospective results from the Women's Health Initiative. Br J Cancer. 2016;115:129-35.
25. Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. American journal of epidemiology. 2007;166:348-54.
26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-83.
27. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;45:613-9.
28. Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. J Clin Epidemiol. 2000;53:1258-67.
29. Klabunde CN, Harlan LC, Warren JL. Data sources for measuring comorbidity: a comparison of hospital records and medicare claims for cancer patients. Med Care. 2006;44:921-8.
30. Joish VN, Malone DC, Wendel C, Draugalis JR, Mohler MJ. Development and validation of a diabetes mellitus severity index: a risk-adjustment tool for predicting health care resource use and costs. Pharmacotherapy. 2005;25:676-84.
31. Young BA, Lin E, Von Korff M, Simon G, Ciechanowski P, Ludman EJ, et al. Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. Am J Manag Care. 2008;14:15-23.
32. Zaher C, Halbert R, Dubois R, George D, Nonikov D. Smoking-related diseases: the importance of COPD. Int J Tuberc Lung Dis. 2004;8:1423-8.
33. Applied Research Program DoCCaPS NCI. Procedure Codes for SEER-Medicare Analyses Rockville, MD: National Cancer Institute; 2013. 2015.

34. Jeon CY, Pandol SJ, Wu B, Cook-Wiens G, Gottlieb RA, Merz CNB, et al. The association of statin use after cancer diagnosis with survival in pancreatic cancer patients: a SEER-medicare analysis. PLoS One. 2015;10:e0121783.
35. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2889-934.
36. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46:399-424.
37. Hosmer DW, Lemeshow S, Sturdivant RX, ebrary Inc. Applied logistic regression. Wiley series in probability and statistics. 3rd ed. Hoboken, N.J.: Wiley,; 2013. p. xvi, 500 p.
38. Sadeghi N, Abbruzzese JL, Yeung S-CJ, Hassan M, Li D. Metformin use is associated with better survival of diabetic patients with pancreatic cancer. Clin Cancer Res. 2012;18:2905-12.
39. Amin S, Mhango G, Lin J, Aronson A, Wisnivesky J, Boffetta P, et al. Metformin Improves Survival in Patients with Pancreatic Ductal Adenocarcinoma and Pre-Existing Diabetes: A Propensity Score Analysis. Am J Gastroenterol. 2016;111:1350-7.
40. Lee SH, Yoon SH, Lee HS, Chung MJ, Park JY, Park SW, et al. Can metformin change the prognosis of pancreatic cancer? Retrospective study for pancreatic cancer patients with pre-existing diabetes mellitus type 2. Dig Liver Dis. 2016;48:435-40.
41. Chaiteerakij R, Petersen GM, Bamlet WR, Chaffee KG, Zhen DB, Burch PA, et al. Metformin Use and Survival of Patients With Pancreatic Cancer: A Cautionary Lesson. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34:1898-904.
42. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. Am J Epidemiol. 2005;162:1016-23.

43. Lee HS, Lee SH, Lee HJ, Chung MJ, Park JY, Park SW, et al. Statin Use and Its Impact on Survival in Pancreatic Cancer Patients. Medicine (Baltimore). 2016;95:e3607.
44. Wong WW, Dimitroulakos J, Minden MD, Penn LZ. HMG-CoA reductase inhibitors and the malignant cell: the statin family of drugs as triggers of tumor-specific apoptosis. Leukemia. 2002;16:508-19.
45. Sala SG, Munoz U, Bartolome F, Bermejo F, Martin-Requero A. HMG-CoA reductase inhibitor simvastatin inhibits cell cycle progression at the G1/S checkpoint in immortalized lymphocytes from Alzheimer's disease patients independently of cholesterol-lowering effects. J Pharmacol Exp Ther. 2008;324:352-9.
46. Chan KK, Oza AM, Siu LL. The statins as anticancer agents. Clin Cancer Res. 2003;9:10-9.
47. Hoque A, Chen H, Xu XC. Statin induces apoptosis and cell growth arrest in prostate cancer cells. Cancer Epidemiol Biomarkers Prev. 2008;17:88-94.
48. Liu H, Liang SL, Kumar S, Weyman CM, Liu W, Zhou A. Statins induce apoptosis in ovarian cancer cells through activation of JNK and enhancement of Bim expression. Cancer Chemother Pharmacol. 2009;63:997-1005.
49. Sleijfer S, van der Gaast A, Planting AS, Stoter G, Verweij J. The potential of statins as part of anti-cancer treatment. Eur J Cancer. 2005;41:516-22.
50. Gbelcova H, Lenicek M, Zelenka J, Knejzlik Z, Dvorakova G, Zadinova M, et al. Differences in antitumor effects of various statins on human pancreatic cancer. Int J Cancer. 2008;122:1214-21.
51. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. 2005;19:117-25.
52. Huang BZ, Chang JI, Li E, Xiang AH, Wu BU. Influence of Statins and Cholesterol on Mortality Among Patients With Pancreatic Cancer. Journal of the National Cancer Institute. 2017;109.

Table 1. Distribution of demographic and clinical characteristics and comorbid conditions by metformin and/or statin use in the study population of elderly PDAC patients

Characteristics	Total (*N* = 12572)	Neither users (*N* = 4671)	Metformin alone (*N* = 950)	Statin alone (*N* = 4506)	Dual users (*N* = 2445)	*P*	Adjusted *P* [a]
Age						< 0.01	< 0.01
65-74	5137 (40.86)	1806 (38.66)	410 (43.16)[c]	1714 (38.04)[c]	1207 (49.37)[c]		
75-84	5228 (41.58)	1872 (40.08)	410 (43.16)	1964 (43.59)	982 (40.16)		
85+	2207 (17.55)	993 (21.26)	130 (13.68)	828 (18.28)	256 (10.47)		
Sex						< 0.01	0.84
Male	5268 (41.90)	1850 (39.61)	393 (41.37)	1919 (42.59)[c]	1106 (45.24)[c]		
Female	7304 (58.10)	2821 (60.39)	557 (58.63)	2587 (57.41)	1339 (54.76)		
Race						< 0.01	0.63
White	9719 (77.31)	3687 (78.93)	712 (74.95) [c]	3547 (78.72)[b]	1773 (72.52)[c]		
Black	1328 (10.56)	512 (10.96)	99 (10.42)	446 (9.90)	271 (11.08)		
Others	1525 (12.13)	472 (10.10)	139 (14.63)	513 (11.38)	401 (16.40)		
Neighborhood median income						0.04	0.99
<$35,000 OR unknown	2881 (22.92)	1038 (22.22)	242 (25.47)[b]	1003 (22.26)	598 (24.46)		
$35,000-$49,999	3416 (27.17)	1281 (27.42)	277 (29.16)	1198 (26.59)	660 (26.99)		
$50,000-74,999	3324 (26.44)	1253 (26.83)	229 (24.11)	1197 (26.56)	645 (26.38)		
$75,000+	2951 (23.47)	1099 (23.53)	202 (21.26)	1108 (24.59)	542 (22.17)		
Tumor Stage						< 0.01	NC
Localized/Regional	5076 (40.38)	1820 (38.96)	392 (41.26)	1834 (40.70)[b]	1030 (42.13)[c]		
Distant	6313 (50.21)	2360 (50.52)	475 (50.00)	2244 (49.80)	1234 (50.47)		
Unknown	1183 (9.41)	491 (10.51)	83 (8.74)	428 (9.50)	181 (7.40)		
Tumor Grade						0.09	NC
I or II	1934 (15.38)	678 (14.52)	139 (14.63)	701 (15.56)	416 (17.01)		
III or IV	1531 (12.18)	551 (11.80)	126 (13.26)	548 (12.16)	306 (12.52)		
Unknown	9107 (72.44)	3442 (73.69)	685 (72.11)	3257 (72.28)	1723 (70.47)		
Tumor Size						< 0.01	NC
< 5cm	6953 (55.31)	2500 (53.52)	518 (54.53)	2542 (56.41)[b]	1393 (56.97)[c]		
>= 5cm	2299 (18.29)	857 (18.35)	188 (19.79)	796 (17.67)	458 (18.73)		
Unknown	3320 (26.41)	1314 (28.13)	244 (25.68)	1168 (25.92)	594 (24.29)		

Resection (Yes)	860 (6.84)	312 (6.68)	74 (7.79)	301 (6.68)	173 (7.08)	0.59	NC
Chemotherapy (Yes)	1747 (13.90)	637 (13.64)	174 (18.32)[c]	602 (13.36)	334 (13.66)	< 0.01	NC
Radiation (Yes)	1235 (9.82)	457 (9.78)	129 (13.58)[c]	416 (9.23)	233 (9.53)	< 0.01	NC
Charlson Comorbidity Score						< 0.01	< 0.01
0	10347(82.30)	4107 (87.93)	629 (66.21)[c]	3807 (84.49)[c]	1804 (73.78)[c]		
1	1332 (10.59)	351 (7.51)	218 (22.95)	388 (8.61)	375 (15.34)		
2	512 (4.07)	122 (2.61)	70 (7.37)	162 (3.60)	158 (6.46)		
>=3	381 (3.03)	91 (1.95)	33 (3.47)	149 (3.31)	108 (4.42)		
Obesity (Yes)	934 (7.43)	294 (6.29)	102 (10.74)[c]	290 (6.44)	248 (10.14)[c]	< 0.01	0.81
Chronic Pancreatitis (Yes)	509 (4.05)	180 (3.85)	58 (6.11)[c]	179 (3.97)	92 (3.76)	< 0.01	0.07
COPD (Yes)	2156 (17.15)	853 (18.26)	203 (21.37)[b]	756 (16.78)	344 (14.07)[c]	< 0.01	NC
Dyslipidemia (Yes)	4492 (35.73)	1442 (30.87)	372 (39.16)[c]	1781 (39.53)[c]	897 (36.69)[c]	< 0.01	< 0.01
Diabetes/IGT (Yes)	3579 (28.47)	999 (21.39)	471 (49.58)[c]	1143 (25.37)[c]	966 (39.51)[c]	< 0.01	< 0.01
Diabetic Comorbidity Severity Index (patients with diabetes/IGT)						< 0.01	NC
0	341 (9.53)	98 (9.81)	62 (13.16)	85 (7.44)[c]	96 (9.94)		
1	243 (6.79)	79 (7.91)	33 (7.01)	49 (4.29)	82 (8.49)		
2	488 (13.64)	150 (15.02)	69 (14.65)	131 (11.46)	138 (14.29)		
>=3	2507 (70.05)	672 (62.27)	307 (65.18)	878 (76.82)	650 (67.29)		

Abbreviations: COPD, chronic obstructive pulmonary disease; IGT, Impaired Glucose Tolerance; NC, not calculated.

[a] Reflects differences between groups after adjusting for propensity score for metformin, statin and dual users.

[b] Reflects $P < 0.05$, compared with neither users.

[c] Reflects $P < 0.01$, compared with neither users.

Table 2. Relative hazard ratios of death among elderly PDAC patients for metformin and/or statin users vs. neither users (N = 12572)

Category	Conventional Cox Model		Time-Varying Cox Model	
	Unadjusted HR (95% CI)	**Adjusted HR (95% CI)** [a]	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)** [a]
Neither users	Referent	Referent	Referent	Referent
Metformin users	0.93 (0.87-1.00)	0.91 (0.85-0.98)	1.05 (0.98-1.13)	1.01 (0.94-1.09)
Statin users	0.93 (0.89-0.97)	0.91 (0.88-0.95)	0.95 (0.91-0.99)	0.94 (0.90-0.98)
Dual users	0.87 (0.83-0.92)	0.90 (0.86-0.95)	0.98 (0.93-1.03)	1.00 (0.95-1.05)

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a] Adjusted for tumor characteristics: stage, grade, tumor size, treatment: resection, radiation, chemotherapy, propensity scores, and imbalanced variables after propensity scores adjustment.

Table 3. Relative hazard of death for metformin use *vs.* non-metformin or statin use *vs.* non-statin use in a separate analysis for pre- and post-diagnosis users using time-dependent covariate Cox regression analysis

Characteristics	No. of Users/Non-Users	Adjusted HR (95% CI)	*P*
Metformin use			
Pre-diagnosis users	3110/9177	1.02 (0.97-1.06) [a]	0.52
Post-diagnosis users	285/9177	0.99 (0.87-1.13) [a]	0.88
Statin use			
Pre-diagnosis users	6833/5621	0.94 (0.91-0.98) [b]	< 0.01
Post-diagnosis users	118/5621	0.69 (0.56-0.86) [b]	< 0.01

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a] Adjusted for tumor characteristics: stage, grade, tumor size, treatment: resection, radiation, chemotherapy, propensity score for metformin use, and statin use (time-dependent variable).

[b] Adjusted for tumor characteristics: stage, grade, tumor size, treatment: resection, radiation, chemotherapy, propensity score for statin use, and metformin use (time-dependent variable).

Table 4. Multivariable association of survival with metformin use (timing initiation and intensity) or statin use (timing initiation, name, type, potency and intensity) among pre-diagnosis users

Characteristics	No. of Users vs. Non-users	Adjusted HR (95% CI)	*P*
Timing of metformin initiation			
≤ 6 months before diagnosis	497/9177	1.06 (0.96-1.16) [b]	0.27
> 6 months before diagnosis	2613/9177	1.04 (0.99-1.09) [b]	0.17
Metformin intensity			
< 1000 mg/day	700/9177	1.00 (0.92-1.08) [b]	0.93
1000-1500 mg/day	1297/9177	1.10 (1.03-1.17) [b]	< 0.01
> 1500 mg/day	1113/9177	1.00 (0.94-1.07) [b]	0.97
Timing of statin initiation			
≤ 6 months before diagnosis	411/5621	0.96 (0.87-1.07) [c]	0.47
> 6 months before diagnosis	6422/5621	0.95 (0.91-0.98) [c]	< 0.01
Statin name [a]			
Atorvastatin	2127/5621	0.97 (0.92-1.02) [c]	0.22
Fluvastatin	85/5621	1.26 (1.00-1.59) [c]	0.05
Lovastatin	1490/5621	0.98 (0.92-1.04) [c]	0.46
Pravastatin	732/5621	0.93 (0.86-1.01) [c]	0.07
Rosuvastatin	561/5621	0.88 (0.81-0.96) [c]	< 0.01
Simvastatin	3794/5621	0.98 (0.94-1.02) [c]	0.30
Statin type [a]			
Lipophilic	6184/5621	0.96 (0.92-1.00) [c]	0.05
Hydrophilic	1236/5621	0.91 (0.86-0.97) [c]	< 0.01
Statin potency [a]			
Low	2230/5621	0.98 (0.93-1.03) [c]	0.41
High	5544/5621	0.95 (0.91-0.99) [c]	< 0.01
Statin intensity			
Low	1817/5621	0.92 (0.87-0.98) [c]	< 0.01
Moderate	2633/5621	0.95 (0.90-1.00) [c]	0.04
High	2383/5621	0.96 (0.92-1.01) [c]	0.15

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a] Categories are not mutually exclusive for these variables.

[b] Adjusted for tumor characteristics: stage, grade, tumor size, treatment: resection, radiation, chemotherapy, propensity score for metformin use, and statin use (time-dependent variable).

[c] Adjusted for tumor characteristics: stage, grade, tumor size, treatment: resection, radiation, chemotherapy, propensity score for statin use, and metformin use (time-dependent variable).

FIGURE LEGENDS:

Figure 1. Selection of patients diagnosed with primary PDAC in 2008-2011. SEER, Surveillance, Epidemiology, and End Results; PDAC, pancreatic ductal adenocarcinoma.

Figure 2. Kaplan-Meier curves showing elderly PDAC patient survival for pre- and post-diagnosis statin users *versus* non-statin users.