Title
Statin use and risk of pancreatic cancer: Results from a large, clinic-based case-control study

Journal
Cancer, 121(8)

ISSN
0008-543X

Authors
Walker, Evan J
Ko, Andrew H
Holly, Elizabeth A
et al.

Publication Date
2015-04-15

DOI
10.1002/cncr.29256

Peer reviewed

HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2016 April 15.

Published in final edited form as:

Cancer. 2015 April 15; 121(8): 1287–1294. doi:10.1002/cncr.29256.

Statin use and risk of pancreatic cancer: Results from a large clinic-based case-control study

Evan J Walker, ScB[1], **Andrew H Ko, MD**[1], **Elizabeth A Holly, PhD, MPH**[2], and **Paige M Bracci, PhD, MS, MPH**[2]

[1]University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

[2]Department of Epidemiology and Biostatistics, University of California, San Francisco

Abstract

Background—Statins are cholesterol-lowering medications with pleiotropic effects including alterations in growth signaling as well as immunomodulatory and anti-inflammatory effects that may alter cancer risk. Evidence from previous epidemiologic studies is inconsistent regarding whether statin use is associated with reduced risk of pancreatic cancer (PC).

Methods—Patients with confirmed diagnoses of PC (cases) were recruited from medical and surgical oncology clinics, with controls (frequency-matched by sex and age) recruited from general medicine clinics, at a high-volume academic medical center over a six-year period (2006–2011). Direct interviews were conducted using an epidemiological risk factor questionnaire covering topics such as medical history, lifestyle factors, and medication usage. Adjusted multivariable logistic regression was used to compute odds ratios (OR) and 95% confidence intervals (95%CI) as estimates of the relative risk of PC.

Results—Data were obtained from 536 cases and 869 controls. Ever use of statins was associated with 34% reduced PC risk (OR=0.66, 95%CI 0.47–0.92). In sex-stratified analyses, risk was statistically significantly reduced in men only (men: OR=0.50, 95%CI 0.32–0.79; women: OR=0.86, 95%CI 0.52–1.43). Duration of use was inversely associated with PC risk (>10 year use: OR=0.51 overall; in men, OR=0.41, 95%CI 0.21–0.80; p_{trend}=0.006).

Conclusions—This is the largest case-control study to demonstrate an inverse association between statin use and PC risk. Risk reduction in statin users appears to be sex-specific and is more pronounced in long-term users. Further research is warranted to better characterize this association and clarify roles of underlying biologic mechanisms.

Keywords

pancreatic adenocarcinoma; statins; HMG-CoA reductase inhibitors; case-control; cancer risk

Correspondence: Paige M Bracci, PhD, MS, MPH, Department of Epidemiology & Biostatistics, University of California San Francisco, 3333 California St, Suite 280, San Francisco, CA, 94118-1944. Paige.bracci@ucsf.edu. Phone:415-476-3354. Fax: 415-563-4602.

Disclosures: None

Introduction

In 2014, pancreatic cancer (PC) represented the fourth-leading cause of cancer-related mortality among U.S. adults, with a projected 46,420 new cases and 39,590 deaths[1]. Approximately 75% of patients die within 1 year following diagnosis and 5-year survival is 6%[1]. Only 15–20% of patients have potentially operable tumors at diagnosis; the majority present with incurable locally advanced or metastatic disease[2]. Population-based risk-reduction strategies require improved understanding of factors that modulate risk, particularly modifiable factors. Known and suggested risk factors include male sex, increasing age, African-American ethnicity, smoking, obesity, type 2 diabetes (T2D), pancreatitis, and family history of PC[3].

Statin medications, currently indicated for coronary heart disease and its risk equivalents[4], lower serum cholesterol levels via competitive inhibition of HMG-CoA reductase (the rate limiting enzyme in cholesterol synthesis). Recently updated preventive health guidelines vastly expand the cohort of U.S. adults deemed likely to benefit from statins[5]. Due to their pleiotropic effects, they have been of considerable interest for cancer prevention and treatment. Data safety analyses of early randomized control trials (RCTs) of statins revealed an inverse association between statin use and cancer incidence[6]. Pre-clinical studies have demonstrated growth suppressive effects on various tumors, and epidemiologic studies have shown inverse associations with overall cancer risk[7, 8] and risk of other gastrointestinal cancers including esophageal[9], colorectal[10], and liver[11].

Previous studies of statin use and PC risk are inconsistent. Some RCTs and cohorts were underpowered[12–17] and of non-trial studies[7,18–26], few examined associations by sex with the exception of a large study of predominantly male veterans[26] and a UK study[19] where inverse relationships were observed only in men and male smokers, respectively.

To further examine the association between use of statin medications and PC risk among women and men combined and separately, we analyzed data collected in our large clinic-based case-control study of PC in the San Francisco, California Bay Area. As anti-neoplastic effects may vary with drug characteristics[27, 28], we also explored differential effects of statins individually and grouped by pharmacologic properties.

Methods

Study Population

Eligible patients diagnosed with exocrine pancreatic adenocarcinoma were recruited primarily from the University of California, San Francisco (UCSF) Gastrointestinal Medical and Surgical Oncology clinics (n=463), supplemented by recruitment from San Francisco's California Pacific Medical Center (n=46) and the Cancer Prevention Institute of California's early case ascertainment in Santa Clara and San Mateo counties (n=27). Eligible cases were U.S. residents 21–85 years old at diagnosis and able to complete a direct interview i.e. spoke English, no cognitive impairment. Diagnoses were confirmed by patients' medical records, cancer registry and Surveillance Epidemiology and End Results abstracts that included histologic or cytologic confirmation of diagnoses. Controls were recruited from UCSF

General Medicine Primary Care clinics and were frequency-matched to cases by sex and age in 5-year groups. Eligibility criteria for controls were the same as for cases with the exception of PC diagnosis. All participants were enrolled from 2006–2011 and provided informed consent for interview and biospecimen collection. Cases provided additional consent for medical record access of data pertaining to their disease and follow-up telephone contact. The study was approved by the UCSF Committee on Human Research.

Data collection

Data were collected during direct interviews using a standard epidemiologic risk factor questionnaire where queries for most exposures were restricted to >1 year before diagnosis (cases) or interview (controls). No proxy interviews were conducted. Specific to these analyses, participants were asked whether they had ever been diagnosed with hypercholesterolemia, had ever taken prescription hypolipidemic medications for ≥4 days per week for ≥3 months and if so, their age at first use, last use, and total duration of use. Cue cards with brand and generic medication names helped facilitate recall.

Statistical analysis

Statistical analyses were conducted using SASv9.3 (SAS Institute, Inc., Cary, NC). Preliminary analyses were conducted using parametric and non-parametric statistics. Age at PC diagnosis (cases) or interview (controls) was grouped as ≤50, 51–60, 61–70, >70 years old. Body mass index (BMI) was computed as usual adult weight/height^2 (kg/m^2) and grouped per World Health Organization categories. Alcohol consumption was analyzed as average drinks/week over the past 10 years and cigarette smoking as never smoker, quit >15 years ago, quit 1–15 years ago, quit <1 year ago/current smoker.

Hypolipidemic medication use was analyzed by drug class and grouped into mutually exclusive categories of use: never, non-statins, non-statins and statins, and statins only. Drug-specific analyses were limited to exclusive use of that medication. Never users of hypolipidemics constituted the referent group in all analyses.

Exploratory analyses of pharmacologic properties of specific statins included potency (recommended starting dose 20–40mg/day vs 10–20mg/day), derivation (biologic vs synthetic), bioavailability (≤5% vs ≥12%), solubility (lipophilic vs hydrophilic), phase I metabolism (CYP450 3A4 vs other), production of active metabolites (none/minor vs major), renal excretion (≤10% vs ≥13%), and half-life (<3 hours vs >11 hours)[29]. Users of multiple statins that crossed categories within a pharmacologic property were analyzed as “mixed” use.

Multivariable unconditional logistic regression was used to compute odds ratios (OR) with 95% confidence intervals (95%CI) as estimates of relative risk. Models were adjusted for matching factors or for all potential confounders of PC (age, sex, race, BMI, alcohol, tobacco, hypercholesterolemia, diabetes, pancreatitis, family history of PC, and duration of statin use for statin subgroup analyses) and are hereto forward referred to as “adjusted” or “fully adjusted” respectively. Ever use of non-statin hypolipidemics did not change risk estimates >10% and therefore was not included in final models. Linear trend in odds ratios was based on the Wald chi-square statistic for the factor modeled as an ordinal variable.

Effect modification by sex was explored in stratified analyses. Demographic characteristics of non-UCSF cases were similar to UCSF cases and sensitivity analyses showed similar results for analyses of all cases and for UCSF cases only. Thus the total case population was used for all analyses. Data are not tabled for ≤5 exposed participants. All statistical tests were two-sided and considered statistically significant for $p<0.05$.

Results

Of potentially eligible cases aged 21–85 years, ~12% were ineligible due to language problems and ~3% were cognitively impaired, not located or dead, leaving 698 eligible PC cases. Of these, 16% refused, 6% were too ill and 2% expressed privacy concerns or participation in another study, for a final participation rate of 76%. Cases were recruited at a median of 61 days after PC diagnosis (interquartile range 25–148 days). Among controls, ~34% of patients approached did not meet eligibility requirements e.g. language problems, incompatible age-group. Of eligible clinic controls, 35% had no time, 3% refused, 6% were too ill and 3% had privacy concerns, for a final participation rate of 53%. These analyses include the eligible 536 cases and 869 frequency-matched controls who completed interviews.

Compared with controls, cases were slightly older and a greater proportion were men, consumed alcohol, were overweight or obese, or had T2D or pancreatitis (Table 1). Nearly half of both cases and controls reported a history of hypercholesterolemia.

Hypolipidemics were ever used by 34.0% of cases and 36.9% of controls (Table 2). Statins were the most commonly used (32.6% cases, 35.7% controls) and 23.9% of statin users took two or more different statins. Both cases and controls with T2D were more likely to have hypercholesterolemia and use cholesterol-lowering drugs including statins. Of note, one-third of the 39 statin users without hypercholesterolemia had T2D and 180 patients with hypercholesterolemia never used statins.

Ever use of statins was associated with a reduced PC risk (adjusted OR=0.66, 95%CI 0.47–0.92, Table 3). Sex-stratified analyses showed this was mainly due to the association in men (men: adjusted OR=0.50, 95%CI 0.32–0.79; women: adjusted OR=0.86, 95%CI 0.52–1.43). In contrast, use of other hypolipidemics was not associated with PC risk regardless of exclusivity of use, although estimates were imprecise.

Duration of statin use was inversely associated with risk, particularly among long-term users (used >10 years: fully adjusted OR=0.51, 95%CI 0.31–0.85, $p_{trend}=0.01$, Table 3). Age at first use was not associated with PC risk in fully adjusted models and did not confound the association between PC risk and duration of use (Table 3). Median age at first use in men, 57 years (interquartile range 50–64), was similar to that in women, 58 years (interquartile range 52–65) (data not tabled). In sex-stratified analyses, a trend of reduced risk with increased duration of use was statistically significant in men only (men, $p_{trend}=0.006$; women $p_{trend}=0.44$; Table 3).

Atorvastatin was the most common exclusively-used statin (Table 4). Only exclusive pravastatin use was associated with a statistically significant decreased PC risk (fully

adjusted OR=0.22, 95%CI 0.06–0.82) and the magnitude of the OR was similar for men and women, although imprecise. Use of multiple statins was associated with a 56% reduced PC risk, statistically significant in men only (OR=0.30, 95%CI 0.10–0.86). Among those who took multiple statins, 86.2% used atorvastatin and 72.4% used simvastatin.

Exploratory analyses of the pharmacologic characteristics of statins disclosed few associations with PC risk (Table 5) with the exception of drug bioavailability. Compared with exclusive use of statins with low bioavailability (≤5%), those who exclusively used high bioavailability (≥12%) statins had reduced risk of PC (p=0.01). However, this was observed in men only (men: p=0.01, women: p=0.26). Interestingly, participants in the "mixed" use group were at lowest risk and were the only group with statistically significantly decreased risk compared with non-users. Other pharmacologic characteristics were not associated with risk when compared with non-users or in comparisons of high and low intensity exposure. However, those in the "mixed" use groups for derivation, renal excretion, and elimination had statistically significantly reduced PC risk compared with non-users.

Discussion

To our knowledge, this is the largest published case-control study to demonstrate an inverse association between statin use and PC risk, and to conduct detailed analyses by sex and pharmacologic properties. Associations were observed in men only. PC risk was inversely associated with duration of statin use and lowest in men long-term users regardless of age at first use. The decreased risk of PC with exclusive pravastatin use was novel to our study but requires confirmation and should be interpreted cautiously.

Statins are hypothesized to decrease cancer risk partly via the downstream effects of HMG-CoA reductase inhibition in the mevalonate pathway. Specifically, inhibition disrupts synthesis of cholesterol and farnesyl or geranylgeranyl disphophates (FPP, GGPP) which function in prenylation of the G-proteins Rho and Ras, as well as other proteins involved in cell signaling[6,30,31]. Relevant to pancreatic cancer, aberrant Ras signaling is integral to pancreatic tumorigenesis[32,33] whereas Rho mediates epidermal growth factor signaling and is implicated in other cancer-related mechanisms including angiogenesis[34,35], tumor invasion and metastasis[36,37], and activation of the NF-κB pathway[38]. Statins also might impact cancer development via other direct anti-inflammatory and immunomodulatory effects[6,39]. Interestingly, results from recent meta-analyses of RCT data show that statins may reduce risk of acute pancreatitis and increase diabetes risk[40], conditions associated with increased PC risk. The association between statin use and cancer is complex, organ dependent and confounded by intermediary health conditions requiring carefully designed studies to better understand the mechanisms driving the observed pleiotropy.

Our findings of sex-specific associations expand on results from a large nested case-control study of predominantly male U.S. veterans that showed statistically significantly reduced PC risk in statin users (OR=0.33), particularly long-term users (>4 years; OR=0.20)[26], as well as a recent UK case-control study that reported a reduced risk of PC with statin use among male smokers (OR=0.11)[19]. Other studies that reported null associations with PC

risk[7,18,20,21,25] typically had matched on sex and had too few cases to conduct sex-stratified analyses. However, earlier results for all-cause mortality and stroke where decreased rates were observed in men only[41,42] provide additional evidence of statins' sex-specific effects. Integration of the accumulating data suggests sex-related effects of statins, including potential anti-neoplastic associations. Underlying mechanisms to explain these differences are uncertain and poorly understood. With few published studies among women, further research is warranted.

Our detailed analyses of pharmacologic properties of statins are unique to our study. Results were null from earlier analyses that assessed medication derivation or solubility[43,44]. Our observed inverse associations with bioavailability are intriguing but could be spurious given that the lowest PC risk was observed among those in the "mixed" group of users. Overall, our results do not suggest that specific pharmacologic characteristics might confer exceptionally low PC risk.

Strengths of this study include the large sample size, the short duration between case diagnosis and interview, and the experienced, well-trained interviewers who administered a structured questionnaire in-person to collect data about potential and known confounders, effect modifiers and risk factors of PC in a standard manner. Data about most exposures excluded the year before diagnosis/interview to diminish effects of reverse causation. Cancer registry and medical record data were used to confirm PC diagnoses. Study limitations include the potential for recall bias inherent in case-control studies although direct interviews and use of cue cards to facilitate recall helped to diminish exposure misclassification. A potential for selection bias among controls is possible as a high frequency of controls "had no time" or could only partially complete an interview during the clinic visit. Our use of clinic-based controls, which compared with population-based controls may include a greater prevalence of unhealthy persons, i.e. smokers, also may have influenced our findings although our controls were largely being seen for acute conditions or healthy annual exams. Also, UCSF is a tertiary care center and cancer patients are often referred for surgery or clinical trial consideration, options that generally necessitate good functional status. Compared with 2006–2011 San Francisco-Oakland SMSA SEER data[45] for pancreatic cancer patients, a greater proportion of study patients were non-Hispanic white (85% vs 61%), were younger at diagnosis (median age 63 vs 70 years), and had earlier stage disease at diagnosis (regional stage, 42% vs 34%; advanced stage 41% vs. 56%). Thus, our results may pertain to a healthier population of PC patients than in the broader community. Finally, statins have been previously associated with increased adherence to preventive health measures[46], suggesting that statin use may be a surrogate for a healthier lifestyle or better functional status. This potential bias should be considered in the interpretation of our findings, although potential confounding due to lifestyle factors associated with increased risk of PC such as obesity, smoking and alcohol consumption was adjusted for in our analyses.

In conclusion, this represents the largest case-control study to demonstrate an inverse relationship between statin use and PC risk, particularly in men and in long-term users. Prospective clinical evaluation of statins as preventive therapy, e.g. in individuals at particularly high risk of PC, represents an intriguing possibility.

Acknowledgments

Funding: Supported in part by NIH-NCI grants (R01CA1009767, R01CA109767-S1), NIH Project TL1TR000144, and the Joan Rombauer Pancreatic Cancer Fund. Collection of cancer incidence data was supported by the California Department of Public Health as part of the statewide cancer reporting program; the NCI's SEER Program under contract HHSN261201000140C awarded to CPIC; and the CDC's National Program of Cancer Registries, under agreement #U58DP003862-01 awarded to the California Department of Public Health.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. Jan-Feb;2014 64(1):9–29. [PubMed: 24399786]
2. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med. Sep 11; 2014 371(11): 1039–1049. [PubMed: 25207767]
3. Lowenfels AB, Maisonneuve P. Epidemiology and risk factors for pancreatic cancer. Best Pract Res Clin Gastroenterol. Apr; 2006 20(2):197–209. [PubMed: 16549324]
4. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013; 1:CD004816. [PubMed: 23440795]
5. Stone NJ, Robinson JG, Lichtenstein AH, 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. Jul 1; 2014 63(25 Pt B):2889–2934. [PubMed: 24239923]
6. Demierre MF, Higgins PD, Gruber SB, Hawk E, Lippman SM. Statins and cancer prevention. Nat Rev Cancer. Dec; 2005 5(12):930–942. [PubMed: 16341084]
7. Graaf MR, Beiderbeck AB, Egberts AC, Richel DJ, Guchelaar HJ. The risk of cancer in users of statins. J Clin Oncol. Jun 15; 2004 22(12):2388–2394. [PubMed: 15197200]
8. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N Engl J Med. Nov 8; 2012 367(19):1792–1802. [PubMed: 23134381]
9. Nguyen DM, Richardson P, El-Serag HB. Medications (NSAIDs, statins, proton pump inhibitors) and the risk of esophageal adenocarcinoma in patients with Barrett's esophagus. Gastroenterology. Jun; 2010 138(7):2260–2266. [PubMed: 20188100]
10. Poynter JN, Gruber SB, Higgins PD, et al. Statins and the risk of colorectal cancer. N Engl J Med. May 26; 2005 352(21):2184–2192. [PubMed: 15917383]
11. Shi M, Zheng H, Nie B, Gong W, Cui X. Statin use and risk of liver cancer: an update meta-analysis. BMJ Open. 2014; 4(9):e005399.
12. Clearfield M, Downs JR, Weis S, et al. Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): efficacy and tolerability of long-term treatment with lovastatin in women. J Womens Health Gend Based Med. Dec; 2001 10(10):971–981. [PubMed: 11788107]
13. Marelli C, Gunnarsson C, Ross S, et al. Statins and risk of cancer: a retrospective cohort analysis of 45,857 matched pairs from an electronic medical records database of 11 million adult Americans. J Am Coll Cardiol. Jul 26; 2011 58(5):530–537. [PubMed: 21777752]
14. Olsen JH, Johansen C, Sorensen HT, et al. Lipid-lowering medication and risk of cancer. J Clin Epidemiol. Feb; 1999 52(2):167–169. [PubMed: 10201659]
15. Sato S, Ajiki W, Kobayashi T, Awata N. Pravastatin use and the five-year incidence of cancer in coronary heart disease patients: from the prevention of coronary sclerosis study. J Epidemiol. Sep; 2006 16(5):201–206. [PubMed: 16951539]
16. Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. JAMA. Jun 26; 2002 287(24):3215–3222. [PubMed: 12076217]
17. Strandberg TE, Pyorala K, Cook TJ, et al. Mortality and incidence of cancer during 10-year follow-up of the Scandinavian Simvastatin Survival Study (4S). Lancet. 2004; 364(9436):771–777. Aug 28–Sep 3. [PubMed: 15337403]
18. Bradley MC, Hughes CM, Cantwell MM, Murray LJ. Statins and pancreatic cancer risk: a nested case-control study. Cancer Causes Control. Dec; 2010 21(12):2093–2100. [PubMed: 20697797]

19. Carey FJ, Little MW, Pugh TF, et al. The differential effects of statins on the risk of developing pancreatic cancer: a case-control study in two centres in the United Kingdom. Dig Dis Sci. Nov; 2013 58(11):3308–3312. [PubMed: 23864194]
20. Chiu HF, Chang CC, Ho SC, Wu TN, Yang CY. Statin use and the risk of pancreatic cancer: a population-based case-control study. Pancreas. Jul; 2011 40(5):669–672. [PubMed: 21654539]
21. Coogan PF, Rosenberg L, Strom BL. Statin use and the risk of 10 cancers. Epidemiology. Mar; 2007 18(2):213–219. [PubMed: 17235211]
22. Friedman GD, Flick ED, Udaltsova N, Chan J, Quesenberry CP Jr, Habel LA. Screening statins for possible carcinogenic risk: up to 9 years of follow-up of 361,859 recipients. Pharmacoepidemiol Drug Saf. Jan; 2008 17(1):27–36. [PubMed: 17944002]
23. Haukka J, Sankila R, Klaukka T, et al. Incidence of cancer and statin usage--record linkage study. Int J Cancer. Jan 1; 2010 126(1):279–284. [PubMed: 19739258]
24. Jacobs EJ, Newton CC, Thun MJ, Gapstur SM. Long-term use of cholesterol-lowering drugs and cancer incidence in a large United States cohort. Cancer Res. Mar 1; 2011 71(5):1763–1771. [PubMed: 21343395]
25. Kaye JA, Jick H. Statin use and cancer risk in the General Practice Research Database. Br J Cancer. Feb 9; 2004 90(3):635–637. [PubMed: 14760377]
26. Khurana V, Sheth A, Caldito G, Barkin JS. Statins reduce the risk of pancreatic cancer in humans: a case-control study of half a million veterans. Pancreas. Mar; 2007 34(2):260–265. [PubMed: 17312467]
27. Duncan RE, El-Sohemy A, Archer MC. Statins and cancer development. Cancer Epidemiol Biomarkers Prev. Aug; 2005 14(8):1897–1898. [PubMed: 16103434]
28. Gbelcova H, Lenicek M, Zelenka J, et al. Differences in antitumor effects of various statins on human pancreatic cancer. Int J Cancer. Mar 15; 2008 122(6):1214–1221. [PubMed: 18027870]
29. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fundam Clin Pharmacol. Feb; 2005 19(1):117–125. [PubMed: 15660968]
30. Jiang K, Coppola D, Crespo NC, et al. The phosphoinositide 3-OH kinase/AKT2 pathway as a critical target for farnesyltransferase inhibitor-induced apoptosis. Mol Cell Biol. Jan; 2000 20(1): 139–148. [PubMed: 10594016]
31. Tamanoi F, Kato-Stankiewicz J, Jiang C, Machado I, Thapar N. Farnesylated proteins and cell cycle progression. J Cell Biochem Suppl. 2001; (Suppl 37):64–70. [PubMed: 11842430]
32. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M. Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell. May 20; 1988 53(4):549–554. [PubMed: 2453289]
33. Jones S, Zhang X, Parsons DW, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science. Sep 26; 2008 321(5897):1801–1806. [PubMed: 18772397]
34. Park HJ, Kong D, Iruela-Arispe L, Begley U, Tang D, Galper JB. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors interfere with angiogenesis by inhibiting the geranylgeranylation of RhoA. Circ Res. Jul 26; 2002 91(2):143–150. [PubMed: 12142347]
35. Weis M, Heeschen C, Glassford AJ, Cooke JP. Statins have biphasic effects on angiogenesis. Circulation. Feb 12; 2002 105(6):739–745. [PubMed: 11839631]
36. Kusama T, Mukai M, Iwasaki T, et al. 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibitors reduce human pancreatic cancer cell invasion and metastasis. Gastroenterology. Feb; 2002 122(2):308–317. [PubMed: 11832446]
37. Kusama T, Mukai M, Iwasaki T, et al. Inhibition of epidermal growth factor-induced RhoA translocation and invasion of human pancreatic cancer cells by 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibitors. Cancer Res. Jun 15; 2001 61(12):4885–4891. [PubMed: 11406567]
38. Perona R, Montaner S, Saniger L, Sanchez-Perez I, Bravo R, Lacal JC. Activation of the nuclear factor-kappaB by Rho, CDC42, and Rac-1 proteins. Genes Dev. Feb 15; 1997 11(4):463–475. [PubMed: 9042860]
39. Dulak J, Jozkowicz A. Anti-angiogenic and anti-inflammatory effects of statins: relevance to anti-cancer therapy. Curr Cancer Drug Targets. Dec; 2005 5(8):579–594. [PubMed: 16375664]

40. Desai CS, Martin SS, Blumenthal RS. Non-cardiovascular effects associated with statins. BMJ. 2014; 349:g3743. [PubMed: 25035309]

41. Dale KM, Coleman CI, Shah SA, Patel AA, Kluger J, White CM. Impact of gender on statin efficacy. Curr Med Res Opin. Mar; 2007 23(3):565–574. [PubMed: 17355737]

42. Gutierrez J, Ramirez G, Rundek T, Sacco RL. Statin therapy in the prevention of recurrent cardiovascular events: a sex-based meta-analysis. Arch Intern Med. Jun 25; 2012 172(12):909–919. [PubMed: 22732744]

43. Cui X, Xie Y, Chen M, et al. Statin use and risk of pancreatic cancer: a meta-analysis. Cancer Causes Control. Jul; 2012 23(7):1099–1111. [PubMed: 22562222]

44. Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. JAMA. Jan 4; 2006 295(1):74–80. [PubMed: 16391219]

45. Surveillance, Epidemiology, and End Results (SEER) Program. Research Data (1973–2011). National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch; (www.seer.cancer.gov)released April 2014, based on the November 2013 submission

46. Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM, Solomon DH. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. Am J Epidemiol. Aug 1; 2007 166(3):348–354. [PubMed: 17504779]

Table 1

Sociodemographic characteristics of pancreatic cancer cases and controls, University of California San Francisco

	Cases (%) n=536	Controls (%) n=869
Sex		
Men	284 (53.0)	420 (48.3)
Women	252 (47.0)	449 (51.7)
Age		
≤50	70 (13.0)	159 (18.3)
51–60	142 (26.5)	299 (34.4)
61–70	178 (33.2)	244 (28.1)
>70	146 (27.2)	167 (19.2)
Race		
Non-Hispanic White	453 (84.5)	744 (85.6)
Non-White	83 (15.5)	125 (14.4)
Body Mass Index		
≤25	267 (49.8)	472 (54.3)
25–30	205 (38.3)	265 (30.5)
>30	64 (11.9)	132 (15.2)
Cigarette Smoking		
Never Smoker	262 (48.9)	425 (48.9)
Quit >15 years ago	147 (27.4)	248 (28.5)
Quit 1–15 years ago	57 (10.6)	91 (10.5)
Current Smoker	70 (13.1)	105 (12.1)
Average Weekly Alcohol Use		
Non-drinker	190 (35.4)	347 (39.9)
1–7 drinks/week	221 (41.2)	362 (41.7)
8–14 drinks/week	71 (13.3)	67 (7.7)
15–21 drinks/week	29 (5.4)	35 (4.0)
>22 drinks/week	25 (4.7)	58 (6.7)
Pancreatitis[1]		
No	496 (92.7)	852 (98.0)
Yes	39 (7.3)	17 (2.0)
Family History of Pancreatic Cancer		
No	507 (94.6)	835 (96.1)
Yes	29 (5.4)	34 (3.9)
Type 2 Diabetes		
No	455 (84.9)	780 (89.8)
Yes	81 (15.1)	89 (10.2)
Hypercholesterolemia[1]		
No	296 (55.2)	457 (52.7)
Yes	240 (44.8)	411 (47.4)

[1] Unknown: N=1.

Table 2

Non-exclusive ever use of hypolipidemic medications, University of California San Francisco case-control study of pancreatic cancer.

Hypolipidemic Medication[1]	Cases (n=536)	Controls (n=869)
	n (%)	n (%)
Never	354 (66.0)	548 (63.1)
Ever	181 (34.0)	320 (36.9)
Any Statin	175 (32.6)	310 (35.7)
Atorvastatin	97 (18.1)	213 (24.5)
Fluvastatin	1 (0.2)	2 (0.2)
Lovastatin	31 (5.8)	46 (5.3)
Pravastatin	7 (1.3)	42 (4.8)
Rosuvastatin	9 (1.7)	11 (1.3)
Simvastatin	70 (13.1)	108 (12.4)
Bile Acid Sequestrants	3 (0.6)	3 (0.3)
Cholesterol Absorption Inhibitors	20 (3.7)	26 (3.0)
Fibrates	8 (1.5)	11 (1.3)
Nicotinic Acid	3 (0.6)	19 (2.2)
No. of Different Statin Medications		
0	360 (67.3)	558 (64.3)
1	144 (26.9)	225 (25.9)
2	26 (4.9)	62 (7.1)
3–4	5 (0.9)	23 (2.7)

[1] Unknown: N=2.

Cancer. Author manuscript; available in PMC 2016 April 15.

Table 3

ORs and 95%CIs for pancreatic cancer risk associated with statin use, University of California San Francisco.

Hypolipidemic Medications[1]	**All Participants**				**Men**		**Women**	
	Cases (%)	**Controls (%)**	**OR (95% CI)**[2]	**OR (95% CI)**[3]	**Cases/Controls**	**OR (95%CI)**[3]	**Cases/Controls**	**OR (95%CI)**[3]
Never	354 (66.2)	548 (63.1)	1.00	1.00	180/240	1.00	174/308	1.00
Non-statins	6 (1.1)	10 (1.2)	0.82 (0.29–2.34)	0.84 (0.29–2.45)	*/7	0.41 (0.10–1.77)	*/*	2.02 (0.38–10.8)
Statins and others	23 (4.3)	33 (3.8)	0.87 (0.50–1.52)	0.73 (0.39–1.37)	13/18	0.53 (0.22–1.28)	10/15	0.94 (0.37–2.36)
Statins only	152 (28.4)	277 (31.9)	0.69 (0.53–0.89)	0.66 (0.47–0.92)	88/154	0.50 (0.32–0.79)	64/123	0.86 (0.52–1.43)
Statin Use (months)[4]								
Never	354 (67.2)	548 (64.2)	1.00	1.00	180/240	1.00 (ref)	174/308	1.00
3–35	39 (7.4)	67 (7.9)	0.77 (0.51–1.18)	0.75 (0.47–1.22)	21/29	0.68 (0.34–1.36)	18/38	0.79 (0.40–1.58)
36–60	48 (9.1)	85 (10.0)	0.74 (0.51–1.09)	0.73 (0.47–1.15)	25/52	0.49 (0.27–0.91)	23/33	1.18 (0.60–2.33)
61–120	50 (9.5)	80 (9.4)	0.78 (0.53–1.15)	0.72 (0.45–1.13)	31/45	0.58 (0.32–1.08)	19/35	0.91 (0.45–1.82)
>120	36 (6.8)	74 (8.7)	0.53 (0.34–0.82)	0.51 (0.31–0.85)	24/44	0.41 (0.21–0.80)	12/30	0.62 (0.28–1.38)
P for trend			0.003	0.01		0.006		0.44
Age first used statins, (yrs)								
Never	354 (66.9)	548 (64.0)	1.00	1.00	180/240	1.00	174/308	1.00
>63	63 (11.9)	75 (8.7)	0.86 (0.57–1.28)	1.04 (0.58–1.85)	35/36	0.87 (0.39–1.95)	28/39	1.06 (0.45–2.54)
58–63	35 (6.6)	70 (8.2)	0.59 (0.38–0.92)	0.72 (0.37–1.43)	19/40	0.61 (0.24–1.54)	16/30	0.85 (0.30–2.40)
51–57	42 (7.9)	85 (9.9)	0.70 (0.47–1.04)	0.85 (0.44–1.64)	22/48	0.60 (0.23–1.58)	20/37	1.07 (0.43–2.69)
≤50	35 (6.6)	78 (9.1)	0.71 (0.46–1.09)	0.80 (0.38–1.71)	25/46	0.86 (0.31–2.36)	10/32	0.59 (0.17–2.02)
P for trend			0.008	0.45		0.64		0.55

[1] Unknown: N=2.

[2] Adjusted for age, sex.

[3] Adjusted for age, sex, race, BMI, diabetes, hypercholesterolemia, pancreatitis, alcohol use, tobacco use, family history of PC (plus duration of statin use for “age first used statins”).

[4] Unknown: N=6.

* Sample sizes of groups with 5 cases or controls are redacted to preserve anonymity.

Table 4

ORs and 95%CIs for pancreatic cancer risk associated with exclusive use of specific statins, University of California San Francisco.

	All Participants		Men		Women	
Hypolipidemic Medication Use[1]	**Ca/Ctrl**	**OR (95% CI)[2]**	**Ca/Ctrl**	**OR (95% CI)[2]**	**Ca/Ctrl**	**OR (95% CI)[2]**
Never	354/548	1.00	180/240	1.00	174/308	1.00
Atorvastatin	71/136	0.68 (0.37–1.25)	39/73	0.52 (0.22–1.22)	32/63	0.85 (0.35–2.09)
Lovastatin	18/23	1.01 (0.45–2.24)	11/11	0.99 (0.33–2.95)	7/12	0.91 (0.27–3.09)
Pravastatin	*/19	0.22 (0.06–0.82)	*/10	0.22 (0.04–1.20)	*/9	0.21 (0.02–1.97)
Rosuvastatin	7/*	2.91 (0.68–12.5)	*/*	1.42 (0.09–21.2)	*/*	4.24 (0.70–25.6)
Simvastatin	45/44	1.28 (0.67–2.44)	29/24	1.05 (0.42–2.61)	16/20	1.40 (0.54–3.60)
Multiple statins	31/85	0.44 (0.21–0.93)	18/53	0.30 (0.10–0.86)	13/32	0.58 (0.19–1.72)

Ca: Cases. Ctrl: Controls.

[1] Numbers may not sum to total N due to missing data.

[2] Adjusted for age, sex, race, BMI, diabetes, hypercholesterolemia, pancreatitis, alcohol use, tobacco use, family history of PC, duration of statin use.

* Groups with 5 cases or controls are redacted to preserve anonymity.

Table 5

ORs and 95%CIs for pancreatic cancer risk associated with statin use grouped by drug characteristics, University of California San Francisco

	All Participants		Men		Women	
Drug Characteristics[1]	**Ca/Ctrl**	**OR (95% CI)[2]**	**Ca/Ctrl**	**OR (95% CI)[2]**	**Ca/Ctrl**	**OR (95% CI)[2]**
No Hypolipidemic Meds[3]	354/548	1.00	180/240	1.00	174/308	1.00
Potency[4]						
Low (F,L,P)	22/45	0.74 (0.36–1.52)	14/24	0.70 (0.27–1.83)	8/21	0.72 (0.23–2.24)
High (A,R,S)	138/226	0.93 (0.53–1.61)	79/126	0.73 (0.33–1.59)	59/100	1.11 (0.50–2.48)
Mixed	15/40	0.58 (0.24–1.40)	8/23	0.45 (0.14–1.49)	7/17	0.70 (0.19–2.59)
Derivation						
Synthetic (A,F,R)	79/140	0.80 (0.44–1.44)	42/75	0.57 (0.25–1.31)	37/65	1.10 (0.46–2.61)
Biologic (L,P,S)	71/94	1.03 (0.57–1.85)	44/49	0.85 (0.38–1.94)	27/45	1.15 (0.48–2.76)
Mixed	25/77	0.42 (0.20–0.90)	15/49	0.28 (0.09–0.81)	10/28	0.58 (0.19–1.76)
Bioavailability[5]						
≤5% (L,S)	66/70	1.24 (0.68–2.24)	41/36	1.04 (0.45–2.39)	25/34	1.34 (0.56–3.20)
≥12% (A,F,P,R)	83/169	0.67 (0.37–1.21)	45/91	0.49 (0.21–1.12)	38/78	0.91 (0.38–2.16)
Mixed	26/72	0.44 (0.21–0.96)	15/46	0.27 (0.09–0.81)	11/26	0.69 (0.22–2.13)
Solubility						
Lipophilic (A,F,L,S)	159/260	0.91 (0.53–1.58)	94/142	0.75 (0.35–1.62)	65/118	1.06 (0.48–2.37)
Hydrophilic (P,R)	10/22	0.69 (0.28–1.72)	*/11	0.40 (0.10–1.63)	6/11	1.18 (0.34–4.18)
Mixed	6/29	0.36 (0.12–1.07)	*/20	0.21 (0.05–0.97)	*/9	0.70 (0.14–3.31)
CYP450 3A4 Metabolization						
No (F,P,R)	10/22	0.69 (0.28–1.71)	*/11	0.40 (0.10–1.65)	6/11	1.15 (0.33–4.09)
Yes (A,L,S)	158/258	0.91 (0.53–1.57)	93/142	0.75 (0.35–1.63)	65/116	1.05 (0.47–2.36)
Mixed	7/31	0.39 (0.14–1.11)	*/20	0.29 (0.07–1.17)	*/11	0.56 (0.12–2.68)
Active Metabolites						
None/Minor (F,P,R)	10/22	0.69 (0.28–1.71)	*/11	0.40 (0.10–1.65)	6/11	1.15 (0.33–4.09)
Major (A,L,S)	158/258	0.91 (0.53–1.57)	93/142	0.75 (0.35–1.63)	65/116	1.05 (0.47–2.36)
Mixed	7/31	0.39 (0.14–1.11)	*/20	0.29 (0.07–1.17)	*/11	0.56 (0.12–2.68)

	All Participants		Men		Women	
Drug Characteristics[1]	**Ca/Ctrl**	**OR (95% CI)**[2]	**Ca/Ctrl**	**OR (95% CI)**[2]	**Ca/Ctrl**	**OR (95% CI)**[2]
Renal Excretion						
≤10% (A,F,L,R)	102/172	0.86 (0.49–1.52)	56/94	0.65 (0.29–1.44)	46/78	1.12 (0.46–2.60)
≥13% (P,S)	49/65	1.06 (0.57–1.96)	31/34	0.92 (0.39–2.18)	18/31	1.16 (0.46–2.91)
Mixed	24/74	0.44 (0.21–0.94)	14/45	0.32 (0.11–0.93)	10/29	0.54 (0.18–1.66)
Elimination						
$t_{1/2}$ ≤ 3h (F,L,P,S)	71/94	1.04 (0.58–1.86)	44/49	0.87 (0.38–1.97)	27/45	1.15 (0.48–2.76)
$t_{1/2}$ ≥ 11h (A,R)	78/140	0.79 (0.44–1.43)	41/75	0.57 (0.25–1.30)	37/65	1.10 (0.46–2.61)
Mixed	26/77	0.44 (0.21–0.94)	16/49	0.30 (0.11–0.88)	10/28	0.58 (0.19–1.76)

[1] Numbers may not sum to total N due to missing data.

[2] Adjusted for age, sex, race, BMI, diabetes, hypercholesterolemia, pancreatitis, alcohol use, tobacco use, family history of PC, duration of statin use.

[3] Referent group for all analyses.

[4] Starting dose (potency): low 20–40mg, high 10–20mg.

[5] ORs for ≥12% and ≤5% bioavailability categories are statistically significantly different in analyses of all participants (p=0.01) and of men (p=0.01).

* Groups with ≤5 cases or controls are redacted to preserve anonymity.