Association of Pancreatic Cancer with Acute Pancreatitis: A Systematic Review and Meta-Analysis

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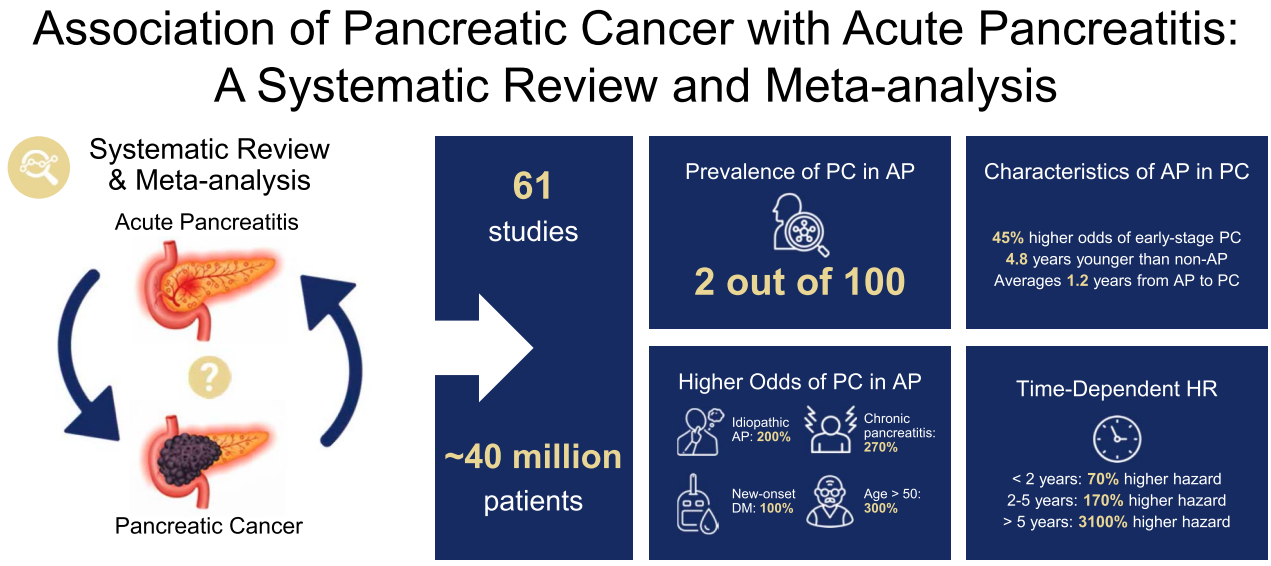
INTRODUCTION: **The magnitude and modifiers of the association between acute pancreatitis (AP) and pancreatic cancer (PC) are unclear. This systematic review and meta-analysis aimed to quantify the occurrence of PC in AP, the association of PC after AP, and the impact of specific risk factors on PC diagnosis.**



Conclusion: Patients with AP have a higher likelihood of PC diagnosis, especially within the first two years. Although the risk decreases with time, it remains higher than in the general population long term. Newly diagnosed CP, NOD, idiopathic AP may further elevate the likelihood of PC diagnosis. PC diagnosed after AP tends to occur at a younger age and more often at an earlier stage. These findings warrant careful investigation in the selected subpopulation, while future research is required to clarify causality and generate adequate surveillance protocols.

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REVIEW ARTICLE

METHODS: **The systematic search was conducted in PubMed, EMBASE, and Central Register of Controlled Trial from inception until July 14, 2025 (PROSPERO: CRD42023470350). Eligible studies included adult populations reporting on the association between AP and PC. Primary outcomes included prevalence, incidence, and diagnosis of PC in individuals with AP, including subset analyses of specific clinical and demographic factors. Meta-analyses were performed using random-effects models to calculate pooled outcome measures and corresponding 95% confidence intervals (CI).**

RESULTS: **A total of 61 studies were included. The prevalence of PC among AP patients was 2% (CI: 2%–4%). The time-dependent analysis revealed an increased hazard of PC in AP vs no AP: <24 months (HR: 31.94, CI: 9.35–109.09), 24–60 months (HR: 2.68, CI: 1.65–4.37), and >60 months (HR: 1.71, CI: 1.22–2.40). AP patients with subsequently diagnosed chronic pancreatitis (OR: 3.71, CI: 2.00–6.90), new-onset diabetes mellitus (OR: 2.22, CI: 1.02–4.84), idiopathic AP (OR: 2.97, CI: 1.44–6.13), and older than 50 years (OR: 4.04, CI: 2.73–5.97) showed significantly increased odds of having PC. We found no evidence for increased odds for PC with AP severity, smoking, and alcoholic and gallstone etiologies.**

DISCUSSION: **Patients with AP have a higher likelihood of PC diagnosis, especially within the first 2 years. Although the association decreases with time, it remains significant long term. Newly diagnosed chronic pancreatitis, new-onset diabetes mellitus, idiopathic AP may further elevate the likelihood of PC diagnosis. PC diagnosed after AP tends to occur at a younger age, more often at an earlier stage, typically in the pancreatic head.**

KEYWORDS: early detection; disease progression; malignancy; inflammation

ABBREVIATIONS: AP, acute pancreatitis; CENTRAL, Central Register of Controlled Trial; CI, confidence interval; CP, chronic pancreatitis; DM, diabetes mellitus; HR, hazards ratio; IR, incidence rate; JBI, Joanna Briggs Institute; KRAS, Kirsten rat sarcoma virus; MD, mean difference; NA, not available/applicable; No., number; NOD, new-onset diabetes mellitus; OR, odds ratio; PC, pancreatic cancer; PRISMA, preferred reporting items for systematic reviews and meta-analyses; RAP, recurrent acute pancreatitis; RF, risk factors; SM, single mean; USA, United States of America

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/B403

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INTRODUCTION

Despite advancements in diagnostics and treatment, pancreatic cancer (PC) remains one of the deadliest forms of cancer. Owing to its asymptomatic nature, it is often diagnosed at an advanced stage, resulting in a 5-year survival rate of 10% (1). Currently, PC ranks as the seventh leading cause of cancer-related mortality worldwide (1–5). Moreover, the global incidence of PC has more than doubled, rising from 195,000 cases in 1990 to 448,000 cases in 2017 (4). PC is now projected to become the second leading cause of cancer-related death. Surgical resection is the only treatment with curative potential; however, only 15%–20% are typically eligible for resection, stressing the need to identify high-risk populations for early detection and improved prognosis (1–5).

Acute pancreatitis (AP), an inflammatory disorder of the pancreas, is a common gastrointestinal condition, affecting 34 per 100,000 people annually worldwide (6). While most AP cases resolve without complication, there were some reports suggesting a potential bidirectional relationship between AP and PC (7). It has been widely speculated that AP may serve as an early manifestation of PC, but emerging evidence suggest the association may not be limited to a short-term window. Large population-based studies observed that the association with PC, although attenuated, remained significantly elevated even after 5–10 years of follow-up (8,9) These long-term associations raise the possibility that AP may in some cases reflect not only an early symptom but also a marker of increased susceptibility to PC.

Preclinical data has provided some biological rationale for this association. In the study by Carriere et al. (10) AP was induced in genetically engineered mouse models with oncogenic Kirsten rat sarcoma virus (KRAS) mutations, where it accelerated acinar-to-ductal metaplasia and progression to PC (10). While these findings support a role for AP in promoting carcinogenesis under certain genetic conditions, causal evidence in humans is lacking and uncertain. Therefore, AP is best considered both a potential indicator for earlier cancer detection and, in select contexts, a possible contributor to long-term risk (10).

Two previous meta-analyses by Liu et al (2020) (11) and Zhang et al (2018) (12) reported markedly higher rates of PC after AP compared to individuals without AP, particularly within the first 2 years. They also found a time-dependent association, with the highest (20-fold) diagnosis rate occurring within the first 2 years after AP, followed by a persistent 2-fold rate of PC diagnosis beyond 2 years. Understanding the burden of PC in this population and quantifying the associated likelihood of PC diagnosis is essential for constructing necessary surveillance

strategies and improving early detection. Furthermore, specific risk factors such as chronic pancreatitis (CP), diabetes mellitus (DM), and smoking may exacerbate this association.

Accordingly, this systematic review and meta-analysis aimed to provide a comprehensive analysis and address knowledge gaps by evaluating the prevalence of PC among patients with AP, the time-dependent association of PC after AP, and the influence of key risk factors on the likelihood of PC being diagnosed in patients with AP.

METHODS

Protocol

This systematic review and meta-analysis was conducted according to the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline (13) (see Supplementary Table S1, http://links.lww.com/CTG/B403) and the Cochrane Handbook (14). This review adhered to the protocol registered with PROSPERO (15) (CRD42023470350), with some deviations to enhance the scope and clarity of the analysis. The details of the deviations can be found in Supplementary Digital Content (see Document S1, http://links.lww.com/CTG/B403). The research project was conducted under the Systems Education model coordinated by the Centre of Translational Medicine, Semmelweis University, and the Hungarian Pancreatic Study Group (16,17).

Eligibility criteria

Studies were eligible for inclusion if they met the predefined criteria based on the Population, Exposure, Comparison, and Outcomes (PECO) framework (18). Eligible studies included adult populations (18 years or older) with a diagnosis of AP compared with populations without AP and reporting the diagnosis of PC in each group. We included studies that report the incidence or prevalence of PC in the AP population according to the Condition, Context, and Population (CoCoPop) framework. Furthermore, we conducted a subset analysis based on the Population, Factors, and Outcome (PFO) framework to assess the influence of certain clinical and demographic factors (e.g., sex, smoking, and DM) on the likelihood of PC diganosis in AP patients. Randomized controlled trials and observational studies were included, while non-human research, case reports, case series, conference abstracts, narrative reviews, systematic reviews, meta-analyses, and pediatric population studies were excluded.

Information sources

A systematic search was conducted in 3 electronic databases: MEDLINE (via PubMed), EMBASE, and Cochrane Central Register of Controlled Trials from database inception until July 14, 2025. All publications were downloaded without any restrictions or filters. In addition to the main search, references of included studies were incorporated into the selection process (19).

Search strategy

The search key was constructed with 2 domains. The first domain contained different terms for AP, while the second domain contained different variations of PC. The full search key can be found in Supplementary Digital Content (see Document S2, http://links.lww.com/CTG/B403).

Selection process

Records retrieved from the systematic search were imported into EndNote 20, where duplicate articles were removed (J.L.). The selection process was conducted using the Rayyan Intelligent Systematic Review program (20). Four independent reviewers (J.L., I.C.-M., J.N., and E.B.G.) screened the records first by title and abstract, followed by full-text assessment according to the inclusion criteria. A fifth reviewer (S.B.) resolved any disagreements when necessary. Cohen's kappa coefficient was calculated after each screening phase to assess inter-reviewer agreement (21).

Data collection process

Four reviewers (J.L., I.C.-M., J.N., and E.B.G.) extracted all relevant data independently into separate, standardized Microsoft Excel (22) spreadsheets. Discrepancies in data extraction were resolved through consensus or by consultation with a fifth reviewer (S.B.).

Data items

The following data were extracted: study characteristics (first author, year of publication, study design, study period, country, and the number of involved centers); population demographics (total number of participants, age, and percentage of male individuals); characteristics of AP and non-AP individuals (age, percentage of male individuals, AP etiology, presence of smoking, DM, alcohol, history of gallstones, and CP); outcome measure values (prevalence, incidence, OR, and HR of PC in AP); and follow-up data, and for the evaluation of risk factors for PC in patients with AP, the number of PC in patients with AP who experienced the evaluated risk factor, those nonexposed to the factor, and the total number of exposed and nonexposed individuals with AP.

Study risk of bias assessment

The risk of bias in individual studies was independently assessed by 2 reviewers (J.L. and J.N.) using the Joanna Briggs Institute (J.B.I.) proportions tool (23) for studies reporting incidence and prevalence data and the Quality in Prognostic Studies tool (24) for prognostic studies. The robvis (Risk-Of-Bias VISualization) tool was used to generate risk-of-bias plots for studies assessed with the JBI proportions tool (25). Details of each tool can be found in Supplementary Digital Content (see Document S3, http://links.lww.com/CTG/B403).

Statistical analysis

As we assumed considerable between-study heterogeneity in all cases, a random-effects model was used to pool effect sizes in a frequentist framework.

The different articles provided different outcome measures (which cannot be converted into each other without individual patient data); therefore, we provided separate meta-analyses on the measures of outcomes provided.

OR was used as an effect size measure to assess the odds of PC among AP vs non-AP patients and to assess the odds of PC in AP patients in the presence vs absence of a given potential risk factor. To calculate the pooled OR, we extracted the total number of patients and those with the event of interest in each group separately from the studies if available. Otherwise, the OR provided among the eligible papers was used in a separate analysis.

To assess the occurrence of PC among AP (vs no AP) patients, we pooled the hazards ratio (HR) and incidence rate (IR) ratios or (also from one-arm studies) the IR (in separate analysis). We performed subset analyses based on follow-up time categorized as

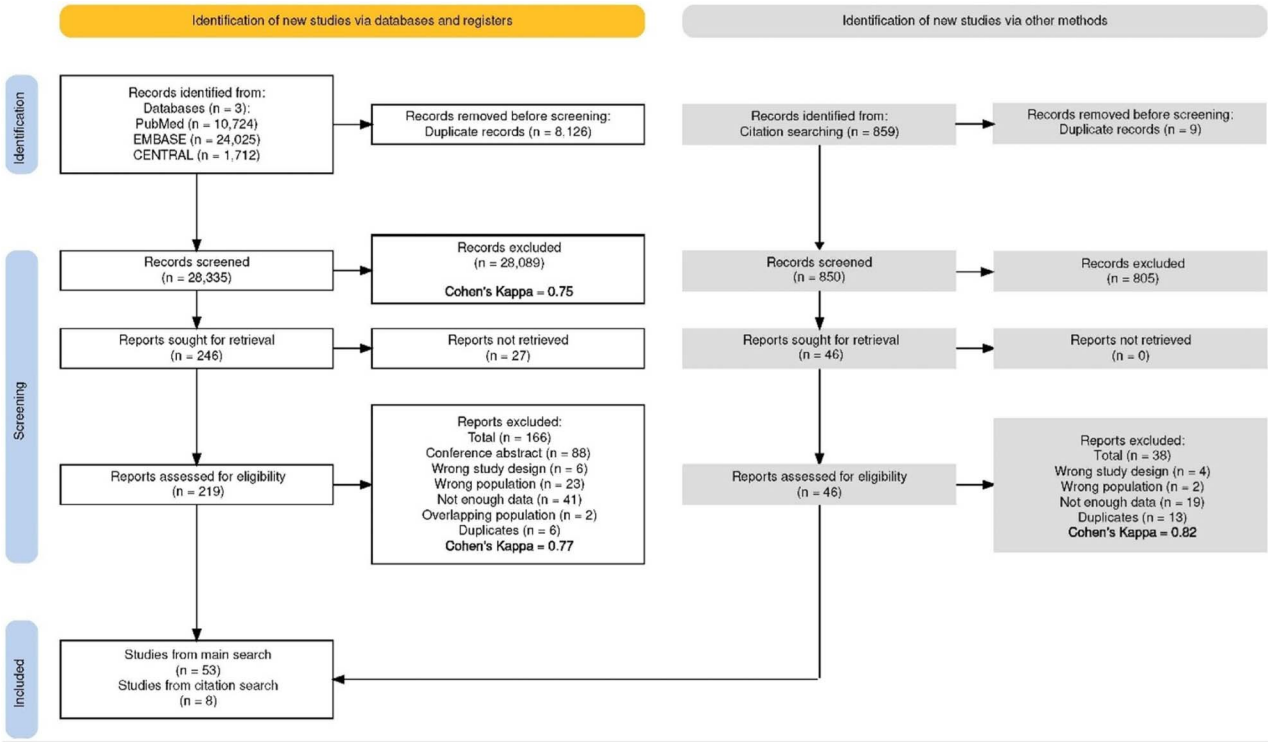

Figure 1. PRISMA flowchart of the article selection process.

short (0–24 months), medium (24–60 months), and long term (>60 months) (for IR, we performed calculations only for medium time values). In addition, we fitted a multivariate regression model to assess the HR (IR ratio) change in time, where several studies provided data for multiple time points. In addition, the prevalence of PC among patients with AP was also pooled because many articles only reported this measure.

To assess the age of patients or the mean difference of age in the comparable groups and the mean time to PC from AP, we used mean or mean difference as effect size measure. We used the given mean and SD values from the articles, or we estimated these values from the quartiles (these studies symbolized with * on the forest plots).

Results were considered statistically significant if the pooled 95% confidence interval (CI) did not contain the null value. We summarized the findings related to the meta-analysis in forest plots. Between-study heterogeneity was described by the between-study variance (τ^2) and the Higgins and Thompson's I^2 statistics (26). We reported the prediction interval if the study number was over 8.

All statistical analyses were calculated by R software (27) using the *meta* (28) package for basic meta-analysis calculations and plots, *dmetar* (29) package for additional influential analysis calculations and plots, *metafor* (30) and *clubSandwich* (31) packages for the multivariate (correlated) calculations.

For additional details on calculations, data synthesis, publication bias assessment, and influential analyses, please refer to Supplementary Digital Content (see Document S4, http://links.lww.com/CTG/B403).

RESULTS

Search and selection

The systematic search and reference chasing identified 36,461 and 859 records, respectively. We included a total of 61 studies in the systematic review, with 53 providing sufficient data for quantitative synthesis. The search and selection process is depicted in the PRISMA 2020 flow diagram (Figure 1).

Basic characteristics of included studies

Of the 61 studies included in the systematic review, we had 43 retrospective cohort studies, 7 retrospective case-control studies, 9 prospective cohort studies, 1 cross-sectional study, and 1 international survey. The studies were published between 1985 and 2025 and collectively included around 40,000,000 participants, with the largest sample size coming from Khoudari et al (2020) (32) (32,970,850) followed by Munigala et al (2023) (33) (7,147,859). The included studies were conducted in diverse regions of the world, including 6 from England, 13 from the United States, 20 from Europe, and 22 from Asia, providing a broad representation of populations. A detailed summary of the baseline characteristics of the included studies is provided in Table 1.

Prevalence of pancreatic cancer in individuals with acute pancreatitis

A total of 19 (32,34,36,37,40–43,46,47,49,55,56,61,63,66,69,71,80) studies comprising 360,517 patients with AP were included in the analysis. Across the included studies, the pooled prevalence of PC in patients with AP was 2% (CI: 2–4%; I^2 = 99.5%, CI: 99%–99.5%) (Figure 2).

Time-dependent frequency of pancreatic cancer after initial episode of acute pancreatitis

Data from 8 studies (8,9,33,38,47,54,73,76) were pooled to evaluate the frequency of PC over time after an initial episode of AP (Figure 3). The likelihood of PC being diagnosed was highest near the episode of AP and gradually declined over time; however, the

Table 1. Main characteristics of included studies

Publication data			Demography							
						Age (yr)				
First author	Year	Design	Country	Center (No)	Population	Mean	SD	Median	Male (%)	Extracted outcome measure
A. Studies included in the meta-analysis (53)										
Corfield et al. (34)	1985	Retrospective cohort	England	NA	AP	60	NA	NA	48.9	Prevalence
Köhler et al. (35)	1987	Retrospective cohort	Germany	1	PC	NA	NA	NA	NA	Prevalence
Thomson et al. (36)	1987	Retrospective cohort	England	1	AP	NA	NA	NA	52.6	Prevalence
Nordestgaard et al. (37)	1988	Prospective cohort	USA	1	AP	44	NA	NA	68.6	Prevalence
Ekbom et al. (38)	1994	Retrospective cohort	Sweden	NA	Pancreatitis	NA	NA	NA	NA	HR
Bansal et al. (39)	1995	Retrospective case-control	USA	NA	PC	NA	NA	NA	NA	OR
Halvorsen et al. (40)	1996	Prospective cohort	Norway	3	AP	NA	NA	63	54.4	Prevalence
Maes et al. (41)	1999	Prospective cohort	France	1	AP	56.7	NA	NA	62.8	Prevalence
Gislason et al. (42)	2004	Retrospective cohort	Norway	2	AP	NA	NA	64	52.0	Prevalence
Goldacre et al. (43)	2008	Retrospective cohort	England	NA	General	NA	NA	NA	49	OR, prevalence
Chung et al. (44)	2012	Retrospective cohort	Taiwan	NA	AP	57.9	NA	NA	66.3	OR
Minato et al. (45)	2013	Retrospective cohort	Japan	1	PC	NA	NA	NA	NA	Prevalence, MD
Tummala et al. (46)	2013	Retrospective cohort	USA	2	AP	NA	NA	NA	40.4	OR, prevalence
Munigala et al. (47)	2014	Retrospective cohort	USA	1	AP	57	11.6	NA	93.0	IR, HR, OR, prevalence
Thorat et al. (48)	2014	Retrospective cohort	Taiwan	1	PC	63	11	NA	60.0	Prevalence
Kimura et al. (49)	2015	Retrospective cohort	Japan	1	AP	57.9	16.8	NA	79.1	Prevalence, SM
Lakatos et al. (50)	2016	Prospective cohort	Hungary	14	PC	65.2	11.5	NA	53.4	Prevalence
Li et al. (51)	2017	Retrospective cohort	China	1	PC + AP	51.7	10.7	NA	74.5	SM
Rijkers et al. (52)	2017	Retrospective cohort	Netherlands	15	AP	NA	NA	58	54.0	IR, OR, SM
Kirkegard et al. (8)	2018	Retrospective cohort	Denmark	NA	AP	NA	NA	55.8	54.7	HR, IR, MD, OR, SM
Phillips et al. (53)	2018	Retrospective case-control	USA	NA	PC	63	10.5	NA	53.6	MD
Sadr-Azodi et al. (54)	2018	Retrospective cohort	Sweden	NA	AP	NA	NA	62	51.4	HR, IR, OR
Teng et al. (55)	2018	Retrospective cohort	China	1	AP	57	15.6	NA	58.3	Prevalence
Baecker et al. (56)	2019	Retrospective case-control	USA	NA	PC	NA	NA	NA	NA	OR
Choi et al. (57)	2019	Retrospective cohort	South Korea	NA	PC	NA	NA	NA	NA	OR, prevalence
Karjula et al. (58)	2019	Retrospective cohort	Finland	1	AP	45.3	11.4	NA	75.1	OR
Syed et al. (59)	2019	Retrospective cohort	USA	NA	PC	NA	NA	NA	NA	Prevalence
Gong et al. (60)	2020	Retrospective cohort	China	1	PC	NA	NA	62	58.9	OR
Khoudari et al. (32)	2020	Retrospective case-control	USA	360	General	NA	NA	NA	NA	OR, prevalence
Kirkegard et al. (61)	2020	Retrospective cohort	Denmark	NA	AP	NA	NA	NA	51.2	OR, prevalence
Kirkegard et al. (62)	2020	Retrospective cohort	Denmark, USA	NA	PC	NA	NA	NA	NA	MD
Pu et al. (63)	2020	Retrospective cohort	China	1	AP	52.5	15.7	51	52.8	Prevalence
Lupinacci et al. (64)	2021	International survey	France, Belgium, Switzerland	37	PC + AP	61	10.2	NA	52.6	MD
Patra et al. (65)	2021	Retrospective cross-sectional	India	1	AP	42	NA	NA	64.0	Prevalence
Xiong et al. (66)	2021	Retrospective cohort	China	1	AP	NA	NA	NA	NA	Prevalence

Table 1. (*continued*)

Publication data			Demography							
						Age (yr)				
First author	Year	Design	Country	Center (No)	Population	Mean	SD	Median	Male (%)	Extracted outcome measure
Choi et al. (67)	2022	Retrospective cohort	South Korea	NA	DM + AP	55.3	12	NA	78	OR
Jeon et al. (68)	2022	Retrospective cohort	USA	1	DM	NA	NA	NA	NA	NA
Rostropowicz-Honka et al. (69)	2022	Retrospective cohort	Poland	1	AP	NA	NA	NA	57.7	Prevalence
Sagami et al. (70)	2022	Retrospective cohort	Japan	8	PC	NA	NA	NA	NA	OR
Spagnolo et al. (71)	2022	Retrospective cohort	England	NA	AP	NA	NA	73	45.9	OR, prevalence
Cook et al. (72)	2023	Retrospective cohort	Denmark	NA	General	50.7	17	NA	NA	IR, MD
Jeong et al. (73)	2023	Retrospective cohort	South Korea	NA	AP	NA	NA	NA	56.8	HR, IR
Ma et al. (74)	2023	Retrospective case-control	England	NA	PC	NA	NA	NA	NA	OR
Munigala et al. (33)	2023	Retrospective cohort	USA	NA	General	NA	NA	60	95.2	HR, OR
Park et al. (9)	2023	Retrospective cohort	South Korea	NA	AP	NA	NA	NA	62.8	HR, IR, OR
Singh et al. (75)	2023	Retrospective cohort	USA	51	AP	58.8	13.5	NA	49.0	MD, OR
Park et al. (76)	2023	Retrospective cohort	South Korea	NA	AP	57.5	15.0	NA	54.9	HR, IR, OR
Cho et al. (77)	2024	Retrospective cohort	South Korea	1	PC	56.8	10.9	NA	74	OR, SM
deRijk et al. (78)	2024	Post hoc of prospective cohort	Netherlands	17	AP	NA	NA	59	56	OR, SM
Kim et al. (79)	2024	Retrospective cohort	South Korea	8	PC	67.2	9.9	NA	52	Prevalence
Hussein et al. (80)	2025	Prospective cohort	Hungary	25	AP	55	17.5	NA	55.1	IR, OR, prevalence, SM
Shi et al. (81)	2025	Retrospective case-control	China	1	AP	59.1	10.6	NA	63	OR
Yamao et al. (82)	2025	Retrospective cohort	Japan	2	AP	NA	NA	NA	70	Prevalence
B. Studies included only in the systematic review (8)										
Karlson et al. (83)	1997	Prospective cohort	Sweden	NA	Pancreatitis	54	NA	NA	49.4	NA
Mujica et al. (84)	2000	Retrospective cohort	USA	NA	PC	58	NA	NA	60	NA
Appelros et al. (85)	2001	Retrospective cohort	Sweden	1	Severe AP	NA	NA	60	66	NA
Takeyama et al. (86)	2009	Prospective cohort	Japan	NA	AP	NA	NA	NA	NA	NA
Keane et al. (87)	2014	Retrospective case-control	England	NA	PC	NA	NA	NA	NA	NA
Pang et al. (88)	2018	Prospective cohort	China	NA	AP	NA	NA	NA	NA	NA
Jeon et al. (89)	2020	Retrospective cohort	USA	1	CP	NA	NA	NA	NA	NA
Belfrage et al. (90)	2022	Retrospective cohort	Finland	1	AP	NA	NA	NA	65.0	NA

AP, acute pancreatitis; CP, chronic pancreatitis; DM, diabetes mellitus; HR, hazards ratio; IR, incidence rate; MD, mean difference; NA, not available/applicable; OR, odds ratio; PC, pancreatic cancer; SM, single mean; USA, United States of America.

association with PC diagnosis remained significantly high even in the long term. In addition, we pooled HR from the same 8 studies (8,9,33,38,47,54,73,76) that adjusted for key confounders, including age and sex; some also adjusted for smoking, alcohol consumption, comorbidities (e.g., DM, gallstone disease, Charlson comorbidity index), and socioeconomic factors (Table 2). The HRs were pooled together in a multivariate model and stratified by follow-up period after AP: short-term (<24 months; HR: 31.94, CI: 9.35–109.09; I^2 = 98.3%, CI: 97.6%–98.8%), medium-term (24–60 months; HR: 2.68, CI: 1.65–4.37; I^2 = 91.2%, CI: 84.5%–95%), and long-term (>60 months; HR: 1.71; CI: 1.22–2.40; I^2 = 76.6%, CI: 50.9%–88.8%). For individual figures, please refer to Supplementary Digital Content (see Supplementary Figures S2-4, http://links.lww.com/CTG/B403).

Risk factors of pancreatic cancer in patients with acute pancreatitis

The association between several clinical and demographic factors and the likelihood of PC diagnosis among patients with AP was

Study	PC present among AP Patients	Sample Size of AP Patients	PC prevalence	95% CI
Corfield et al., 1985	3	650	0.00	[0.00; 0.01]
Kirkegard et al., 2020	283	28,231	0.01	[0.01; 0.01]
Pu et al. , 2020	33	3,028	0.01	[0.01; 0.02]
Teng et al., 2018	10	693	0.01	[0.01; 0.03]
Hussein et al., 2025	34	2,356	0.01	[0.01; 0.02]
Goldacre et al., 2008	91	6,076	0.01	[0.01; 0.02]
Munigala et al., 2014	86	5,720	0.02	[0.01; 0.02]
Maes et al., 1999	2	121	0.02	[0.00; 0.06]
Thomson et al., 1987	6	359	0.02	[0.01; 0.04]
Khoudari et al., 2020	4,780	277,260	0.02	[0.02; 0.02]
Spagnolo et al., 2022	69	3,229	0.02	[0.02; 0.03]
Xiong et al., 2021	40	1,792	0.02	[0.02; 0.03]
Gislason et al., 2004	13	487	0.03	[0.02; 0.05]
Rostropowicz-Honka et al., 2022	11	333	0.03	[0.02; 0.06]
Nordestgaard et al., 1988	3	51	0.06	[0.01; 0.17]
Halvorsen et al., 1996	6	90	0.07	[0.03; 0.14]
Kimura et al., 2015	12	177	0.07	[0.04; 0.12]
Baecker et al., 2019	2,045	29,646	0.07	[0.07; 0.07]
Tummala et al., 2013	38	218	0.17	[0.13; 0.23]
Pooled (random) effect			**0.02**	**[0.02; 0.04]**
Prediction interval				**[0.00; 0.13]**

I^2 = 99.5% [99.4%; 99.5%], τ = 0.83

Figure 2. Prevalence of pancreatic cancer in acute pancreatitis. AP, acute pancreatitis; CI, confidence interval; PC, pancreatic cancer.

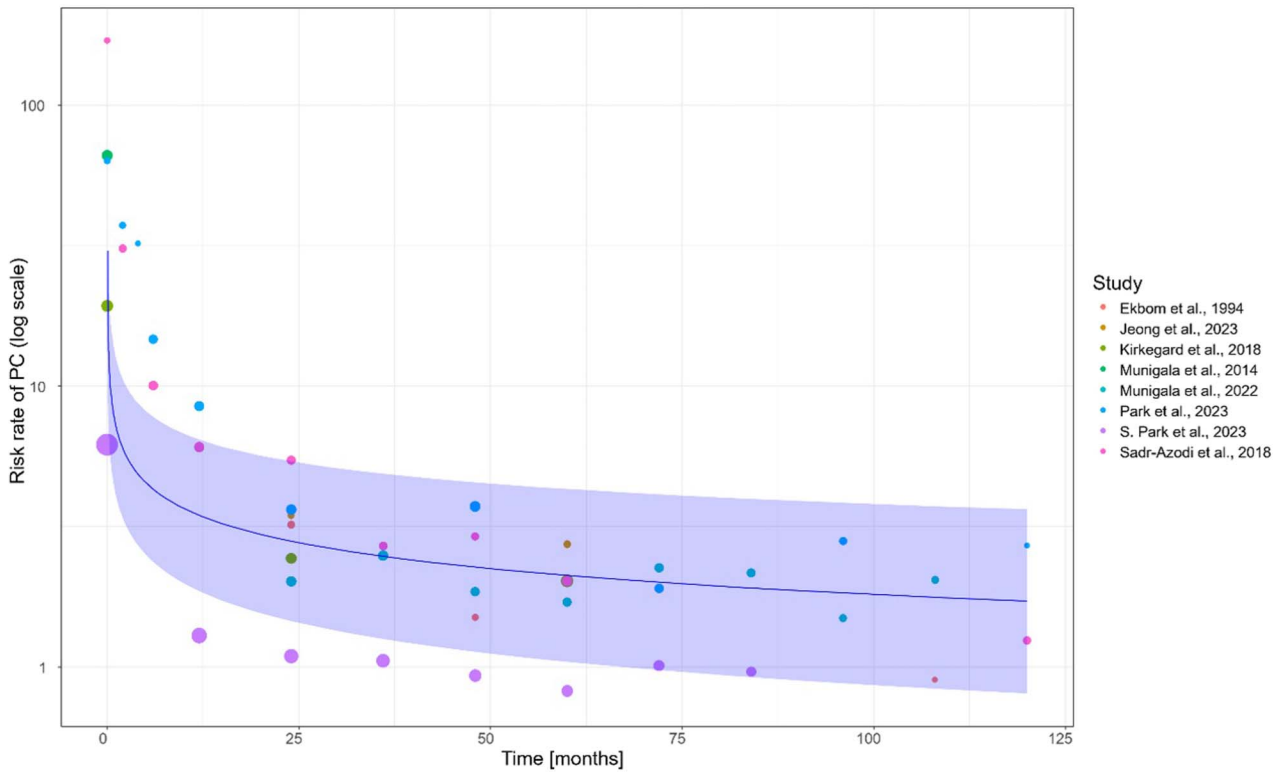

Figure 3. Risk rate of pancreatic cancer according to follow-up time after acute pancreatitis. PC, pancreatic cancer.

Table 2. Risk rate of pancreatic cancer following acute pancreatitis stratified according to follow-up periods

Time after initial AP episode	No. of studies	Pooled HR	Pooled 95% CI	I^2	I^2 95% CI	Adjusted for
<24 mo	6	31.94	9.35–109.09	98%	98%–99%	Age, sex, smoking, alcohol, other
24–60 mo	7	2.68	1.65–4.37	91%	85%–95%	Age, sex, smoking, alcohol, other
> 60 mo	7	1.71	1.22–2.40	77%	51%–89%	Age, sex, smoking alcohol, other

AP, acute pancreatitis; CI, confidence interval; HR, hazards ratio, No., Number; PC, pancreatic cancer.

explored. Subsequent CP (44,52,54,61,76,80) diagnosed after an episode of AP demonstrated a strong association with PC (OR: 3.71, CI: 2.00–6.90; I^2 = 85%, CI: 70%–93%). Patients with AP older than 50 years were also strongly associated with PC (OR: 4.04, CI: 2.73–5.97; I^2 = 12%, CI: 0%–87%) (see Supplementary Figure S16, http://links.lww.com/CTG/B403) (46,47,54,61).

Among metabolic factors, new-onset diabetes (NOD) (46,56,61,80) carried a significant association with subsequent PC diagnosis (OR: 2.22, CI: 1.02–4.84; I^2 = 21%, CI: 0%–92%) (see Supplementary Figure S8, http://links.lww.com/CTG/B403). Smoking (33,46,61,81) showed a nonsignificant trend toward higher PC diagnosis (OR: 1.49, CI: 0.61–3.63; I^2 = 74%, CI: 27%–91%) (see Supplementary Figure S10, http://links.lww.com/CTG/B403).

Regarding AP etiologies, idiopathic AP (8,52,78,80,81) was associated with nearly a 3-fold higher likelihood of PC diagnosis compared with nonidiopathic AP (OR: 2.97, CI: 1.44–6.13, I^2 = 63%, CI: 3%–86%) (see Supplementary Figure S18, http://links.lww.com/CTG/B403). By contrast, the effects of gallstone-related AP (see Supplementary Figure S9, http://links.lww.com/CTG/B403) (8,33,52,54,61,78,80,81) and alcoholic AP (see Supplementary Figure S5, http://links.lww.com/CTG/B403) (8,47,52,58,78,80,81) were evaluated, revealing no significant associations with PC (Table 3).

Other factors, including AP severity (see Supplementary Figures S20-22, http://links.lww.com/CTG/B403) (42,46,61,80,81), recurrent AP (see Supplementary Figure S19, http://links.lww.com/CTG/B403) (33,42,54,76,80), and male sex (see Supplementary Figure S27, http://links.lww.com/CTG/B403) (8,46,49,54,76,81), did not exhibit significant associations with PC diagnosis.

Patient characteristics and tumor features of pancreatic cancer in acute pancreatitis

Patients who developed PC after an episode of AP tended to be younger at diagnosis compared with PC patients without a history of AP (mean difference: −4.8 years, CI: −9.0 to −0.7; 7 studies, n = 7,184 vs 113,738) (see Supplementary Figure S14, http://links.lww.com/CTG/B403) (8,45,53,62,64,72,75). The interval from AP to PC diagnosis was typically short, with a pooled mean time of 1.2 years (CI: 0.4–1.9; 7 studies, n = 620) (see Supplementary Figure S15, http://links.lww.com/CTG/B403) (8,49,51,52,77,78,80). Nevertheless, as shown in large population-based cohorts, the association between AP and subsequent PC diagnosis persisted even at longer follow-up, though at lower magnitude.

Importantly, PC diagnosed after AP was more likely to be detected at an earlier stage (OR: 1.45, CI: 1.26–1.67; 3 studies, n = 6,302 vs 98,298) (see Supplementary Figure S17, http://links.lww.com/CTG/B403), which may reflect comprehensive diagnostic evaluation triggered by the AP episode. With respect to tumor location, most cancers occurred in the pancreatic head (61%, CI: 46%–75%; 9 studies, n = 6,855), followed by the body (12%, CI: 6%–22%; 6 studies, n = 4,429) and tail (6%, CI: 3%–10%; 6 studies, n = 4,429) (see Supplementary Figures S24-26, http://links.lww.com/CTG/B403).

Quality of the included studies

Methodological quality of 42 studies was assessed with the JBI proportions checklist where 29 studies had an overall low risk of bias, 13 studies had moderate, and 1 study had a high risk. With

Table 3. Influence of clinical and demographic factors on the likelihood of pancreatic cancer diagnosis in acute pancreatitis

Risk factor	No. of studies	PC in AP with RF	No. of AP with RF	No. of PC among AP without RF	No. of AP without RF	I^2 (95% CI)	Pooled OR (95% CI)
Subsequent CP	6	478	46,634	1,085	258,635	85% (70%–93%)	3.71 (2.00–6.90)
Smoking	4	140	17,248	343	33,790	74% (27%–91%)	1.49 (0.61–3.63)
DM + AP vs AP	5	98	10,335	459	31,104	70% (23%–88%)	0.73 (0.40–1.31)
New-onset DM	3	32+	1,375+	281+	26,945+	21% (0%–92%)	2.22 (1.02–4.84)
Gallstone AP	8	328	49,173	777	76,636	87% (77%–93%)	0.56 (0.30–1.03)
Alcoholic AP	7	59	7,376	252	25,944	69% (31%–86%)	0.65 (0.32–1.30)
Idiopathic AP	5	135	12,918	94	13,017	63% (3%–86%)	2.97 (1.44–6.13)
Mild AP	5	433	27,249	42	2,251	60% (0%–85%)	1.73 (0.57–5.23)
RAP	5	334	25,514	878	286,221	97% (96%–98%)	2.50 (0.78–7.95)
Male	6	720	264,554	584	259,077	0% (0%–75%)	1.10 (0.97–1.26)
Age older than 50	4	834	57,944	92	25,974	12% (0%–87%)	4.04 (2.73–5.97)

AP, acute pancreatitis; CI, confidence interval; CP, chronic pancreatitis; DM, diabetes mellitus, No, number; OR, odds ratio; PC, pancreatic cancer; RAP, recurrent acute pancreatitis; RF, risk factor.

the Quality in Prognostic Studies tool, we assessed 33 studies, where 21 studies had low risk, 11 studies had moderate risk, and 1 study had high risk of bias. The main reasons for the potential bias in the studies were the lack of consideration for the confounders and the lack of details in how the prognostic factor and outcomes were measured. The risk of bias assessments for each outcome can be found in Supplementary Digital Content (see Supplementary Tables S2-3, http://links.lww.com/CTG/B403).

Heterogeneity and publication bias

Moderate-to-high heterogeneity was observed in all evaluated outcomes, which may arise from several factors. First, potential confounders such as smoking, alcohol consumption, and DM—known risk factors for PC—could contribute to variations in the associations across studies. Second, differences in study design and demographics may play a role; while some studies were conducted in single-center settings, others used national databases with broader, more diverse cohorts. In addition, the inclusion of studies from multiple regions and countries may introduce further heterogeneity, as the IR of PC differs based on the region.

Among the analyses, publication bias could be assessed only for the prevalence of PC which did not suggest any small-study effects ($P = 0.5376$), indicating no statistical evidence of publication bias. Visualization with funnel plots and the Egger's test result (with Peters' modification) can be found in Supplementary Digital Content (see Supplementary Figures S1, http://links.lww.com/CTG/B403).

DISCUSSION

In this systematic review and meta-analysis, we found a clinically relevant prevalence of PC in AP, an increased likelihood of PC diagnosis after AP, and the potential influence of specific clinical and demographic factors. These findings strengthen the association between AP and PC, which warrants increased clinical awareness.

The prevalence of PC among patients with AP in our meta-analysis was 2%, suggesting that at a given time point, approximately 2 out of every 100 patients with AP have a concurrent or previously undiagnosed PC. Although this may seem low, it is clinically relevant given the poor prognosis of PC and the potential for it being missed when AP occurs. This highlights the need for careful investigation for underlying malignancy in patients with AP.

The underlying mechanisms of PC-AP association remain unclear and are likely multifactorial (2). In the short term, AP often represents the first clinical manifestation of an occult cancer, where reverse causation, careful diagnostic workup after AP, potential surveillance bias, or a delay in the diagnosis of pre-existing PC likely explain the increase in PC diagnoses within the first 2 years. Our meta-analysis revealed a gradual time-dependent decline in the frequency of PC diagnosis after AP but still remained significant. These estimates were adjusted for various confounding variables, suggesting that the observed trends were independent of these variables. Many studies (8,9,38,39,47,49,53,54,56,75,80,83,87,88,90) have reported similar trends. Pang et al (2018) (88) reported a HR of 9.99 (CI: 3.20–31.16) in a cohort of 1,079 AP patients with a 2-year lag period. Beyond 2 years after AP, the likelihood of PC diagnosis gradually decreases; however, it persists for at least 5 years, with Kirkegard et al (2018) (8) and Sadr-Azodi et al (2018) (54) reporting a 2-fold increased hazards even after 10 years. This suggests that while some early cases may be due to pre-existing PC, AP itself could still contribute to long-term pancreatic carcinogenesis, potentially through chronic inflammation, fibrosis, or metabolic alterations.

Large registry studies have also shown that patients with AP-related PC are diagnosed at younger ages and more often at earlier stages (see Supplementary Figure S17, http://links.lww.com/CTG/B403) (60,61,75), consistent with earlier detection triggered by the pancreatitis episode. Our analysis shows distinct clinical characteristics of PC diagnosed in AP. Compared with patients without prior AP, those with AP were diagnosed with PC at a younger age (see Supplementary Figure S14, http://links.lww.com/CTG/B403) (8,45,53,62,64,72,75), and the interval from AP to cancer diagnosis was typically short (see Supplementary Figure S15, http://links.lww.com/CTG/B403) (8,49,51,52,77,78,80). This supports that AP can serve as an initial manifestation that prompts earlier clinical evaluation, thereby resulting in the earlier detection of PC. Indeed, the higher likelihood of early-stage diagnosis among AP patients suggests that AP-triggered investigations may uncover PC at a resectable stage, which has important implications for prognosis. Furthermore, the predominance of tumors in the pancreatic head is consistent with the pathophysiology of AP because head lesions are more likely to obstruct the pancreatic duct and precipitate an attack, with Singh et al (75) observing that the head of pancreas cancer occurred twice as commonly in patients with prior AP compared with those without AP. While these findings strengthen the rationale for targeted surveillance after AP—particularly in older patients or those with idiopathic etiology—they should be interpreted with caution. The younger age at diagnosis may reflect detection bias, and the short interval again raises the possibility of reverse causation, where AP represents the first clinical manifestation of an occult tumor rather than an independent risk factor. Nonetheless, the combination of earlier stages at diagnosis and distinct anatomical distribution emphasizes the need for clinicians to maintain a high level of suspicion for PC in patients presenting with AP.

We performed subset analyses to gain a deeper insight into how different risk factors influence the odds of developing PC in AP patients. Among the factors analyzed, subsequently diagnosed CP after AP was significantly associated with an increased odds of PC. This aligns with evidence suggesting that the transition from AP to CP reflects underlying pancreatic injury and fibrosis, which is known to contribute to carcinogenesis (91). However, a study conducted by Jeon et al (2020) (89) reported negligible risk of PC in CP patients with prior AP (HR: 0.92; 95% CI: 0.49–1.73) likely because of differences in study population, as their focus was exclusively on patients with CP. Nonetheless, our findings suggest the importance of close monitoring of patients with AP who progress to CP. In addition to CP, recurrent AP also appears to be frequently associated with PC. Two studies (33,54) reported a higher association of PC with increasing number of recurrent episodes of AP, with one study (54) finding the highest rate of PC diagnosis when multiple episodes occurred near the initial episode of AP (<2 years). Although our analysis could not reach statistical significance (see Supplementary Figure S19, http://links.lww.com/CTG/B403), there is a trend in all except one study (42) that suggests increased odds for PC.

By contrast, alcoholic or biliary etiology did not significantly increase the likelihood of PC diagnosis, though both analyses exhibited substantial heterogeneity. In addition, both are self-limiting, acute, inflammatory conditions with a specific cause that

does not necessarily lead to progressive pancreatic damage. However, alcoholic pancreatitis can result in chronic inflammation and fibrosis if alcohol abuse continues, but this was not clear within the included studies. While alcoholic and biliary etiology were insignificant, idiopathic AP was found to have a significant association with PC, with Hussein et al (80) reporting that 3% of patients with AP who developed PC had idiopathic AP compared with 1% in the nonidiopathic group (see Supplementary Figure S18, http://links.lww.com/CTG/B403).

Smoking and prevalent DM in AP were not significantly associated with PC. New-onset DM in AP, however, was observed to have a significant association with PC diagnosis (see Supplementary Figure S8, http://links.lww.com/CTG/B403) (56,61,80). Choi et al (67) found a 6-fold increased risk in patients with DM with AP compared with those without AP. In addition, Jeon et al (68) found a higher prevalence of PC in early-stage patients with DM with AP compared with late-stage patients with DM (5% vs 2%), suggesting that new-onset DM may reflect early pancreatic carcinogenesis rather than being an independent risk factor.

The lack of statistical significance in our subset analyses of the pancreatitis etiologies, smoking, and prevalent DM may be due to sample size limitations, heterogeneity, or insufficient long-term follow-up to notice delayed carcinogenic effects. The lack of association between PC and the other assessed factors indicates that the progression to CP or the presence of NOD, rather than AP itself or traditional risk factors, plays a key role in carcinogenesis.

Strengths and limitations

Our comprehensive analysis incorporates a robust methodology and a large, diverse sample, enhancing the generalizability of our findings. In addition, despite considerable heterogeneity in the time-dependent analysis, new-onset CP, and OR of PC in AP, the consistency of the effect estimates across diverse studies reinforces the validity and generalizability of our findings. Furthermore, the time-stratified analyses allowed us to distinguish the short-term clustering of PC diagnoses, likely reflecting reverse causation, from the persistently elevated long-term association. In addition, we evaluated clinically relevant modifiers such as age, idiopathic AP, and NODs, and we summarized tumor characteristics, including stage and location, which have not been addressed in prior meta-analyses. However, some limitations must be acknowledged. First, the retrospective design of most of the included studies limits causal inference and introduces potential selection bias. In addition, there was considerable heterogeneity across multiple analyses, suggesting variations in diagnostic criteria, follow-up durations, and study designs which may have influenced the pooled estimates. Several confounding lifestyle factors, including smoking or alcohol, could not be fully accounted for in each analysis. Furthermore, three studies (9,73,76) included in the time-dependent analysis (**Figures S2-4, http://links.lww.com/CTG/B403**) used partially overlapping populations from the Korean National Health Insurance Service (NHIS) and the National Health Screening Program (NHSP) databases. To provide a comprehensive overview, we included these studies in the analysis while acknowledging the potential overlap. Leave-one-out sensitivity analyses excluding the overlapping studies showed that the pooled hazard ratios remained materially unchanged, supporting the robustness of our findings, with only S. Park et al.(76) exerting notable influence (**Figures S28-30, http://links.lww.com/CTG/B403**) Finally, although the association between AP and PC diagnosis remained significant after 5 years, causality cannot be inferred.

Clinical and research implications

Translating scientific results into real-world benefits has high importance (92,93). Our findings suggest that AP can serve as an early sign for PC, especially in patients older than 50 years, those with idiopathic AP, those who develop NOD, and those who progress to CP. Given this, clinicians should maintain a high level of awareness in these subgroups with careful consideration of follow-up or detailed diagnostic evaluation. Future prospective studies should be conducted, implementing risk stratification models, integrating biomarkers, and conducting biology-focused research in humans to clarify the causal relationship between AP and PC, if any.

CONCLUSION

Patients with AP have a higher likelihood of PC diagnosis, especially within the first 2 years. Although the risk decreases with time, it remains higher than in the general population long term. Newly diagnosed CP, NOD, idiopathic AP may further elevate the likelihood of PC diagnosis. PC diagnosed after AP tends to occur at a younger age, more often at an earlier stage, typically in the pancreatic head. These findings warrant careful investigation in the selected subpopulation, while future research is required to clarify causality and generate adequate surveillance protocols.

CONFLICTS OF INTEREST

Guarantor of the article:

Specific author contributions: J.L.: conceptualization, data curation, investigation, project administration, writing–original draft. I.C.-M.: conceptualization, data curation, investigation, writing–review and editing. J.N.: conceptualization, data curation, investigation, writing–review and editing. E.B.G.: conceptualization, data curation, investigation, writing–review and editing. D.S.V.: conceptualization, formal analysis, investigation, validation, visualization, writing–review and editing. E.Á.Sz.: conceptualization, methodology, supervision, writing–review and editing. M.O.: conceptualization, supervision, writing–review and editing. R.P.: conceptualization, supervision, writing–review and editing. S.B.: conceptualization, methodology, supervision, writing–review and editing. P.H.: conceptualization, methodology, supervision, writing–review and editing. All authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript.

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Potential competing interests: None to report.

Ethical approval: No ethical approval was required for this systematic review with meta-analysis, as all data were already published in peer-reviewed journals. No patients were involved in the design, conduct or interpretation of our study. The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis.

Data availability: All the data analyzed in this study are available in the full text of the studies and supplementary material included.

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Study Highlights

WHAT IS KNOWN

- ✓ Pancreatic cancer is sometimes diagnosed shortly after an episode of acute pancreatitis.
- ✓ The long-term association of pancreatic cancer in patients with acute pancreatitis remains uncertain.

WHAT IS NEW HERE

- ✓ Patients with acute pancreatitis (AP) have a higher likelihood of pancreatic cancer (PC) diagnosis, especially within the first 2 years. Although the association decreases with time, it remains significant long term.
- ✓ Newly diagnosed chronic pancreatitis (CP), new-onset diabetes, idiopathic AP may further elevate the likelihood of PC diagnosis. PC diagnosed after AP tends to occur at a younger age, more often at an earlier stage, typically in the pancreatic head.

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