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Authors

Wu, Bechien U
Chang, Jonathan
Jeon, Christie Y
et al.

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Impact of Statin Use on Survival in Patients Undergoing Resection for Early-Stage Pancreatic Cancer

Bechien U. Wu, MD, MPH[1], **Jonathan Chang, MD**[2], **Christie Y. Jeon, ScD**[3], **Stephen J. Pandol, MD**[4], **Brian Huang, MPH**[5], **Eunis W. Ngor, MS**[5], **Andrew L. Difronzo, MD**[6], and **Robert M. Cooper, MD**[7]

[1]Division of Gastroenterology, Center for Pancreatic Care, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California, USA

[2]Department of Medicine, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California, USA

[3]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA

[4]Program in Basic and Translational Pancreatic Research, Cedars-Sinai Medical Center, Los Angeles, California, USA

[5]Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California, USA

[6]Department of Hepatobiliary and Oncologic Surgery, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California, USA

[7]Department of Pediatric Hematology and Oncology, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California, USA

Abstract

OBJECTIVES—It has been suggested that statins exert potential anti-tumor effects. The relationship between statin use and outcomes in pancreatic cancer is controversial. We hypothesized that statin use at baseline would impact survival among patients with early-stage pancreatic cancer and that the effect might vary by individual statin agent.

METHODS—We conducted a retrospective cohort study on data from an integrated healthcare system. We included patients with pancreatic cancer stage I-IIb who underwent resection for

Correspondence: Bechien U. Wu, MD, MPH, Division of Gastroenterology, Center for Pancreatic Care, Kaiser Permanente Los Angeles Medical Center, 1526N Edgemont Ave, Los Angeles, California 90027, USA. ; Email: Bechien.u.wu@kp.org

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CONFLICT OF INTEREST

Guarantor of the article: Bechien U. Wu, MD, MPH.

Specific author contributions: Study concept and design, data analysis, preparation and revision of the manuscript: Bechien U. Wu; study design, data collection, critical revision of the manuscript: Jonathan Chang; study concept, study design, critical revision of the manuscript: Christie Y. Jeon and Stephen J. Pandol; data collection, data analysis, critical revision of the manuscript: Brian Huang and Eunis W. Ngor; study concept, interpretation of findings, critical revision of manuscript: Andrew L. Difronzo and Robert M. Cooper.

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curative intent between January 2005 and January 2011. Baseline statin use was characterized as any prior use as well as active use of either simvastatin or lovastatin. Intensity of exposure was calculated as average daily dose prior to surgery. Overall and disease-free survival was assessed from surgery until the end of study (April 2014). We used the Kaplan-Meier method and Cox proportional hazards regression to evaluate the impact of baseline statin use on survival, adjusting for age, sex, Charlson comorbidity score, resection margin, disease stage, and receipt of adjuvant chemotherapy.

RESULTS—Among 226 patients, 71 (31.4%) had prior simvastatin use and 27 (11.9%) had prior lovastatin use at baseline. Prior simvastatin but not lovastatin use was associated with improved survival (median 28.5 months (95% confidence limit (CL) 20.8, 38.4) for simvastatin vs. 12.9 months (9.6, 15.5) for lovastatin vs. 16.5 months (14.1, 18.9) for non-statin users; log-rank P=0.0035). In Cox regression, active simvastatin use was independently associated with reduced risk for mortality (adjusted hazard ratio (HR) 0.56 (95% CL 0.38, 0.83), P=0.004) and risk for recurrence (adjusted HR 0.61 (0.41, 0.89), P=0.01). Survival improved significantly among patients who received moderate-high-intensity (median 42.1 months (24.0,52.7)) doses compared with those who received low-intensity doses of simvastatin (median 14.1 months (8.6, 23.8), log-rank P=0.03).

CONCLUSIONS—The effects of statins varied by agent and dose. Active use of moderate-high-dose simvastatin at baseline was associated with improved overall and disease-free survival among patients undergoing resection for pancreatic cancer.

INTRODUCTION

Pancreatic ductal adenocarcinoma is currently the fourth leading cause of cancer-related death in the United States and is projected to become the second leading cause by 2020 (1). Despite advances in therapy, pancreatic cancer continues to have a poor prognosis. Surgical resection remains the only potential for cure. However, even among patients with early-stage disease undergoing resection, disease recurrence remains high. Median survival following resection is 24–25 months even in the setting of adjuvant or neoadjuvant chemotherapy (2). As a result, there remains a substantial need for additional therapy to improve outcome among patients undergoing resection for pancreatic cancer.

Statins (HMG-CoA reductase inhibitors) comprise a group of lipid-lowering drugs that have proven efficacy in both the primary and secondary prevention of cardiovascular events (3). In addition to their inhibition of cholesterol biosynthesis, statins exhibit a pleiotropic effect with experimental studies, suggesting a potential impact on key proteins involved in tumor proliferation as well as metastasis (4,5).

The relationship between statins and pancreatic cancer remains controversial. Epidemiologic studies have failed to identify a consistent relationship between statin use and risk for pancreatic cancer (6). Several potential explanations for the discrepancy in the literature exist, including grouping of various statin agents together in previous analyses. In addition, more recent data suggest that statin use may be linked to improved survival among patients after a diagnosis of pancreatic cancer (7).

The objective of the present study was to evaluate the relationship between statins and survival among patients undergoing resection for early-stage pancreatic cancer. In addition, we sought to further characterize the impact of individual statin agents as well as intensity of exposure on survival.

METHODS

Study design and setting

We conducted a retrospective cohort study on data from the Kaiser Permanente Southern California (KPSC) Health System collected from January 2005 to April 2014. KPSC is an integrated healthcare system that serves a socio-economically diverse population broadly representative of the racial/ethnic groups living in Southern California. KPSC is one of Kaiser Permanente's (KP) largest regions, comprising 15 acute care hospitals and 202 ambulatory medical centers. Members enroll through the Kaiser Foundation Health Plan for prepaid comprehensive healthcare insurance that includes pharmaceutical benefits. The KPSC institutional review board approved the present study.

Patient population

Potentially eligible patients were identified through a prospectively maintained internal cancer registry. All health plan members diagnosed or treated for pancreatic cancer are entered into this registry for reporting purposes. Patients with stage I-IIB pancreatic cancer diagnosed between January 2005 and January 2011 with at least 6 months of continuous enrollment prior to cancer diagnosis were potentially eligible for study inclusion. Further patient inclusion criteria were as follows:

1. Completion of resection for curative intent e.g., pancreati-coduodenectomy, lateral pancreatectomy.
2. Histologic diagnosis of pancreatic ductal adenocarcinoma.

Patients were excluded if they had undergone palliative resection, were deemed to have had an unresectable tumor at the time of surgery, or had died during the immediate postoperative period--i.e., during the same hospitalization period. In addition, patients with histologic diagnoses other than pancreatic ductal adenocarcinoma were excluded. Final disease staging was based on surgical pathology from pancreatic resection.

Treatment protocol(s)

All treatment decisions including use of adjuvant chemotherapy or radiation treatment had been at the discretion of the primary treatment team. During the study period, all patients who were prescribed chemotherapy either as adjuvant or neoadjuvant therapy received gemcitabine. Patients were deemed to have completed chemotherapy if they completed the treatment protocol recommended by their treating oncologist.

Exposure assessment

Simvastatin and lovastatin were the two primary statin agents on KPSC formulary during the study period. Use of either simvastatin or lovastatin was determined by cross-referencing the

unique electronic health record number with electronic pharmacy data. Only patients with exposure to medication (initial medication dispensation) prior to the date of surgery were considered to have baseline statin exposure. Because the typical prescription for a statin agent within the KPSC pharmacies is for a 90-day supply, active statin use was defined as medication dispensation within 90 days prior to surgery or thereafter. Patients whose last recorded dispensation was more than 90 days prior to the date of surgery were considered former statin users.

Outcome

Overall survival—Survival was assessed from the time of resection until the end of the study follow-up period (30 April 2014). For patients who died during the follow-up period, the date of death was determined through an internal death registry that was also cross-referenced with the California state death index.

Disease-free survival—Disease recurrence was defined as the date of earliest appearance of suspicious findings for either local or distant disease on radiographic imaging with documentation of disease recurrence by the treating oncologist or subsequent histologic confirmation of disease recurrence. In the absence of objective imaging findings, recurrence was dated at the time of documentation of disease recurrence by the patient's oncologist based on clinical assessment e.g., rapid clinical deterioration in the setting of rising CA 19-9.

Patient demographic and clinical parameters

Patient demographic features were obtained from the electronic health record. Pathology reports and chemotherapy records were manually abstracted to obtain data on tumor margin, node status, and lymphovascular invasion. Patients were noted to have either initiated or completed adjuvant chemotherapy with gemcitabine during the study period.

Data analysis

Impact of statin use at baseline on overall survival—Patient outcome with respect to overall survival was assessed from the time of their resection until death from any cause. We used the Kaplan-Meier method to evaluate the impact of baseline statin use on survival (log-rank test). We first performed analysis on the basis of any previous exposure to either simvastatin or lovastatin. Subsequently we repeated the analysis by further categorizing patients according to baseline statin use as either active or former statin use. We then performed multivariable Cox proportional hazards regression to assess the impact of statin use on survival (hazard ratio) while adjusting for age, gender, race/ethnicity, tumor margin, disease stage, receipt of adjuvant or neoadjuvant gemcitabine-based chemotherapy, and Charlson comorbidity score.

Impact of statin use at baseline on disease-free survival—We used the Kaplan-Meier method to evaluate the relationship between statin use and disease-free survival among patients undergoing resection for pancreatic cancer. To assess the independent effect of baseline statin use we used Cox proportional hazards regression including tumor margin, disease stage, and receipt of adjuvant gemcitabine as covariates.

Subgroup analyses—We performed a series of subgroup analyses to further characterize the relationship between statin use and survival. First, we evaluated the impact of statin dose on overall survival. Dose was calculated as the average daily dose (cumulative dose/total days of exposure) while taking medication. Average daily dose ranges were classified on the basis of intensity (for simvastatin: low intensity ≤10 mg/day; moderate intensity 10–40 mg/day; high intensity >40 mg/day) based on current American College of Cardiology/American Heart Association guidelines (8). Multivariable analysis was not performed because of sample size constraints. In a second subgroup analysis, we analyzed the effect of baseline statin use among patients who had successfully completed chemotherapy.

All analyses were performed using SAS statistical software (SAS version 9.2, Cary, NC, USA). All reported *P*-values are two-sided with an alpha 0.05 significance level. Proportionality for Cox regression models was confirmed on the basis of Schoenfeld residuals.

RESULTS

From a total of 2,010 cases of pancreatic cancer in the KPSC cancer registry, we identified 226 patients who met the study criteria. Details of the cohort assembly are presented in **Figure 1.** Among the 226 patients, 98 (45.1%) used either simvastatin or lovastatin prior to their cancer diagnosis (71 simvastatin, 27 lovastatin). Among simvastatin users, 51 (72%) were active, whereas 13 (48%) lovastatin users were active at the time of cancer diagnosis. Baseline demographics and clinical characteristics of the study cohort stratified by statin use are presented in **Table 1**. Approximately two-thirds (66.3%) of the patients received adjuvant chemotherapy, 26% underwent radiation therapy, and 3.5% received neoadjuvant chemotherapy. Of note, a greater proportion of simvastatin users received adjuvant chemotherapy compared with the non-statin reference group (80.3% simvastatin vs. 60.9% non-statin users, χ^2 P=0.005). There were a total of 185 (82%) deaths during the study period, of which 94% were related to pancreatic cancer.

Impact of statin use on survival

As shown in **Figure 2a**, simvastatin users had improved overall survival: median 28.5 months (95% confidence limit 20.8, 38.4) among simvastatin users vs. 12.9 months (9.6, 15.5) among lovastatin users vs. 16.5 months (14.1, 18.9) among non-statin users (log-rank P=0.0035). Upon further characterization of statin use at baseline, active simvastatin users were noted to have improved survival compared with all-other categories: median survival 31.6 months (20.9,43.8) among active simvastatin users vs. 16.0 months (14.1,18.3) for all-other categories (log-rank P=0.001). **Figure 2b** depicts the Kaplan-Meier plot stratified by individual categories of statin use at baseline. In multivariable Cox regression analysis (**Table 2**), active simvastatin use was independently associated with improved survival (hazard ratio 0.56 (95% confidence limit 0.38, 0.83)) after adjusting for age at diagnosis, sex, tumor resection margin, disease stage, receipt of adjuvant chemotherapy, and Charlson comorbidity score.

Active simvastatin use at baseline was also associated with improved disease-free survival (**Figure 3a**): median disease-free survival was 20.3 months (95% confidence limit 11.1,

27.9) among active simvastatin users vs. 11.7 months (95% confidence limit 9.3, 13.0) among all others (log-rank P=0.016). In multivariable analysis (**Table 3**), active simvastatin use was independently associated with reduced risk of recurrence (hazard ratio 0.61 (0.41, 0.89)) after adjusting for the effects of tumor resection margin, disease stage, and receipt of chemotherapy.

Impact of simvastatin dose on overall survival (subgroup analysis I)

We performed a subgroup analysis among the patients who were active simvastatin users at baseline. Median duration of prior simvastatin use was 43.2 months (interquartile range 22.8, 55.2 months). Intensity of statin exposure was categorized according to 2013 American College of Cardiology/American Heart Association guidelines. Thirteen of 51 (25.5%) patients received low-intensity (≤10 mg/day average daily dose), 28/51 (54.9%) received moderate-intensity (between 10 mg to 40 mg/day), and 10/51 (19.6%) patients received high-intensity therapy (>40 mg/day average daily dose) of simvastatin. There appeared to be a threshold effect such that patients who had received low-intensity exposure had significantly reduced overall survival compared with patients who had received moderate-high-intensity therapy (median 14.1 (8.6, 23.8) months among patients on low-intensity therapy vs. 42.1 months (24.0, 52.7) among patients exposed to moderate-high-intensity simvastatin ((log-rank P=0.032), **Figure 3b**).

Impact of active simvastatin use on survival among patients who completed adjuvant chemotherapy (subgroup analysis II)

A total of 150 (66%) patients received adjuvant chemotherapy, with 93/150 (62%) completing their assigned regimen. Among the patients who completed adjuvant chemotherapy, 30/93 (32%) were active simvastatin users at baseline. There was a significant improvement in overall survival among active simvastatin users (median survival 43.7 (31.6,52.7) months) compared with others (median survival 23.9 (19.6,29.3) months), log-rank P=0.028 (**Supplementary Figure 1** online).

DISCUSSION

In this retrospective cohort study we determined that active simvastatin use at baseline was associated with significantly improved overall and disease-free survival among patients who had undergone resection for early-stage pancreatic cancer. The relationship between simvastatin use and improved survival persisted after adjusting for age, gender, comorbidity, tumor margin, disease stage, and use of adjuvant chemotherapy. Among active simvastatin users, patients who received moderate- or high-intensity therapy had improved survival compared with patients who received low-intensity drug exposure.

Pancreatic cancer is the fourth most common cause of cancer-related death in the United States with a 5-year survival rate of 6.7% (9). Surgical resection of early-stage disease remains the only opportunity for potential cure. However, up to 80–85% of patients undergoing resection experience disease recurrence (10,11). Although advances such as adjuvant and neoadjuvant chemotherapy have improved outcomes, median survival remains

<2 years (2). Therefore, additional therapies are desperately needed to improve outcomes for this group of patients.

Although HMG-CoA reductase inhibitors or statins are widely prescribed for their role in management of cardiovascular disease, attention has recently focused on their potential anti-cancer properties. Data from observational studies and randomized controlled trials have failed to consistently demonstrate an impact on pancreatic cancer incidence with statin use (6,12). However, several lines of evidence now suggest that statins may have a potential impact on survival after cancer diagnosis. A large population-based study found reduced overall cancer-related mortality among patients with 13 cancer types in those who had used statins regularly before their cancer diagnosis (7). In addition, a smaller retrospective study suggested survival benefit with statin use among diabetic patients with pancreatic cancer (13).

The present study adds to the available evidence about the relationship between statin use and survival in pancreatic cancer. Similar to a recent analysis of the Medicare population (14), the observed effect on survival was not uniform across agents within the class. Only moderate-high doses of simvastatin were associated with improved survival. These findings indicate that the intensity of statin exposure may be important and also support previous assertions that individual statin agents may exert varied effects with respect to their anti-tumor properties (15).

In the present study, a greater proportion of simvastatin users completed adjuvant chemotherapy compared with non-users. Therefore, one explanation for the observed effect of simvastatin could have been related to increased tumor susceptibility to adjuvant chemotherapy or greater adherence to chemotherapy among simvastatin users. We therefore conducted an additional subgroup analysis specifically among patients who had completed adjuvant chemotherapy. We noted a continued survival benefit with simvastatin use even among this highly selected group of patients, suggesting a potential alternate mechanism of action.

At the moment it is unclear whether the observed effect of simvastatin use was related to a lipid-mediated vs. a lipid-independent pathway. Experimental data support several additional mechanisms for a possible beneficial impact of statins on pancreatic cancer. These include modification of k-ras activity through decreased production of isoprenoids (16), delayed progression of pancreatic intraepithelial neoplasia (5), and inhibition of tumor cell invasion via epidermal growth factor-mediated signaling pathways (4).

There were several limitations to the present study. Despite adjustment for established patient-related and resection characteristics associated with increased risk for disease recurrence and/or mortality, there is the possibility of residual confounding. Statin users may have been more likely to pursue healthier lifestyles or dietary habits that could have contributed to improved survival. In addition, patients taking statins in the period leading up to their cancer diagnosis may have benefited from earlier detection or been more likely to adhere to subsequent recommendations for cancer treatment. We therefore adjusted for disease stage and limited the study to patients who had undergone successful resection for

curative intent. Reverse causation is also a potential concern when evaluating the relationship between medication exposure and outcomes such as disease recurrence or survival in that patients experiencing clinical deterioration may be more likely to discontinue or avoid initiation of new treatment. Immortal time bias can also arise when members of the exposed group by definition are unable to experience an outcome of interest for some period of time. For example, if initiation of statin use after cancer diagnosis was included as part of the definition for exposure status, patients would by definition have survived to the point of their initial medication dispensation. We therefore restricted our analysis to medication usage prior to resection (baseline statin use) in order to limit the potential effects of reverse causation as well as immortal time bias. However, as a result we were unable to specifically evaluate the effect of initiation of simvastatin use after surgery. In addition, the present analysis was limited to two agents within the statin class, simvastatin and lovastatin, as these were the two predominant statins prescribed in the KPSC health system during the study period.

Findings from the present study suggest several potential areas for further investigation. First, further experimental studies are needed to characterize the mechanisms by which treatment with simvastatin or other statin agents might alter pathways related to recurrence of pancreatic cancer in patients undergoing resection. Although a previous double-blind, randomized controlled trial failed to demonstrate improved survival with the addition of 3 weeks of simvastatin to gemcitabine in patients with advanced disease (17), on the basis of the present study findings it is tempting to speculate that improved outcomes may be observed when statins are applied as adjuvant or neoadjuvant therapy in patients undergoing resection for early-stage disease. Nevertheless, further investigation into the potential mechanisms by which statins impact tumor development or progression in pancreatic cancer may yield important insights into novel therapeutic targets.

In summary, active simvastatin use at baseline was associated with improved overall and disease-free survival among patients undergoing resection for early-stage pancreatic cancer. This effect persisted after controlling for individual patient characteristics, comorbid illnesses, disease stage, resection margin, node status, and receipt of adjuvant chemotherapy. Further elaboration of the potential mechanistic pathways by which simvastatin or other agents in this class may impact tumor biology may provide new insight into potential therapeutic pathways for the treatment of pancreatic cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Survival among patients undergoing resection for early-stage pancreatic cancer remains poor.
- Experimental data suggest that statins may exert anti-tumor effects.

WHAT IS NEW HERE

- Impact of statin use at baseline varied by agent as well as by intensity of prior exposure.
- Active (current) use of moderate-high-dose simvastatin at baseline was associated with improved overall and disease-free survival.

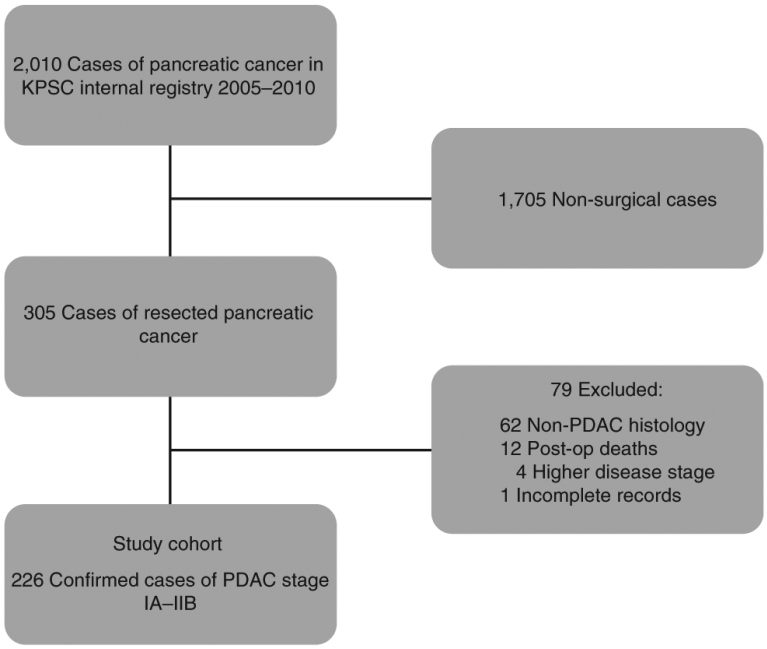

Figure 1.
Assembly of study cohort. PDAC, pancreatic ductal adenocarcinoma.

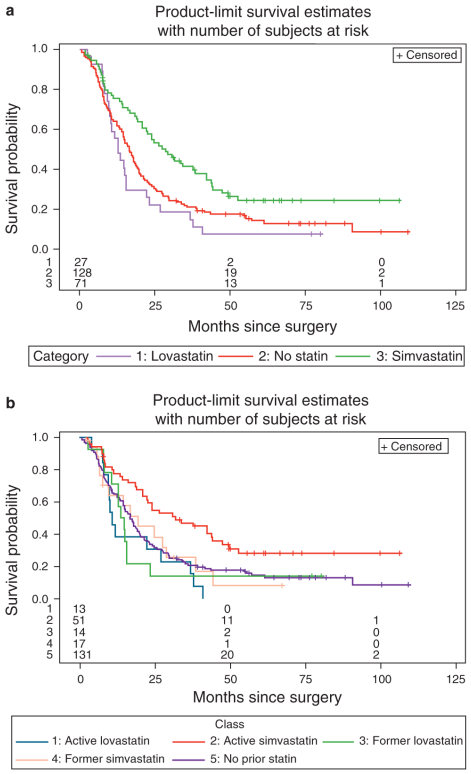

Figure 2.

(**a**) Survival by prior statin use, log-rank *P*=0.0035. Median survival (95% confidence limits) in months: simvastatin, 28.5 (20.8, 38.4); lovastatin, 12.9 (9.6, 15.5); no statin, 16.5 (14.1, 18.9). (**b**) Survival stratified by statin status at baseline, log-rank *P*=0.013. Median survival (95% confidence limits) in months: no prior statin, 16.7 (14.4, 19.6); active simvastatin, 31.6 (20.9, 43.8); active lovastatin, 10.7 (7.67,26.7); former simvastatin, 19.4 (6.5, 28.5); former lovastatin, 14.1 (8.1, 15.5).

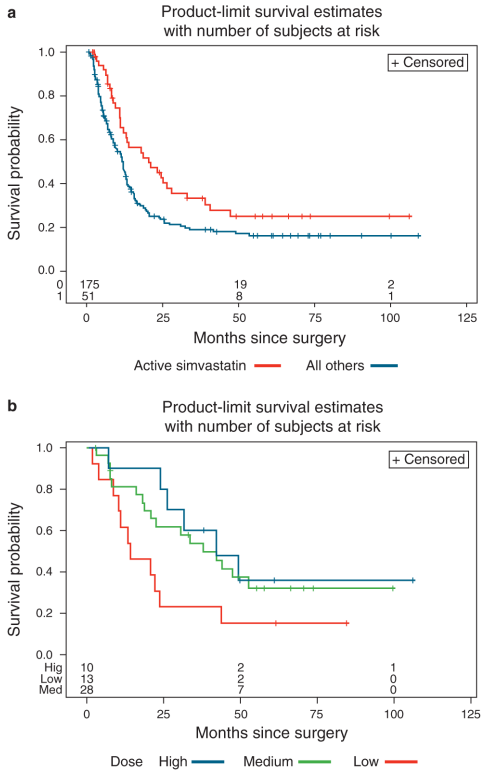

Figure 3.

(**a**) Disease-free survival by baseline simvastatin use: active simvastatin use vs. other, log-rank *P*=0.016. Median survival (95% confidence limits) in months: active simvastatin use at baseline, 20.3 (11.1, 27.9); others, 11.7 (9.3, 13.0). (**b**) Survival among active simvastatin users by dose category, low- vs. medium-high-intensity, log-rank *P*=0.032. Median survival (95% confidence limits) in months: medium and high-intensity (>10 mg/day), 42.1 (24.0,52.7); low intensity (≤10 mg/day), 14.1 (8.6,23.8).

Table 1

Baseline demographic and clinical features of the study cohort, *n*=226

	No prior statin *n*=128	**Simvastatin *n*=71**	**Lovastatin *n*=27**
Age, median (IQR)	64 (57, 73)	66 (62, 73)	64 (60, 71)
Female sex (%)	59 (47.6)	31 (43.7)	12 (44.4)
Race/ethnicity			
Non-Hispanic White	89 (69.5)	44 (62.0)	12 (44.4)
Non-Hispanic Black	16 (12.5)	12 (16.9)	7 (25.9)
Hispanic	14 (10.9)	10 (14.1)	1 (3.7)
Asian	7 (5.8)	5 (7.0)	7 (25.9)
Other	2 (1.6)	0 (0)	0 (0)
Positive resection margin	45 (35.2)	25 (35.2)	11 (40.7)
Stage II disease	113 (88.3)	67 (94.4)	24 (88.9)
Perineural invasion	101 (78.9)	53 (74.7)	20 (74.1)
Received adjuvant chemotherapy	78 (60.9)	57 (80.3)	15 (55.6)
Charlson comorbidity score, median (IQR)	2 (0, 2)	2 (1, 3)	3 (2, 5)

IQR, interquartile range.

Table 2

Multivariable Cox proportional hazards regression: risk of mortality

	Comparison	Hazard ratio (95% CL)	*P* value
Active simvastatin use	Yes vs. no	0.56 (0.38, 0.83)	0.004
Positive margin	Yes vs. no	1.72 (1.26, 2.35)	0.0007
Age ≥65 at diagnosis	Yes vs. no	1.24 (0.89, 1.73)	0.19
Sex	Male vs. female	1.32 (0.98, 1.78)	0.07
Stage	II vs. I	2.27 (1.24, 4.13)	0.008
Chemotherapy [a]	Any vs. none	0.64 (0.46, 0.89)	0.0008
Charlson score		1.02 (0.96, 1.08)	0.57

CL, confidence limit.

[a]Adjuvant or neoadjuvant treatment with gemcitabine.

Table 3

Multivariable Cox proportional hazards regression for disease recurrence

	Comparison	Hazard ratio (95% CL)	*P* value
Active simvastatin use	Yes vs. no	0.61 (0.41, 0.89)	0.01
Positive margin	Yes vs. no	1.13 (0.81, 1.58)	0.48
Stage	II vs. I	2.23 (1.22, 4.0)	0.009
Chemotherapy [a]	Any vs. none	1.04 (0.72, 1.49)	0.85

CL, confidence limit.

[a]Adjuvant or neoadjuvant treatment with gemcitabine.