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Meta-Analysis

Statin use is associated to a reduced risk of pancreatic cancer: A meta-analysis

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ABSTRACT

Background: Previous studies investigating the association between statin use and pancreatic cancer (PDAC) risk for a possible chemopreventive effect gathered heterogeneous results.
Aims: To conduct a systematic review and meta-analysis to clarify this association.
Methods: Comprehensive literature search of articles published up to February 2018, including case-control (CC),cohort studies (C), randomized controlled trials (RCTs) assessing association between statin use and PDAC risk. Studies had to report odds ratio (OR)/relative risk (RR), estimates with 95% confidence interval (CI), or provide data for their calculation. Pooled ORs with 95%CIs were calculated using random effects model, publication bias through Begg and Mazumdar test and heterogeneity by I^2 value.
Results: 27 studies(13 CC, 9C, 5 RCTs) for a total population of 11,975 PDAC/3,433,175 controls contributed to the analysis. The overall pooled result demonstrated a reduced PDAC risk among statin users (OR 0.70; 95% CI 0.60–0.82; $p < 0.0001$), compared to non-users. Sensitivity analyses suggested the risk reduction to be more important in CC studies, studies conducted in Asia and Europe, in males and atorvastatin users. No publication bias found.
Conclusions: The present meta-analysis suggests that statin use is associated with an overall PDAC risk reduction of 30%. Further studies are needed to clarify the association.

1. Introduction

Pancreatic adenocarcinoma (PDAC) has a dismal prognosis with a 5-year survival rate of less than 6%, and is estimated to become the 2nd cause of cancer-related death within 2030 [1,2]. The delayed diagnosis leads to only 20% of patients being eligible for surgery at diagnosis [3]. Furthermore, chemotherapy and radiotherapy can only slightly improve survival [4]. Screening policies are currently under investigation only for high risk individuals and in experimental settings [5].

In this context, prevention might play a key role both in terms of modifying lifestyle risk factors such as smoking, excessive alcohol intake, and overweight, but also in terms of investigating the role of chemopreventive drugs which, at the moment, lack of evidence supporting their use to reduce the incidence of PDAC.

Statins are very commonly prescribed for primary and secondary cardiovascular prevention and act as inhibitors of the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase [6]. The mevalonate pathway they act on also impacts on multiple signaling cascades such as Ras, MEK, mTOR, BCL-2 and Rho kinases, which play a role in carcinogenesis and tumor progression [7–9]. Statins also have an immunomodulatory and anti-inflammatory activity and can inhibit angiogenesis [10,11], which can all be related to their antineoplastic effect. Nevertheless, their role as chemopreventive agents is still controversial, although a few meta-analyses associated their use to a risk reduction mostly for gastrointestinal tract tumors [12–14]. Data on the association between the use of statins and the risk of PDAC are heterogeneous and the latest meta-analysis on the topic by Cui et al. from 2012 showed no significant pooled effect [15]. However, in the past few years, many other large studies conducted specifically on the topic have been published, most of which suggested a protective effect.

Therefore, the primary aim of the study was to perform an updated meta-analysis to assess the association between the use of statins and the risk of PDAC.

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2. Materials and methods

2.1. Search strategy

A computerized literature search of MEDLINE and the Cochrane Database of Systematic Reviews for prior systematic reviews and meta-analyses on association between the use of statins and the occurrence of PDAC revealed two previous meta-analyses on this topic published in 2008 [16] and in 2012 [15]. In the search for original studies, a MEDLINE search was run until February 1st, 2018. Specific search terms were defined and are detailed in Appendix A. The titles of all identified articles were screened to evaluate their relevance and the abstracts and/or full texts of selected, potentially relevant papers were further evaluated. With a snowball method, additional articles were searched by hand-searching reference lists of all the articles retrieved to identify potentially relevant studies. Searchers were physicians with experience in pancreatic disorders.

2.2. Inclusion and exclusion criteria

Studies related to our research question were included if they were either randomized controlled trials (RCTs), cohort (C) or case-control (CC) studies with available data for a quantitative synthesis; studies had, therefore, to include the relative risk (RR) or odds ratio (OR) for occurrence of PDAC associated with the exposure to statin versus placebo or no treatment, or sufficient information necessary for their estimate. Thus, included studies had to: (a) evaluate exposure to statin in a cohort or population that included internal controls; (b) evaluate the occurrence or diagnosis of PDAC, and (c) report the RR or OR with 95% CI or original raw data sufficient to evaluate the hypothesized effect. In case of report of adjusted and unadjusted OR or RR, the adjusted one was selected. No language filters were applied. In the event of duplicate publications, the most recent or more complete publication was used. Two independent reviewers (L.A. and G.C.) completed study identification and selection, and disagreements were discussed with another reviewer (P.G.A.). Excluded studies and reasons for exclusion were recorded.

2.3. Data extraction and quality assessment

From the studies that met the eligibility criteria, the following data were extracted into a Microsoft Excel spreadsheet (2016 Edition; Microsoft Corp., Redmond, Washington, USA): (a) study — first author, year of publication, study design, country, study accrual period, and type of interview; (b) cases — definition (i.e. clinical charts, histological diagnosis, or other means), number, gender, and age; (c) controls — number and source of controls and matching design if appropriate; (d) type of exposure — definition, type of statin used, dosage, and length of exposure if available, and (f) main study outcome, type of outcome measures and eventual adjustment to the analysis.

Quality of each study included in the quantitative synthesis was assessed by two independent reviewers (L.A. and G.C.) using specific quality appraisal tools developed for either case-control studies, cohort studies [17] and randomized controlled studies [18]. Disagreements were discussed with a third reviewer (P.G.A.). We considered the 50th percentile of each scale to separate low-quality and high-quality studies.

2.4. Statistical analysis

A meta-analysis of all eligible studies identified was planned using the software package Comprehensive Meta-Analysis (Biostat, Englewood, N.J., USA) with calculation of the pooled estimates (OR and 95% CI) using the DerSimonian–Laird method and a random-effects model. Random-effects models were used as they consider both sampling variance within the different studies and the variation in the underlying effect across studies. The assumption of variation in the underlying effect seems plausible given the different populations, study designs, drug type, and exposure assessment methods used in the original studies. The quantity of heterogeneity was assessed by means of the I^2 value and Cochran's Q statistics [19–21]. An I^2 value of $\leq$25% was considered as trivial heterogeneity and an I^2 value of $\geq$75% as important heterogeneity. Publication bias was assessed using the Begg and Mazumdar's test. A p-value < 0.05 was accepted as statistically significant. We developed the following a priori hypotheses that would explain heterogeneity and planned sensitivity analyses for (a) study design (RCT or Cohort or Case-Control); (b) quality of the study (high or low quality); (c) area of origin (i.e. Asia, or Europe or Americas); (d) gender; (e) type of statins, dosage and length of use; (f) smoking status; (g) presence of diabetes. The methodology was developed and reviewed with the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) statement [22] and the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) [23] and the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist were checked for items that should be included in the report.

3. Results

3.1. Search result and study selection

A total of 2040 references were identified by the MEDLINE search (Fig. 1). After the evaluation of titles and abstracts, 1161 records were removed as not related to the study topic. Thus, the remaining 879 studies were examined in detail, leaving 21 as potentially appropriate for inclusion into the meta-analysis. An additional 7 records were added after reference list evaluation. Eventually, 28 relevant studies were therefore identified. However, 1 of these studies [24] reported on a duplicate cohort, and, accordingly, the smaller study [25] was excluded. Therefore 27 studies [24,26–51] were included in the quantitative synthesis (5 RCTs, 9C studies and 13 CC studies), examining a total population of 4,978,706 subjects. There was absolute agreement amongst the reviewers for the assessment of eligibility and selection of studies.

3.2. Study characteristics

A summary of relevant studies, listing the population characteristics, exposures, and outcome is shown in Tables 1 and 2.

Concerning geographic area of enrollment, 11 studies came from North America, 9 from Europe, 4 from Asia, 1 from Australia, 2 included a worldwide population. Accrual periods ranged between 1976 and 2016; 14 studies recruited prospectively, 13 retrospectively. Most PDAC diagnoses were based on health registries, exposure to statins was assessed in 8 studies through direct patient interview or obtained by health registries for prescriptions in 14 studies. In the 5 RCTs statins were administered as part of study design. Controls enrolled were either hospital controls, visitors or population controls for case-control studies. For cohort studies, mean follow-up was 4.8 years. Most of the studies included all types of statins, except for five which evaluated only some specific statin type. Most studies included both genders, except for three that were only conducted on women, and one which included mostly men. Ten studies aimed specifically at PDAC onset, while twelve aimed at any cancer onset, and the other five aimed either at cardiovascular events or events generally related to statin use.

Table 1
Characteristics of the included studies in terms of Country, study accrual period, study design, case definition source of controls and matching design if appropriate, sex and age of included individuals, follow-up length.

Reference	Year	Country	Study accrual period	Study setting and design	Study cases	Source of controls	Male Female	Age (years)	FU (years)
Clearfield	2001	USA	1990–1993	Multicentre RCT	Patients with hypertriglyceridemia/hypercholesterolemia	Same as cases	997 F	Mean 57 ± 7	5.2
Serruys	2002	Worldwide	1996–1998	Multicentre RCT	Patients undergoing percutaneous coronary intervention	Same as cases	1406 M 271 F	Mean 60	3.9
Strandberg	2004	Scandinavia	1988–1989	Multicentre RCT	Patients with coronary heart disease	Same as cases	3617 M 827 F	Range 35–70	10.4
Graaf	2004	Holland	1985–1998	Multicentre CC	Subjects with prescriptions of cardiovascular drugs from pharmacies database and cancer	Same as cases, without cancer	9785 M 10,320 F	NR	NA
Kaye	2004	USA	1990–2002	Multicentre CC	Subjects with prescriptions of cardiovascular drugs from pharmacies database and cancer	Random subjects who neither used antihyperlipidaemic drugs nor had hyperlipidaemia	8978 M 9110 F	NR	NA
Sato	2006	Japan	1991–1995	Unicentre RCT	Patients with coronary heart disease	Same as cases	215 M 48 F	NR	5
Coogan	2007	USA	1991–2005	Multicentre CC	Hospital cancer patients	Hospital controls with diagnoses unrelated to statin use and no cancer.	NR	NR	NA
Khurana	2007	USA	1998–2004	Multicentre CC	Veterans seen at the clinic	Same as cases without cancer	443,567 M 40,166 F	Mean 61.2 ± 15.1	NA
Peto	2008	Worldwide	2001–2008	Multicentre RCTs	Patients included in trials with: aortic stenosis (SEAS), chronic kidney disease (SHARP), acute coronary syndrome (IMPROVE-IT)	Same as cases	NR	Mean 68, 61 and 62 in the 3 RCTs	4.1 and 2.7 and 1 in the 3 RCTs
Karp	2008	Canada	1998–2004	Multicentre C	Subjects discharged after AMI and cancer	Same as cases, without cancer	18,312 M 11,764 F	NR	1
Bradley	2010	UK	1995–2006	Multicentre CC	Patients from GP practice	Same as cases without cancer	4884 M 4211 F	Mean 57.3	NA
Haukka	2010	Finland	1996–2005	Multicentre C	National prescription register	Same as cases	471,660 M 473,302 F	Mean 60	3
Chiu	2011	Taiwan	2003–2008	Multicentre CC	National Health Insurance (NHI) database	Hospital controls with diagnoses unrelated to statin use and no cancer	520 M 430 F	Mean 68.8	NA
Vinogradova	2011	UK	1998–2008	Multicentre CC	Patients from GP database	Same as cases without cancer	NR	NR	NA
Marelli	2011	USA	1990–2009	Unicentre C	General Electric (GE) Centricity database	Same as cases	48,059 M 43,655 F	Mean 62.2	4.6 ± 2.2
Jacobs	2011	USA	1997–2007	Multicentre C	Study-II (CPS-II) Nutrition Cohort	Same as cases	60,059 M 73,196 F	NR	NR
Leung	2013	Taiwan	2000–2008	Multicentre CC	Patients registered with the national health insurance bureau that contributed to the national health insurance research database	Same as cases, without cancer	16,150 M 18,055 F	Mean 58.3 ± 12.1	4.05 ± 2 and 4.2 ± 2.5
Carey	2013	UK	2004–2008	Multicentre CC	Norfolk and Norwich University Hospital NHS Trust and The Leicester General Hospital NHS Trust patients.	Dermatology patients with basal cell carcinoma	379 M 379 F	Median 71, range 48–73	NA
Chen	2015	Taiwan	1997–2010	Multicentre C	Patients with type II diabetes	Same as cases	607,215 M 533,402 F	Mean 57,5 ± 13,5	6.1
Walker	2015	USA	2006–2011	Multicentre CC	UCSF gastrointestinal medical and surgical oncology clinics, San Francisco's California Pacific Medical Center and the Cancer Prevention Institute of California patients	Same as cases, but recruited at UCSF general medicine primary care clinics, without cancer	704 M 701 F	NR	NA
Fang Kho	2016	Australia	2007–2011	Multicentre CC	Residents of Queensland	Selected from the Australian Electoral Roll, without cancer	708 M 467 F	Mean 65.3 and 66.6	NA
Simon	2016	USA	1993–2005	Multicentre C	Postmenopausal women participating to Woman Health Initiatives	Same as cases	160,578 F	NR	8.69 ± 4.59
Kautzky-Willer	2016	Austria	2006–2007	Multicentre C	Austrian hospitalized patients	Same as cases	733,069 M 998,241 F	NR	NR
Archibugi	2017	Italy	2006–1016	Unicentre CC	Consecutive PDAC cases	Hospital controls and Visitors, without cancer	627 M 597 F	Mean 68.1 ± 11.6 cases, 67.9 ± 11.9 controls	NA
Kabat	2017	USA	1993–1998	Multicentre C	Postmenopausal women taking part to Women's Health Initiative	Same as cases	16,522 F	Mean 65.9 ± 7.1 and 64.1 ± 7.3	NR
Bang	2018	Denmark	1995–2014	Multicentre C	Patients with chronic pancreatitis	Same as cases	400 M 278 F	Mean 53	NA
Hamada	2018	USA	1976–1986	Multicentre C	Nurses' health study and health professionals follow-up study	Same as cases	51,529 M 121,700 F	Mean 65.8 and 68 and 65.7 and 67.1	8.08

USA = United States of America; UK = United Kingdom; RCT = randomized controlled trial; C = cohort; CC = case-control; GP = general practitioner; NHS = national health service; UCSF = University of California San Francisco PDAC = pancreatic ductal adenocarcinoma; M = males; F = females; FU = follow-up; NR = not reported; NA = not applicable.

Table 2
Characteristics of the included studies in terms of case diagnosis, type of exposure, type of statin, main study outcome, type of outcome measures and adjustment to the analysis.

Reference	Case diagnosis	Exposure source	Main outcome	Outcome measure	Type of statin	Adjustment for confounders	Study quality
Clearfield	Not reported	Trial records	Efficacy and safety of statins	RR	Lovastatin	ND	4
Serruys	Not reported	Trial records	Efficacy and safety of statins on CVD	Incidence rate	Fluvastatin	ND	7
Strandberg	Cancer registries	Trial records	Cancer diagnosis	RR	Simvastatin	Age, sex, hypertension, smoking, myocardial infarction, and diabetes at baseline	4
Graaf	Hospital discharge records	Pharmacy database	Cancer diagnosis	Risk estimate	All (79% simvas-tatin)	Diabetes, prior hospitalizations, chronic disease score, use of diuretics, ACE inhibitors, calcium channel blockers, hormones, NSAIDs, other lipid-lowering drugs.	6
Kaye	GP records	GP records	Cancer diagnosis	RR	All	ND	5
Sato	Cancer registries	Trial records	Cancer diagnosis	HR	Pravastatin	Sex, age, smoking status	2
Coogan	hospital discharge and pathology records	Nurse administered questionnaire	Cancer diagnosis	OR	All	Gender, BMI, alcohol use, race, years of education, pack-years of smoking and NSAID use	3
Khurana	Veterans Integrated Service Networks and Veteran Affairs database	Computerized pharmacy database	Pancreatic cancer diagnosis	OR	All	"significant covariates for pancreatic cancer"	2
Peto	safety data from RCTs	Trial records	Cancer diagnosis	RR	Simvastatin	ND	5
Karp	hospital discharge records	Provincial physicians and drug claims database	Cancer diagnosis	Incidence rate	All	ND	3
Bradley	GP records	GP records	Pancreatic cancer diagnosis	OR	All	Smoking status, BMI, alcohol use, history of pancreatitis, history of diabetes and history of cancer	6
Haukka	National Cancer Registry	National Prescription Database	Cancer diagnosis	RR	All	Sex, age, and follow-up period	5
Chiu	National Health Insurance (NHI) database records	National Health Insurance Prescription Database	Pancreatic cancer diagnosis	OR	All	Diabetes, chronic pancreatitis, number of hospitalizations, and use of other lipid-lowering drugs	5
Vinogradova	GP records	GP records	Cancer diagnosis	OR	All	Townsend quintile, BMI, smoking status, myocardial infarction, coronary heart disease, diabetes, hypertension, stroke, rheumatoid arthritis, use of NSAIDs, Cox2-inhibitors, aspirin	6
Marelli	Database record	Database record	Cancer diagnosis	HR	N.R.	Propensity score, concomitant diagnoses, use of various medications, and metabolic measurements (LDL, VLDL, total cholesterol, triglycerides, BMI), diabetes, hypertension, peripheral vascular disease, and ischemic heart disease	6
Jacobs	Self-report or cancer registries or through medical records	Questionnaire	Cancer diagnosis	RR	N.R.	Age, sex, race, education, smoking status, use of NSAIDs, BMI, physical activity, history of elevated cholesterol, diabetes, heart disease and hypertension.	8
Leung	Database record	Database record	Cancer diagnosis	HR	All	Charlson comorbidity index, diabetes mellitus, use of NSAIDs, other lipid-lowering agents, cardiovascular drugs, or hormone-replacement therapy	4
Carey	Hospital records	Hospital records	Pancreatic cancer diagnosis	OR	All	Smoking status and type 2 diabetes mellitus	4
Chen	Database record	Database record	Pancreatic cancer diagnosis	HR	All	Age, gender, urbanization, monthly insured amount with unit of New Taiwan Dollars, history of pancreatitis, use of metformin, thiazolidinedione, sulfonylurea, insulin, NSAIDs	5

Table 2 (*Continued*)

Reference	Case diagnosis	Exposure source	Main outcome	Outcome measure	Type of statin	Adjustment for confounders	Study quality
Walker	Medical records that included histological or cytological confirmation	Direct interview	Pancreatic cancer diagnosis	OR	All	Age, sex, race, BMI, diabetes, hypercholesterolemia, pancreatitis, alcohol use, tobacco use, family history of pancreatic cancer (plus duration of statin use for "age at first statin use")	3
Fang Kho	Clinical or cancer registry	Direct interview	Pancreatic cancer diagnosis	OR	N.R.	Age, sex, pack-years of smoking, alcohol use, diabetes history, and adult BMI, aspirin use	6
Simon	Review of medical and pathology record	Direct interview	Pancreatic cancer diagnosis	HR	All	Age, BMI, ethnicity, smoking status, education, alcohol use, physical activity, >30% energy from fat, waist circumference, current medical care provider, NSAID use, general health, medical history	6
Kautzky-Willer	Medical record	Medical record	Cancer diagnosis	OR	All	N.R.	3
Archibugi	Histologic diagnosis	Questionnaire	PDAC diagnosis	OR	All	Age, sex, BMI, PDAC family history, chronic pancreatitis, diabetes, smoking, alcohol drinking	5
Kabat	Review of medical and pathology reports	Direct interview	Cancer diagnosis	HR	N.R.	Age, smoking status, pack-years of smoking, alcohol intake, BMI, physical activity, aspirin use, education, ethnicity, allocation to the OS or specific arm of clinical trials	7
Bang	Hospital discharge records	Claims database	All-cause mortality an PDAC diagnosis	HR	All	Age, sex, year at cohort entry, socioeconomic status, Charlson index score, use of multienzyme preparations, alcohol dependence, chronic obstructive lung disease together with nicotine dependence as a marker of smoking, indication for statin use	4
Hamada	Review of medical records, death certificates and cancer registries	Questionnaire	PDAC diagnosis	HR	All	Age, sex, race/ethnicity, smoking status, history of diabetes mellitus, BMI, physical activity, alcohol intake and multivitamin use	8

RCT = randomized controlled trial; GP = general practitioner; CVD = cardiovascular disease; PDAC = pancreatic ductal adenocarcinoma; HR = hazard ratio; RR = relative risk; OR = odds ratio; NR = not reported; ND = not done; BMI = body mass index; OS = overall survival; ACE = angiotensin-converting enzyme; NSAID = non-steroidal anti-inflammatory drug; LDL = low density lipoprotein; VLDL = very low density lipoprotein.

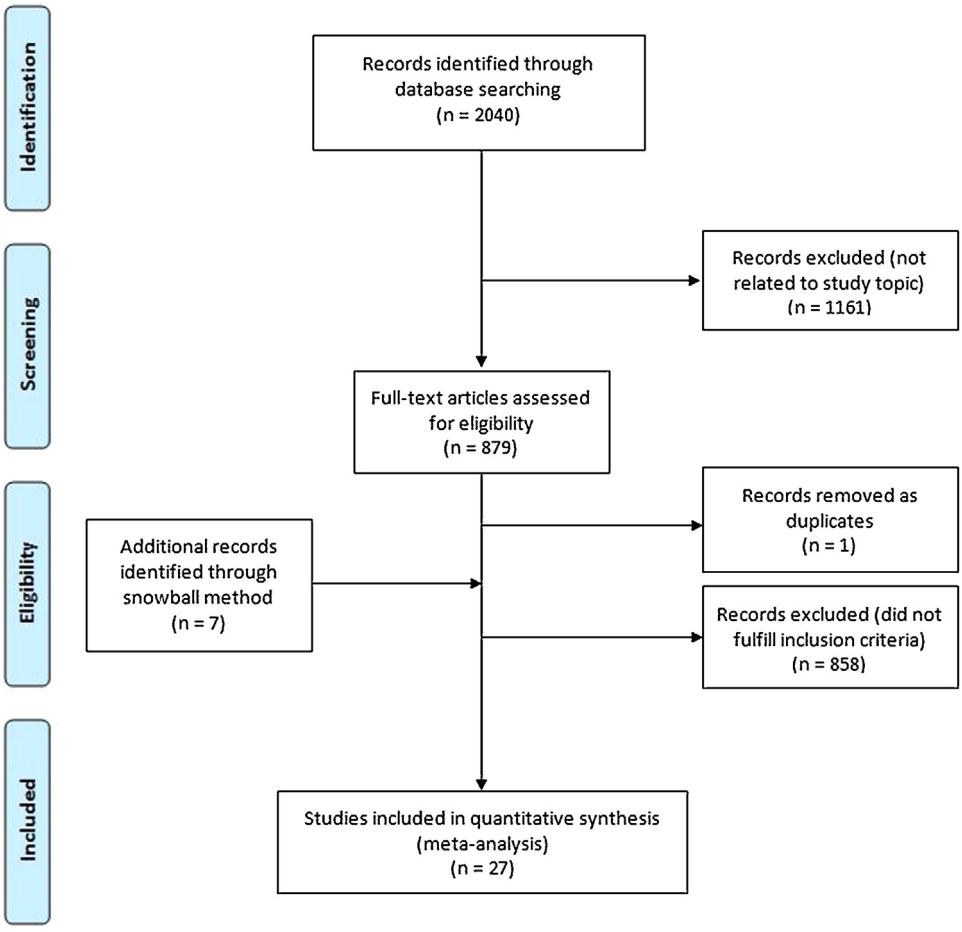

Fig. 1. Database search and selection of studies according with PRISMA guidelines.

3.3. Association between the use of statins and risk of pancreatic cancer

The overall rate of PDAC in the studies providing this information was 0.27% (3,428/1,261,902) in subjects exposed to statins, and 0.42% (9,315/2,184,016) in non-exposed ones. Fig. 2 shows the estimated OR for the risk of PDAC among statin users compared to non-users in all the 27 studies. The pooled estimated OR was 0.70 (95% CI: 0.60–0.82; $p < 0.0001$) suggesting a protective effect. There was considerable heterogeneity for this global analysis with an I^2 value of 90.05% and Q value being 321.65. No publication bias was found (Begg and Mazudmar Kendall's tau = −0.12; $p = 0.29$).

3.4. Sensitivity analyses

In order to evaluate reasons for heterogeneity and investigate which patients would benefit the most of a possible chemopreventive action of statins or which statin was the most effective, further pre-planned sensitivity analyses were performed. When considering separately studies with different design (see Supplementary Fig. 1), a protective effect was confirmed with a similar figure for the 13 case-control studies with an OR = 0.61 (95% CI: 0.50–0.75; $p < 0.0001$) and slightly reduced heterogeneity ($I^2 = 89.4\%$, Q = 160.50) as compared to the global analysis. On the other hand, in the 9 cohort studies (OR 0.85; 95% CI 0.66–1.09; $p = 0.20$) and in the 5 RCTs (OR = 1.00; 95% CI 0.54–1.85; $p = 0.98$) there was no statistically significant effect of statins. Heterogeneity was considerable for cohort studies ($I^2 = 92.0\%$, Q = 113.44) while there was no heterogeneity for RCTs ($I^2 = 0\%$, Q = 0.406). The quality score of the included studies ranged between 2 and 7 for RCTs (on a maximum of 7), between 2 and 6 for CC and between 3 and 8 for C studies (as shown in Table 2) (on a maximum of 9). Among the 18 high quality studies a protective effect of statins was not confirmed (OR 0.89; 95% CI: 0.70–1.14; $p = 0.39$; $I^2 = 92.9\%$), while for the 9 lower quality studies, which comprehended mostly case-control studies, a lower risk of PDAC was registered (OR 0.57; 95% CI: 0.45–0.73; $p < 0.0001$; $I^2 = 90.1\%$).

In keeping with our a priori hypotheses for heterogeneity, we also performed a sensitivity analysis for geographic area of origin. Notably, while a protective effect of statins was confirmed in studies conducted in Asia (OR 0.60; 95% CI: 0.42–0.86; $p = 0.006$) with a lower heterogeneity ($I^2 = 47.4\%$) and Europe (OR 0.61; 95% CI: 0.48–0.78; $p < 0.0001$; $I^2 = 93.3\%$), this was not the case for studies conducted in North America (OR 0.81; 95% CI: 0.61–1.08; $p = 0.16$; $I^2 = 86.1\%$).

Fig. 3 shows the sensitivity analysis for area of origin, as well as for gender and type of statin, suggesting that the protective effect is limited to males and to atorvastatin users, but with heterogeneity persistently high for gender (respectively 95.9% for females, 94.7% for males), and variable for type of statin (95.6% for simvastatin, 85% for rosuvastatin, 50.6% for atorvastatin, 96% for fluvastatin, 0% for lovastatin, 40.2% for pravastatin). Analysis on smokers/non-smokers, diabetic/non-diabetic patients or stratified for statin dosage were planned but not performed as these data were reported only in a minority of studies. As far as regards the length of statin use, although this information was only available for 7 of the 27 studies, and the cut-offs for subgroups of "Length of treatment" were different, an additional analysis on these 7 studies

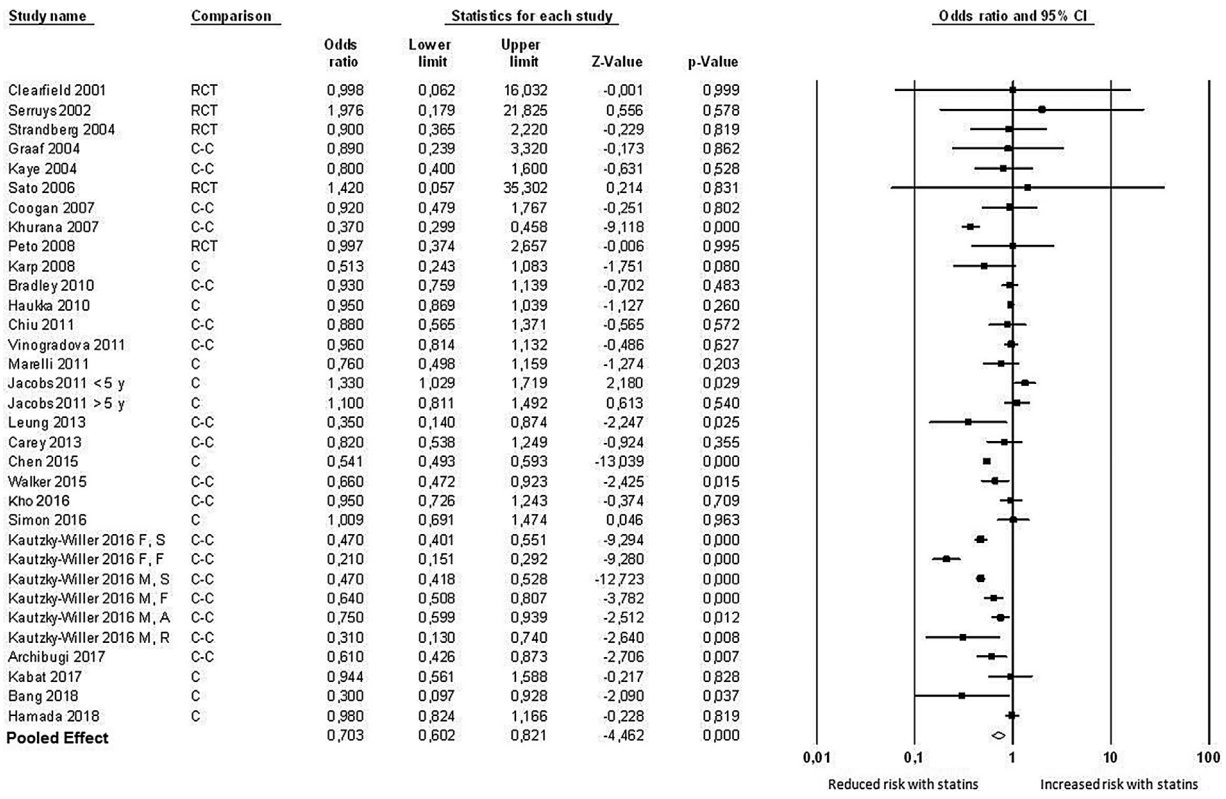

Fig. 2. Overall analysis with pooled odds ratio (OR) showing a significant risk reduction of pancreatic cancer associated with the use of statins: OR = 0.70 (95% CI: 0.60–0.82; $p < 0.0001$). There is considerable heterogeneity ($I^2 = 90\%$).

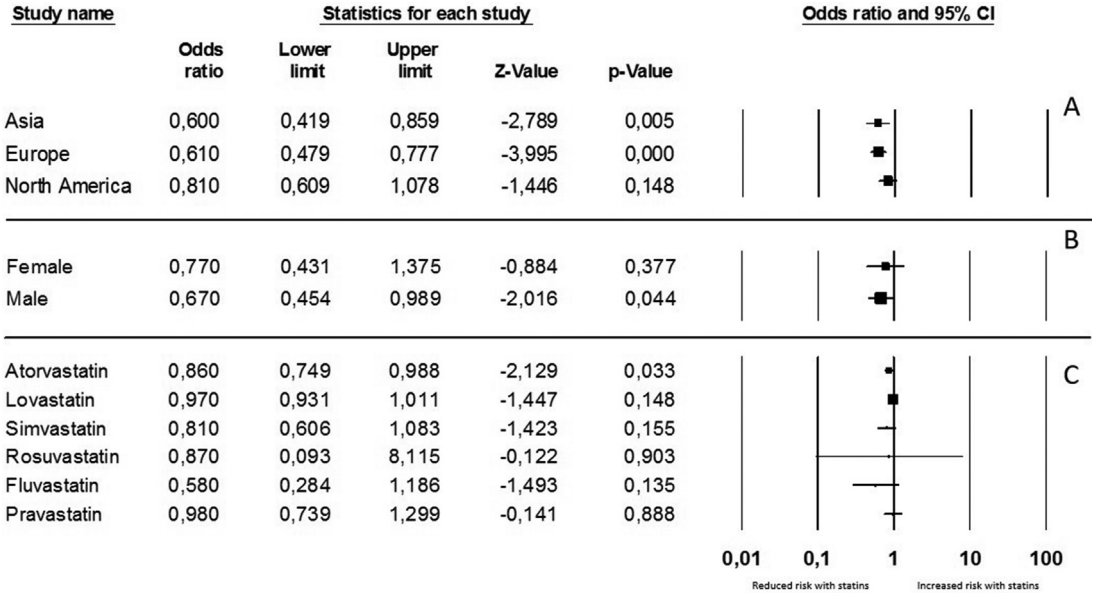

Fig. 3. Sensitivity analyses according with country of origin of included studies (A), gender (B) and type of statin (C). A protective effect is evident for studies conducted in Asia and Europe, unlike for those conducted in North America, and for males but not females. Among the different statin types a protective effect is significant for atorvastatin only.

separating "short-term" from "long-term" statin users was performed (see Supplementary Fig. 2). A similar, non-significant, risk reduction for short-term (OR 0.9; 95% CI 0.71–1.12) and long-term (OR 0.85; 95% CI 0.69–1.03) statin users was registered, although some trend toward significant risk reduction for longer exposure was appreciated.

4. Discussion

The present meta-analysis examining the association between the use of statins and occurrence of pancreatic cancer included 27 studies (13 case-control studies, 9 cohort studies and 5 randomized controlled trials) for a total population of about 5 million subjects.

Overall, we found a protective association between the use of statins and the risk of pancreatic cancer with a 30% risk reduction (OR 0.70; 95% CI 0.60–0.82; p < 0.0001).

The previous most recent meta-analysis on the topic by Cui et al. [15] included only 16 studies and found no association with the risk.

In the present meta-analysis, significant heterogeneity was observed among all studies (I^2 = 90.05), especially in case-control studies (I^2 = 89.4%) and cohort studies (I^2 = 92.0%), while RCTs had no heterogeneity (I^2 = 0%); this supports the importance of having adopted a random-effects model.

In our sensitivity analyses, case-control studies showed similar results with a significant risk reduction of 40%, while this was not the case for cohort studies and RCTs. While case-control studies are known to be lower in the evidence hierarchy, they might, however, present some advantages in certain circumstances compared to RCTs and cohort studies. Case-control studies, importantly, accounted alone for about half of included PDAC cases included in the present meta-analysis and represented most of the studies aiming primarily at PDAC diagnosis (see Table 2). Also, case-control studies might be more efficient than cohort studies for rare diseases or diseases with a long latency period between exposure and disease manifestation such as PDAC [52].

On the other hand the included RCTs typically reported data on PDAC incidence as part of a *post hoc* analysis aiming mainly on the effect of statins on cardiovascular mortality. Moreover, given the small number of PDAC cases in the RCTs (41 cases in total), these studies were not adequately powered to detect a significant difference between the statin and placebo groups regarding the development of PDAC. Finally, as patients enrolled in RCTs were not actively screened for PDAC development, affecting therefore its detection rate, given the relatively short follow-up duration of these RCTs results should be considered with caution.

One should, however, consider the possibility that the observed PDAC risk reduction of case-control studies represents an overestimate of its true effect. In fact, observational studies lack, by study design, the experimental random allocation of the intervention which is necessary to test the exposure-outcome hypotheses. Despite adjusting for many covariates, it is not possible to eliminate the potential residual confounding, such as the confounding by indication.

As far as regards country of origin, a similar risk reduction was seen in our sensitivity analysis for studies performed in Europe and Asia. This was not the case for studies conducted in USA, probably due to different environmental factors such as diet, diabetes and obesity condition.

Concerning our sensitivity analysis for gender, the protective effect was confirmed for males but not for females, which could be explained as the male population was overall larger (about 500,000 males) compared to females (about 200,000), or as PDAC is generally more incident in males [53].

Regarding statin type, a protective effect was clear for atorvastatin, but not for other statins (see Fig. 3). Atorvastatin is one of the lipophilic statins, together with lovastatin, simvastatin and fluvastatin, which differ from hydrophilic statins (e.g., pravastatin, rosuvastatin) in terms of better lipid solubility and membrane permeability [54], which could partly explain this effect. Another reason could be as atorvastatin is one of the most commonly employed statin type.

The strengths of the present study are represented by the systematical appraisal of the available literature and by the inclusion of recent studies that were not considered in previous publications with a similar aim. Indeed, compared to the previous latest meta-analysis on this topic by Cui et al., the present study: (1) included 13 additional studies [24,34,35,39,42–51], with a final population that is more than twice as numerous compared to the one reported by Cui et al. Two studies included by Cui et al. were instead not included [55,56] as they were either published as abstract or would not present data on RR or OR or sufficient raw data for their calculation; (2) some additional sensitivity analyses were performed concerning study design, geographic area of origin, quality of the included studies, type of statins and patients' gender, which highlighted important differences in the potential protective effect. (3) Finally, among the 10 studies included in our analysis that aimed specifically at evaluating PDAC incidence or risk (see Table 2), only 4 were included in the analysis by Cui et al., as most of them were published in the latest few years. In fact, as shown in the performed cumulative analysis (Supplementary Fig. 3), these more recent studies, whose primary aim was related to PDAC risk, helped the forest plot get a twist toward statins being protective.

There are, however, some limitations that need to be considered. First, the wide heterogeneity among studies. To deal with this heterogeneity we employed a random-effects model for all analyses, which might nevertheless produce wider CIs, and developed a priori hypotheses for sensitivity analyses considering likely sources of heterogeneity. Howbeit, the observed heterogeneity between studies remained substantial. An explanation for this heterogeneity could be that the included studies vary greatly in terms of design (retrospective vs prospective), aim (specific risk of PDAC or of multiple cancers or other complications/benefits related to statin use), population (only females or males in some studies), exposure definition (interventional trial vs general practitioner database vs hospital medical records vs national prescriptions or pharmacy databases vs questionnaire), baseline statin use, cancer diagnosis, control definition, confounders evaluated and follow-up length.

Another limitation is that analysis on smokers/non-smokers, diabetic/non-diabetic patients were not performed as these data were reported only in a minority of studies. Furthermore, the analysis by length of statin use (Supplementary Fig. 1) is limited to a small number of studies which also employed different definitions for "long-term" use.

Another potential limitation of the study might be represented by the fact that statin use may be associated with a particular healthier lifestyle that may result protective per se. However, data on the association between statin use and relevant lifestyle factors for pancreatic cancer are sparse. In a recent study conducted in Australia, factors associated with "high-intensity" use of statins were previous cardiovascular disease, no or insufficient physical activity, obesity and >2 alcoholic drinks daily [57] which are, indeed, associated with an increased risk of pancreatic cancer. In a previous study, smoking status, alcohol consumption and exercise level did not differ between users and non-users of statins [58]. Similarly, in a general practice database study from the UK [59], subjects who were prescribed statins did not change their lifestyle in terms of diet and physical activity. Overall, it seems that subjects who are prescribed statins do not change their lifestyle toward a healthier one. Unfortunately, the studies included in the present meta-analysis did not contain individual patients' data sufficient to investigate these factors. At any rate, the included risk estimates from individual studies were usually corrected for factors such as BMI, smoking, alcohol intake and in some instances smoking (see Table 2).

As our findings might only suggest an association between the use of statins and reduced risk of developing PDAC, evaluation of the possible mechanisms is crucial. In fact, the mechanisms through which statins might exert a protective effect on the onset of PDAC are not completely clear. The mevalonate pathway impact on multiple signaling cascades, playing a role in carcinogenesis and tumor progression [12,60,61] and have an immunomodulatory, anti-inflammatory and anti-angiogenetic activity [62,63]. Statins block the conversion of HMG-CoA into mevalonate, inhibiting the downstream production of isoprenoids, involved in small GTPases such as Ras/Rho signaling activation which are well known

mediators of cell growth, differentiation and survival [64]. They also act through the regulation of RAF/mitogen-activated protein kinase1/extracellular signal-regulated kinase (MEK-ERK) pathway [65,66] and cyclin-dependent kinases involved in cell cycle [67]. Another less known but interesting effect is the inhibition on matrix metalloproteinases, involved in the degradation of the stroma components [68]. An additional hint suggesting the activity of statins in this context is represented by recent data supporting their role in terms of prolonging survival in PDAC patients after surgical resection [69,70]. In this context, the development of clinical studies investigating either the effect of statins in an adjuvant setting after PDAC resection or studies evaluating their possible chemopreventive role in individuals at consistently high risk of PDAC onset or in patients diagnosed with pancreatic pre-neoplastic lesions such as Intraductal Papillary Mucinous Neoplasia (IPMNs) [71] might be of great interest.

In conclusion, the present study suggests that statin use, especially atorvastatin and especially in males, is associated to a reduced risk of PDAC. These findings, although needing to be considered with caution given the above-mentioned limitations, support the need for further research on the chemopreventive action of statins on PDAC onset.

Conflict of interests

None declared.

Appendix A.

Search terms: (statin OR statins OR simvastatin OR cerivastatin OR rosuvastatin OR pravastatin OR fluvastatin OR atorvastatin OR lovastatin OR Hydroxymethylglutaryl CoA Reductase Inhibitors OR HMG-CoA reductase inhibitors) AND (neoplasm OR neoplasms OR cancer OR cancers OR tumor OR adenocarcinoma OR tumors OR malignancy OR malignancies) AND (risk OR occurrence OR incidence)

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.09.007.

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