Gut and Liver
https://doi.org/10.5009/gnl20297
pISSN 1976-2283 eISSN 2005-1212

Original Article

Bisphosphonate Use Does Not Impact Survival in Patients with Pancreatic Cancer: A Propensity Score Matching Analysis

Haley M. Zylberberg[1], Sheila D. Rustgi[1,2], Anthony Yang[2], Anne Aronson[2], Elizabeth Kessel[2], Sunil Amin[3], and Aimee L. Lucas[1,2]

[1]Department of Internal Medicine and [2]Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, and [3]Division of Gastroenterology, University of Miami Leonard Miller School of Medicine, Miami, FL, USA

Article Info
Received September 29, 2020
Revised March 8, 2021
Accepted April 1, 2021
Published online June 25, 2021

Corresponding Author
Aimee L. Lucas
ORCID https://orcid.org/0000-0003-0341-4826
E-mail aimee.lucas@mssm.edu

Background/Aims: Bisphosphonates are increasingly recognized for their anti-neoplastic properties, which are the result of their action on the mevalonate pathway. Our primary aim was to investigate the association between bisphosphonate use and survival in patients with pancreatic cancer. Since statins also act on the mevalonate pathway, we also investigated the effect of the combined use of bisphosphonates and statins on survival.

Methods: The Surveillance, Epidemiology, and End Results registry (SEER)-Medicare linked database was used to identify patients with pancreatic ductal adenocarcinoma (PDAC) between 2007 and 2015. Kaplan-Meier models were used to examine the association between survival with bisphosphonate use alone and in combination with statins within 1 year prior to the diagnosis of PDAC. Propensity score matching analysis and Cox-proportional hazard models were used to determine the association between overall survival with bisphosphonate use alone and combined with statins, after adjusting for relevant confounders, such as the Charlson comorbidity index score, stage, treatment, sociodemographic characteristics, and propensity score.

Results: In total, 13,639 patients with PDAC were identified, and 1,203 (8.82%) used bisphosphonates. There was no difference in the mean survival duration between bisphosphonate users (7.27 months) and nonusers (7.25 months, p=0.61). After adjustment for confounders, bisphosphonate use was still not associated with improved survival (hazard ratio, 1.00; 95% confidence interval, 0.93 to 1.08; p=0.96). Combined bisphosphonate and statin use was also not associated with improved survival (hazard ratio, 0.97; 95% confidence interval, 0.87 to 1.07; p=0.48) after adjustment for confounders.

Conclusions: Our findings suggest that the use of bisphosphonates, whether alone or in combination with statins, does not confer a survival advantage in patients with PDAC. **(Gut Liver 2021;15:782-790)**

Key Words: Pancreas; Survival; Bisphosphonate; Statin

INTRODUCTION

Pancreatic cancer is the 4th leading causing of cancer mortality in the United States, with a bleak 5-year survival of 8%.[1,2] The mortality from pancreatic cancer is high since most patients have advanced unresectable disease at the time of initial diagnosis.[2] Given poor outcomes, there has been increased focus on determining if common pharmaceutical agents may play a role in pancreatic cancer prevention and survival.[3]

Bisphosphonates are a class of medications that promote bone integrity. Traditionally, bisphosphonates have been used to treat osteoporosis; however, they are now recognized as having wide reaching anti-neoplastic properties. Preclinical trials have shown that bisphosphonates inhibit cancer cell growth, invasion, and migration, and induce cancer cell apoptosis in a wide range of cancers.[4-7] Observational studies have shown that bisphosphonate use reduces the risk of acquiring breast and colorectal cancer,[8,9] and clinical trials in breast cancer patients have shown a

role of bisphosphonates as adjuvant therapy.[10,11] Only two observational studies have investigated the relationship between bisphosphonates use and risk of pancreatic cancer, with heterogenous results.[12,13] Currently, there have been no studies assessing if bisphosphonate use in patients with pancreatic cancer impacts survival.

One proposed mechanism is that bisphosphonates inhibit the activity of farnesyl diphosphate synthase, an enzyme in the mevalonate pathway, which subsequently blocks the downstream signaling of the small G proteins Ras and Rho that are necessary for tumorigenesis,[4,14] and are commonly associated with pancreatic tumors.[15] Another group of medications, statins, also act on this pathway by inhibiting hydroxy-3-methyl-glutaryl-coenzyme A reductase, preventing the synthesis of mevalonic acid, which is upstream to Ras and Rho.[16] A recent meta-analysis of five studies found that statin use prior to pancreatic cancer diagnosis and continued use after diagnosis leads to improved survival when compared to nonusers.[17] As statins and bisphosphonates both operate on the mevalonate pathway, the two medications may act synergistically to prevent tumorigenesis. *In vitro* studies of human pancreatic cancer cell lines have shown anti-proliferative effects when bisphosphonate and statins were combined.[18,19] Additionally, a 2017 observational study found an improvement in cancer survival in patients who used both bisphosphonates and statins, though this study was not powered to assess the effect in the subgroup of patients with pancreatic cancer.[20]

Thus, our study used a large national cancer database in order to investigate whether bisphosphonate use improves survival among patients with pancreatic cancer. As a secondary aim, we also investigated whether bisphosphonate use combined with statin use impacts survival in pancreatic cancer.

MATERIALS AND METHODS

1. Data acquisition

Data was acquired from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked registry. The SEER and Medicare linkage combines two large population-based sources of data that includes information about patients with cancer who are covered by Medicare health insurance. The SEER registry consists of patient information pertaining specifically to cancer diagnosis, treatment and survival from across the United States. Claims from Medicare consist of data from patients aged 65 years and older who have health insurance through Medicare, and includes data regarding inpatient and outpatient services, (Part A and Part B) as well as prescription drug coverages (Part D).

2. Patient population and medication usage

We identified patients in the SEER-Medicare linkage who were aged 65 years and older and who were diagnosed with pancreatic ductal adenocarcinoma (PDAC) between 2007 and 2015 and who had claims data through 2017 (Fig. 1). Our sample was limited to this time range since Medicare Part D coverage was only available starting from 2007. We next limited our sample to patients with only one primary cancer so as to prevent any possible confounding effect of having additional lesions. Only patients with PDAC confirmed by histology were included to ensure accuracy of diagnosis. Adenocarcinoma specific histology codes used included 8000, 8010, 8140, 8500, 8550, and 8560 as specified by the International Classification of Diseases for Oncology, 2nd edition (ICD-O-2). Patients with diagnosed PDAC at time of death or on autopsy were excluded in order to determine the effect of treatment on survival.

In order to ensure all Medicare claims data were captured, we eliminated patients with missing claims data. We excluded patients without Medicare Part A and B and those who were enrolled in health maintenance organization from the period of 1 year prior to pancreatic cancer diagnosis through time of death or end of available data (12/2017). We then limited our sample to patients who were covered by Medicare Part D, which we defined as at least 1 month of Part D coverage within 12 months prior to the diagnosis of pancreatic cancer. This study was approved by the Icahn School of Medicine at Mount Sinai's Institutional Review Board (IRB number: 19-02095) and by SEER-Medicare. Written informed consent was waived.

3. Sociodemographic and clinical variables

The SEER-Medicare linkage was used to obtain sociodemographic characteristics and clinical data. Sociodemographic data included age at time of cancer diagnosis, sex, marital status, race, and income. Income was identified by linking patients' zip code to census data which specified average income per household, and then dividing the variable into four quartiles. Clinical data included American Joint Committee on Cancer (AJCC) staging 6th edition, cancer-directed surgery, radiation therapy, chemotherapy, tumor differentiation, lymph nodes with metastatic disease, the comorbid conditions used in the Charlson comorbidity index,[21] and presence of osteoporosis and diabetes mellitus. Patients were considered to have a comorbid medical condition of osteoporosis or diabetes if there were at least two claims among inpatient and outpatient claims data 1 year prior to pancreatic cancer diagnosis (ICD 9 & 10 codes

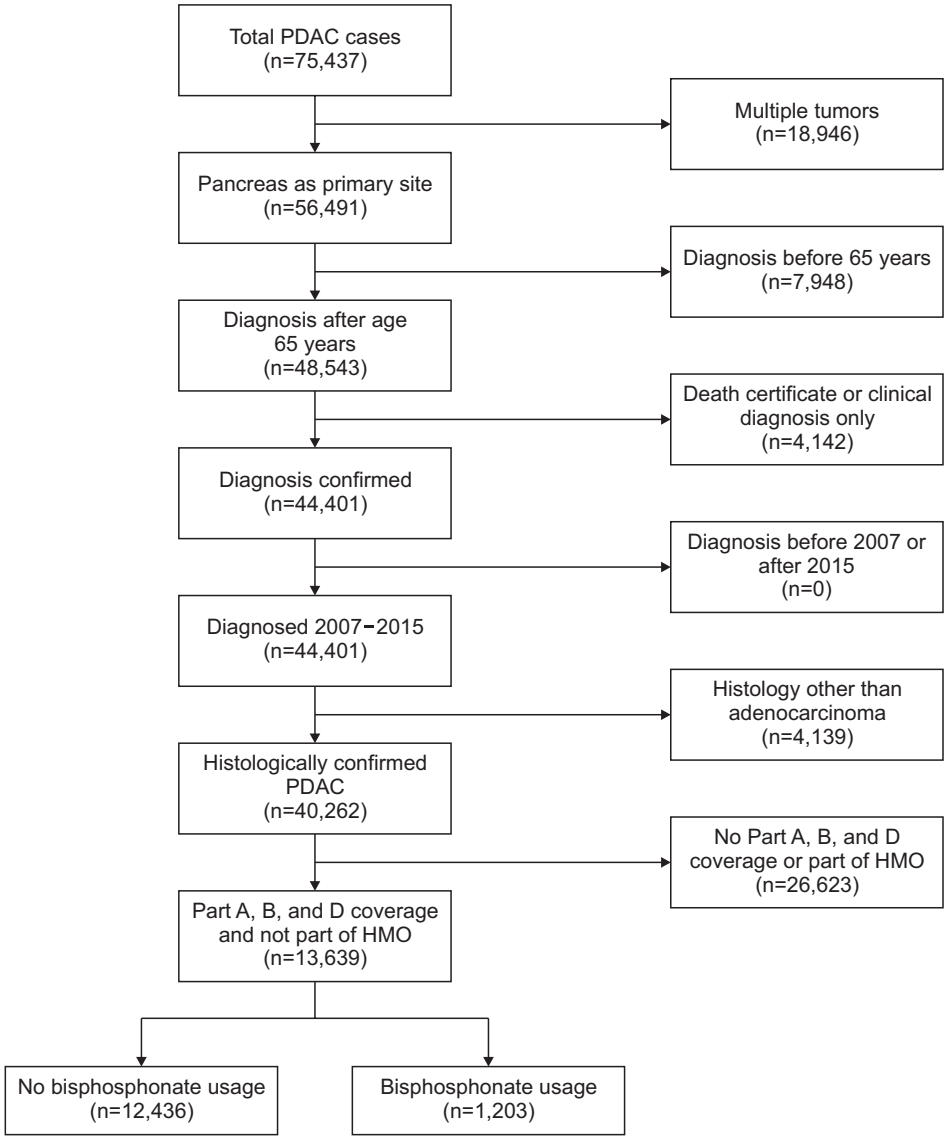

Fig. 1. Cohort selection.
PDAC, pancreatic ductal adenocarcinoma; HMO, health maintenance organization.

for osteoporosis 733.0X, M80.XX, M81.XX; for diabetes 250.XX, E09.X, E11.XX, E13.XX), as has been previously described.[22] Medicare Part D claims were used to identify medications used in the year prior to pancreatic cancer diagnosis. Medication use was based on at least one instance of medication dispensed during the 1-year time period. A sensitivity analysis was performed where bisphosphonate use was defined as a 90-day supply of a bisphosphonate or two instances of medication prescriptions filled at least 1 month apart. Medications identified included bisphosphonates such as alendronate, etidronate, ibandronate, and risedronate and statins such as atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

4. Outcomes

The primary outcome of interest was overall survival in bisphosphonate users compared to nonusers. Survival time was defined as the time from the diagnosis of pancreatic cancer to death or end of the dataset. The study end date was set to December 2017. The secondary outcome of interest was overall survival in patients who used a combination of bisphosphonate and statin compared to patients who used neither.

5. Statistical analysis

Sociodemographic characteristics were compared using the chi-square test and the Student t-test. Kaplan-Meier models were used to examine the association between survival and bisphosphonate use and combined bisphosphonate and statin use within 1 year prior to pancreatic cancer diagnosis. We used a propensity score weighted analysis to adjust for potential confounding factors that may predispose to bisphosphonate use and combined bisphosphonate

and statin use. The propensity score was calculated by using a logistic regression model that included sex, age, marital status, race, income and Charlson comorbidity score. Cox-proportional hazard models were used to determine the association between overall survival and bisphosphonate use and combined bisphosphonate and statin use, respectively. The Cox-proportional hazard models were adjusted for propensity score, cancer stage, cancer-directed surgery, radiation therapy, and chemotherapy, and an additional model was performed which included tumor differentiation and number of lymph nodes with metastases. Kaplan-Meier models and Cox-proportional hazard models with propensity score weighting were also used to assess for survival in subgroups of patients, such as those with osteoporosis and diabetes who used bisphosphonates. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 13,639 PDAC patients were identified from 2007 to 2015 (Table 1). Of these, 1,203 patients (8.82%) used bisphosphonates in the period 1 year prior to pancreatic cancer diagnosis. Patients who used bisphosphonates had a higher mean age, and were more likely to be female and less likely to be married (p<0.01). Bisphosphonate users were also more likely to have a diagnosis of osteoporosis and have lower Charlson comorbidity scores (p<0.01). After propensity weighting for the likelihood of a patient receiving a bisphosphonate, there were no significant differences in patient demographics.

Cancer-related characteristics are specified in Table 2. There was no significant difference in AJCC stage between those who used bisphosphonates and those who did not (p=0.30). There was also no significant difference in cancer-directed surgery, and radiation between both groups (p>0.05), though bisphosphonate users showed a trend towards less chemotherapy use (bisphosphonate users 40.57% vs 43.51%, p=0.05).

Table 3 shows mean overall survival by cancer characteristics. Patients using bisphosphonates had no difference in mean survival time; users survived 7.27 months compared to nonusers who survived 7.25 months (p=0.61) (Fig. 2). The lack of survival difference remained when stratified by AJCC stage, cancer-directed surgery, radiation, and chemotherapy (p>0.05). After adjustment for confounders, such as propensity score, AJCC stage, cancer-directed

Table 1. Patient Demographics

Variable	Patients not receiving bisphosphonate	Patients receiving bisphosphonate	p-value	Adjusted p-value*
No.	12,436 (91.18)	1,203 (8.82)		
Age, yr	77.61±7.70	78.90±7.40	<0.001	0.96
Sex			<0.001	0.84
Male	5,304 (42.65)	122 (10.14)		
Female	7,132 (57.35)	1,081 (89.96)		
Marital status at diagnosis			<0.001	0.95
Not married	6,187 (51.96)	733 (62.60)		
Married	5,720 (48.04)	438 (37.40)		
Race			<0.001	0.23
White	10,314 (82.94)	933 (77.56)		
Black	1,249 (10.04)	76 (6.32)		
Other	873 (7.02)	194 (16.13)		
Charlson comorbidity score			0.002	0.72
0	4,091 (39.90)	430 (41.83)		
1	2,670 (26.04)	303 (29.47)		
2	1,443 (14.07)	135 (13.13)		
≥3	2,049 (19.98)	160 (15.56)		
Income quartile			0.34	0.97
0–25th	2,939 (24.12)	264 (22.39)		
26–50th	3,007 (24.68)	280 (23.75)		
51–75th	3,069 (25.19)	307 (26.04)		
76–100th	3,169 (26.01)	328 (27.82)		
Osteoporosis	247 (1.99)	90 (33.7)	<0.001	

Data are presented as number (%) or mean±SD.
*Adjusted p-value reflects the p-value after adjusting for the propensity score, which included age, sex, ethnicity, Charlson comorbidity index score, and income quartile.

Table 2. Pancreatic Cancer and Treatment Characteristics

Treatment characteristics	Patients not receiving bisphosphonate	Patients receiving bisphosphonate	p-value
Stage			0.30
I	985 (9.12)	94 (9.18)	
II	2,768 (25.63)	279 (27.25)	
III	960 (8.89)	103 (10.06)	
IV	6,085 (56.35)	548 (53.52)	
Cancer-directed surgery			0.93
No	10,823 (87.03)	1,048 (87.12)	
Yes	1,613 (12.97)	155 (17.87)	
Radiation			0.90
No	10,196 (81.99)	988 (82.13)	
Yes	2,240 (18.01)	215 (17.87)	
Chemotherapy			0.05
No	7,025 (56.49)	715 (59.43)	
Yes	5,411 (43.51)	488 (40.57)	

Data are presented as number (%).

Table 3. Mean Overall Survival Stratified by Cancer Characteristics

Variable	Survival time, mo		Log-rank p-value
	No bisphosphonate	Bisphosphonate	
Overall	7.25±11.50	7.27±11.74	0.61
Stage			
I	11.71±16.75	12.90±18.74	0.91
II	13.29±14.90	12.98±15.60	0.22
III	9.36±9.85	7.90±7.88	0.15
IV	3.83±6.17	3.92±6.97	1.00
Surgery			
No	5.18±7.96	5.26±8.50	0.98
Yes	21.08±19.16	20.85±12.29	0.23
Radiation			
No	5.73±9.99	6.01±11.12	0.78
Yes	14.16±14.69	13.05±12.77	0.14
Chemotherapy			
No	3.48±8.42	3.80±8.96	0.14
Yes	12.13±12.93	12.34±13.39	0.76

Data are presented as mean±SD.

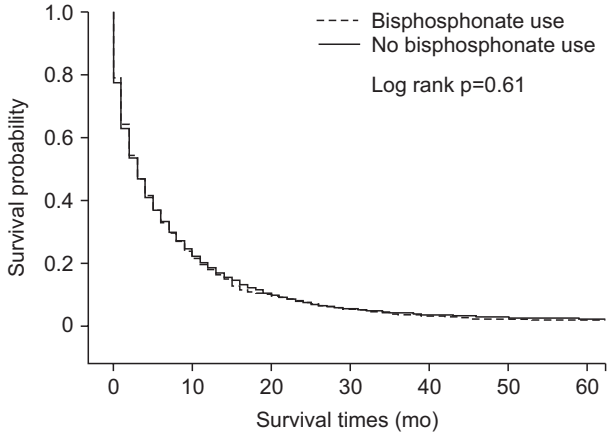

Fig. 2. Kaplan-Meier curve comparing survival between pancreatic cancer patients using and not using bisphosphonates.

Table 4. Propensity Score-Adjusted Cox-Proportional Hazards Model for Bisphosphonates

Variable	Hazard ratio (95% CI)	p-value
Bisphosphonate	1.00 (0.93–1.08)	0.96
Stage		
I	Reference	
II	1.39 (1.28–1.52)	<0.001
III	1.49 (1.35–1.65)	<0.001
IV	2.44 (2.25–2.64)	<0.001
Surgery	0.44 (0.40–0.48)	<0.001
Radiation	0.80 (0.75–0.85)	<0.001
Chemotherapy	0.39 (0.37–0.41)	<0.001

CI, confidence interval.

surgery, radiation and chemotherapy, bisphosphonate use was still not associated with improved survival (hazard ratio [HR], 1.00; 95% confidence interval [CI], 0.93 to 1.08;

p=0.96) (Table 4). Advanced AJCC stage cancer was associated with worse survival (p<0.01 for stages II/III/IV). Cancer treatments were associated with better survival; cancer-directed surgery (HR, 0.44; 95% CI, 0.40 to 0.48; p<0.001), radiation therapy (HR, 0.80; 95% CI, 0.75 to 0.85; p<0.001) and chemotherapy (HR, 0.39; 95% CI, 0.37 to 0.41; p<0.001). When tumor differentiation category and number of lymph nodes containing metastatic disease were included in the Cox-proportional hazard model, our sample was limited to 983 patients, and there was still no association between bisphosphonates and survival (Supplementary Table 1). Both increasing grade and number of lymph nodes with metastatic disease were associated with worse survival (p<0.05).

When stratified by type of bisphosphate in Table 5, the lack of association with survival persisted (p>0.05 for all). When stratified by presence of osteoporosis (n=337), patients without osteoporosis had an increased mean survival (7.32 months) compared to those with osteoporosis (4.38 months, p<0.001). However, this was no longer significant on Cox-proportional hazard model analysis after adjustment for confounders and propensity score (HR, 1.05; 95% CI, 0.92 to 1.20). When survival was assessed in bisphosphonate users compared to nonusers limited to those with osteoporosis, there was no difference in survival (p=0.12). However, after adjustment for confounders on Cox-proportional hazard model analysis, use of bisphosphonates in patients with osteoporosis showed improved survival (HR, 0.67; 95% CI, 0.49 to 0.91).

When stratified by diabetes, there was no difference in survival in bisphosphonate users compared to nonusers among patients with diabetes (n=1,266; 5.26 months, standard deviation [SD] 9.25 vs 4.24 months, SD 8.31; p=0.50) or without diabetes (n=12,373; 7.44 months, SD 9.25 vs 7.56 months, SD 11.69; p=0.36). No survival advantage of bisphosphonates was seen on multivariate analysis among patients with diabetes (HR, 0.86; 95% CI, 0.94 to 1.01) or without diabetes (HR, 1.02; 95% CI, 0.94 to 1.01).

A sensitivity analysis was performed with a more stringent criterion for bisphosphonate use (either a 90-day supply or two filled prescriptions at least 1 month apart). Eight hundred and ninety-three patients (6.55%) who used bisphosphonates were identified, with the remaining 12,746 identified as controls. There was still no difference in the mean survival on univariate analysis with bisphosphonate users having a mean survival of 7.42 months (SD 11.85) and nonusers having a mean survival of 7.23 months (SD 11.45, p=0.83). When adjusted for confounders, bisphosphonate use was also not associated with improved survival (HR, 1.03; 95% CI, 0.95 to 1.12; p=0.49).

A secondary analysis was performed to evaluate survival in patients who used a combination of a bisphosphonate and a statin (n=647, 9.03%) compared to those who used neither medication (n=6,519, 90.97%). On univariate analysis, combined bisphosphonate and statin use showed a trend for prolonged survival; survival in combination users was 7.84 months compared to 7.04 months in nonusers (p=0.08). When adjusted for confounders using Cox-proportional hazard modeling, combined bisphosphonate and statin use was not associated with improved survival (HR, 0.96; 95% CI, 0.87 to 1.06; p=0.46).

DISCUSSION

In our study of a large registry of U.S. patients with pancreatic cancer, we found that bisphosphonate use prior to pancreatic cancer diagnosis did not impact pancreatic cancer survival. This held true when adjusting for confounders and when stratifying by type of bisphosphate.

In theory, bisphosphonates have a mechanism that makes it a prime agent to combat pancreatic cancer. Bisphosphonates inhibit an enzyme in the mevalonate pathway, which interferes with the downstream signaling of the G proteins Ras, a group of proteins involved in mediating cell proliferation and survival.[4,14] Dysregulated Ras

Table 5. Mean Survival Stratified by Use of Bisphosphonates and the Presence of Osteoporosis

Variable	No. of patients (%)	Survival time, mo		Log-rank p-value
		No	Yes	
Bisphosphonate use	1,203 (100)	7.24±11.45	7.27±11.74	0.61
Alendronate use	859 (6.30)	7.26±11.55	7.09±11.77	0.40
Etidronate use	*			
Ibandronate use	161 (1.18)	7.24±11.49	7.11±10.69	0.75
Risedronate use	249 (1.83)	7.20±11.48	7.98±11.69	0.45
Presence of osteoporosis	337 (2.47)	7.32±11.54	4.38±8.29	<0.001
Bisphosphonate use limited to those with osteoporosis	90 (26.71)	4.13±8.61	5.08±7.34	0.12

Data are presented as mean±SD.
*Data not reported for values <11 per Surveillance, Epidemiology, and End Results (SEER) guidelines.

proteins may therefore lead to tumorigenesis.[4] Mutations in the KRAS gene, which encode the Ras protein family, are the most common genetic abnormality in pancreatic tumors.[15] Since bisphosphonates block the activation of the Ras protein, it is conceivable that the medication may prevent pancreatic cancer cell growth. A study performed in *in vitro* pancreatic cancer cells showed that bisphosphonates promote growth reduction and apoptosis, in part through a reduction in Ras.[7] Other studies of pancreatic cancer in *in vivo* models have also shown that bisphosphonates prevent cancer dissemination and inhibit tumor educated macrophages.[23,24]

To date, the literature is mostly comprised of epidemiological studies assessing the incidence of pancreatic cancer in those who use bisphosphonates.[12,13] The first, a 2012 case-control study of 41,826 cancer patients in the United Kingdom, found no difference in risk of pancreatic cancer in 62 bisphosphonate users compared to 60 controls (adjusted HR, 0.84; 95% CI, 0.53 to 1.35; p=0.048).[12] The second, a 2013 nested case-control study of 180,000 cancer patients in the United Kingdom, reported a reduced risk of pancreatic cancer in 374 patients who used bisphosphonates compared to 1,084 controls when two U.K. databases were combined (pooled odds ratio, 0.79; 95% CI, 0.68 to 0.93; p=0.003).[13] As these studies show conflicting results,[12,13] additional studies are needed to determine if bisphosphonate use prevents pancreatic cancer.

Our study is especially unique as it is the first to assess whether bisphosphonate use impacts pancreatic cancer survival and failed to show a survival benefit. It is possible that the lack of effect could be due to the high affinity of bisphosphonates for bone mineral and rapid clearance from the bloodstream.[25] Bisphosphonates may not penetrate the pancreas and so may not be able to exert their effect on the Ras system *in vivo*. Alternatively, bisphosphonates may exert its positive impact by promoting bone integrity in hormone dependent disease, which could be why it has been shown to be impactful in patients with breast cancer and prostate cancer.[25] Since pancreatic cancer rarely metastasizes to the bone and has not been linked to hormone imbalances,[26,27] bisphosphonates may have less of an effect. Unfortunately, we were unable to determine the effect of bisphosphonate use among patients with pancreatic cancer who had bone metastases in our dataset given the unreliability of this in SEER.

The secondary aim of our study was to assess survival in patients who used a combination of a bisphosphonate and statin. This was investigated as statins also work on the mevalonate pathway and have shown to improve survival in *in vitro*, observational, and analysis of clinical trial data in patients pancreatic cancer.[17,28,29] In our study, while we found a trend for prolonged survival with combined use on univariate analysis (p=0.08), on multivariate analysis there was no survival advantage. It is possible therefore that bisphosphonates do not augment the effect of statins despite both acting on the mevalonate pathway, or the beneficial effects seen in statins may be confounded by concomitant use of aspirin or metformin or by the effect of statin use in preventing venous thromboembolisms in patients with pancreatic cancer.[30]

Only one other study has looked at combined bisphosphonate and statin use and was performed in 2017 by El-Refai *et al.*[20] in cancer patients of all types. They found an increased survival among 4,090 cancer patients who used combined therapy compared with 12,165 patients who were nonusers (HR, 0.60; 95% CI, 0.45 to 0.81). Although this study included patients with pancreatic cancer, analysis of survival specifically in pancreatic cancer was not performed given the small sample size.[20] It is therefore possible that a survival benefit of combined medication use may be limited to other cancers. Our findings may also differ to due duration of medication use. While El-Refai *et al.*[20] included patients who used the medications for 90 days in the 6-month period before diagnosis, we included at least one instance of medication use over a 1 year period. However, when we performed a sensitivity analysis of bisphosphonates alone using the stricter criteria of a 90-day supply or two filled prescriptions at least 1 month apart, bisphosphonate use did not show an improved survival.

Our study has several limitations and strengths. Since the data were based on claims, patients purchased their medications, but it is impossible to know if patients were adherent. We were also unable to control for other prognostic factors such as smoking status, carbohydrate antigen 19-9, margin negative pancreatic resection, or presence of bone metastases which are not available or are unreliable in the registry and which may have biased our cohort. Although we did include statin use in our analysis, we did not include other medications, such as metformin, which may confer a survival benefit.[22] Since the SEER-Medicare registry is compiled based on health care professional reporting and coding, there may be errors related to the quality of reporting. To that effect, in our sample many more patients used bisphosphonates (n=1,203) than had osteoporosis (n=337). While this may reflect under-reporting of osteoporosis, it may instead suggest that bisphosphonates are prescribed for cancer specific indications such as bony metastases or hypercalcemia, which in turn may impact survival. Finally, while the strength of our study lies in our use of a large U.S. registry, the management of pancreatic cancer may vary widely across the United States and may impact survival. Strengths of our study include use of a

large national cancer registry and our ability to control for cancer-directed therapies and comorbid conditions. Additionally, to our knowledge this is the first study to assess whether bisphosphonate use impacts survival in pancreatic cancer.

In conclusion, our study found no significant difference in survival among patients with pancreatic cancer who used bisphosphonates or combined bisphosphonates and statins and those who did not. Future prospective studies should continue to investigate the role of bisphosphonates in pancreatic cancer.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

A.L.L. receives support from an American Cancer Society Mentored Research Scholar Award.

AUTHOR CONTRIBUTIONS

Guarantor of the article: A.L.L. Study concept and design: H.M.Z., A.Y., S.D.R., A.L.L. Acquisition of data: H.M.Z., A.A., E.K., A.L.L. Analysis and interpretation of data: H.M.Z., S.D.R., S.A., A.L.L. Drafting of the manuscript: H.M.Z., A.L.L. Critical revision of the manuscript for important intellectual content: H.M.Z., A.Y., S.D.R., A.A., E.K., A.L.L. Statistical analysis: H.M.Z., A.L.L. Study supervision: A.L.L. All authors approved the final manuscript submitted and they authorship list.

ORCID

Haley M. Zylberberg https://orcid.org/0000-0002-4198-542X
Sheila D. Rustgi https://orcid.org/0000-0002-1889-1652
Anthony Yang https://orcid.org/0000-0002-5415-297X
Anne Aronson https://orcid.org/0000-0001-9114-2239
Elizabeth Kessel https://orcid.org/0000-0002-8484-0706
Sunil Amin https://orcid.org/0000-0002-3067-4730
Aimee L. Lucas https://orcid.org/0000-0003-0341-4826

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
2. Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet 2011;378:607-620.
3. Amin S, Boffetta P, Lucas AL. The role of common pharmaceutical agents on the prevention and treatment of pancreatic cancer. Gut Liver 2016;10:665-671.
4. Gnant M, Clézardin P. Direct and indirect anticancer activity of bisphosphonates: a brief review of published literature. Cancer Treat Rev 2012;38:407-415.
5. Asahi H, Mizokami A, Miwa S, Keller ET, Koshida K, Namiki M. Bisphosphonate induces apoptosis and inhibits pro-osteoclastic gene expression in prostate cancer cells. Int J Urol 2006;13:593-600.
6. Daubiné F, Le Gall C, Gasser J, Green J, Clézardin P. Antitumor effects of clinical dosing regimens of bisphosphonates in experimental breast cancer bone metastasis. J Natl Cancer Inst 2007;99:322-330.
7. Tassone P, Tagliaferri P, Viscomi C, et al. Zoledronic acid induces antiproliferative and apoptotic effects in human pancreatic cancer cells in vitro. Br J Cancer 2003;88:1971-1978.
8. Singh S, Singh AG, Murad MH, Limburg PJ. Bisphosphonates are associated with reduced risk of colorectal cancer: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2013;11:232-239.
9. Ou YJ, Chiu HF, Wong YH, Yang CC, Yang YH. Bisphosphonate use and the risk of breast cancer: a meta-analysis of observational studies. Pharmacoepidemiol Drug Saf 2017;26:1286-1295.
10. Powles T, Paterson A, McCloskey E, et al. Reduction in bone relapse and improved survival with oral clodronate for adjuvant treatment of operable breast cancer [ISRCTN83688026]. Breast Cancer Res 2006;8:R13.
11. Gnant M, Mlineritsch B, Luschin-Ebengreuth G, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy. Lancet Oncol 2008;9:840-849.
12. Cardwell CR, Abnet CC, Veal P, Hughes CM, Cantwell MM, Murray LJ. Exposure to oral bisphosphonates and risk of cancer. Int J Cancer 2012;131:E717-E725.
13. Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to bisphosphonates and risk of common non-gastrointestinal cancers: series of nested case-control studies using two primary-care databases. Br J Cancer 2013;109:795-806.
14. Thurnher M, Nussbaumer O, Gruenbacher G. Novel aspects of mevalonate pathway inhibitors as antitumor agents. Clin Cancer Res 2012;18:3524-3531.
15. Biankin AV, Waddell N, Kassahn KS, et al. Pancreatic cancer

genomes reveal aberrations in axon guidance pathway genes. Nature 2012;491:399-405.
16. Vallianou NG, Kostantinou A, Kougias M, Kazazis C. Statins and cancer. Anticancer Agents Med Chem 2014;14:706-712.
17. Wang D, Rodriguez EA, Barkin JS, Donath EM, Pakravan AS. Statin use shows increased overall survival in patients diagnosed with pancreatic cancer: a meta-analysis. Pancreas 2019;48:e22-e23.
18. Elsayed M, Kobayashi D, Kubota T, et al. Synergistic antiproliferative effects of zoledronic acid and fluvastatin on human pancreatic cancer cell lines: an in vitro study. Biol Pharm Bull 2016;39:1238-1246.
19. Kawashiri T, Tokunaga A, Kobayashi D, Shimazoe T. Antitumor activities of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and bisphosphonates in pancreatic cell lines which show poor responses to gemcitabine. Biol Pharm Bull 2020;43:49-52.
20. El-Refai SM, Brown JD, Arnold SM, Black EP, Leggas M, Talbert JC. Epidemiologic analysis along the mevalonate pathway reveals improved cancer survival in patients who receive statins alone and in combination with bisphosphonates. JCO Clin Cancer Inform 2017;1:1-12.
21. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-619.
22. Amin S, Mhango G, Lin J, et al. Metformin improves survival in patients with pancreatic ductal adenocarcinoma and pre-existing diabetes: a propensity score analysis. Am J Gastroenterol 2016;111:1350-1357.
23. Takiguchi S, Nishino Y, Inoue K, et al. The bisphosphonate incadronate inhibits intraperitoneal dissemination in an in vivo pancreatic cancer model. Oncol Rep 2012;28:111-116.
24. Hiroshima Y, Maawy A, Hassanein MK, et al. The tumor-educated-macrophage increase of malignancy of human pancreatic cancer is prevented by zoledronic acid. PLoS One 2014;9:e103382.
25. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc 2008;83:1032-1045.
26. Borad MJ, Saadati H, Lakshmipathy A, et al. Skeletal metastases in pancreatic cancer: a retrospective study and review of the literature. Yale J Biol Med 2009;82:1-6.
27. Peila R, Arthur RS, Rohan TE. Association of sex hormones with risk of cancers of the pancreas, kidney, and brain in the UK Biobank cohort study. Cancer Epidemiol Biomarkers Prev 2020;29:1832-1836.
28. Abdel-Rahman O. Statin treatment and outcomes of metastatic pancreatic cancer: a pooled analysis of two phase III studies. Clin Transl Oncol 2019;21:810-816.
29. Gbelcová H, Lenícek M, Zelenka J, et al. Differences in antitumor effects of various statins on human pancreatic cancer. Int J Cancer 2008;122:1214-1221.
30. Dai C, Jiang M. Statin use and the overall survival in patients diagnosed with pancreatic cancer. Pancreas 2020;49:e19.