Chronic Pancreatitis Is a Risk Factor for Pancreatic Cancer, and Incidence Increases With Duration of Disease: A Systematic Review and Meta-analysis

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INTRODUCTION: **Observational studies have suggested an increased risk of pancreatic ductal adenocarcinoma (PDAC) in patients with acute and chronic pancreatitis. We conducted a systematic review and meta-analysis to evaluate the magnitude of this association and summarize the published epidemiological evidence.**

METHODS: **We searched electronic databases (MEDLINE, Embase, Web of Science, Cochrane, and Scopus) and reference lists until January 18, 2021. Studies reporting quantitative association between pancreatitis and PDAC were included and assessed for eligibility, data abstraction, and risk of bias. Standardized incidence ratios (SIRs) were pooled using the random-effects model.**

RESULTS: **Twenty-five cohort and case-control studies met inclusion criteria. Meta-analysis of 12 chronic pancreatitis (CP) studies demonstrated an increased risk of PDAC in patients with CP (SIR: 22.61, 95% confidence interval [CI]: 14.42–35.44). This elevated risk persisted in subgroup analysis of studies that excluded patients diagnosed with PDAC within 2 years of CP diagnosis (SIR: 21.77, 95% CI: 14.43–32.720). The risk was higher in hereditary pancreatitis (SIR: 63.36, 95% CI: 45.39–88.46). The cumulative incidence rates of PDAC in CP increased with follow-up duration. Limited evidence in acute pancreatitis indicates higher PDAC risk in the subset of patients eventually diagnosed with CP. PDAC seems to be uncommon in patients with autoimmune pancreatitis, with 8 reported cases in 358 patients with autoimmune pancreatitis across 4 studies.**

DISCUSSION: **There is an increased risk of PDAC in patients with CP, and incidence rates increase with CP disease duration. Our results indicate that PDAC surveillance may be considered in individuals with long-standing CP.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A764

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a lethal malignancy with rising global incidence. Most patients present with incurable metastatic disease at diagnosis, and the 5-year survival in United States is approximately 10% (1–3). However, survival is substantially higher in the subgroup of patients diagnosed at an early stage. There is currently no recommended population screening tool for PDAC (4), but risk factor–based identification of individuals who are at a greater than average lifetime risk of PDAC has been proposed as a strategy to identify a cohort that may benefit from screening.

Chronic pancreatitis (CP) is a fibroinflammatory disease of the exocrine pancreas with varied etiology and a broad spectrum of clinical manifestations that range from asymptomatic disease to debilitating chronic pain and exocrine and endocrine insufficiency (5). CP is an established risk factor for PDAC (6–8). Long-standing inflammation increases cell turnover and stellate cell proliferation, and in CP, this creates a pancreatic tissue microenvironment that promotes carcinogenesis (9). The lifetime risk of PDAC is further elevated in the forms of CP characterized by an early onset of pancreatic inflammation, such as hereditary and tropical pancreatitis (5). Autoimmune pancreatitis (AIP) is a steroid-responsive form of CP associated with a marked inflammatory phase, potentially increasing the risk of malignancy (10). Although both pancreatic and extrapancreatic malignancies have been reported in patients with AIP, the lifetime risk of developing PDAC does not seem to be elevated in patients with AIP compared with the general population, and long-term follow-up

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data are limited (11). The relationship between acute pancreatitis (AP) and PDAC risk also remains unclear. Although AP can be the first clinical manifestation of PDAC, believed to be due to tumor-related ductal obstruction, the long-term risk of PDAC in individuals with AP has not been defined (12). Considering the clinical relevance of understanding the association between different forms of pancreatitis and pancreatic cancer, we conducted this systematic review and meta-analysis to evaluate the magnitude of association and the strength of the supporting evidence.

METHODS

This report adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement to complete of the systematic review (13).

Eligibility criteria

Studies were considered eligible for inclusion if participants were men and women older than 18 years. Also, diagnosis of 1 of the following:

1. AP diagnosed using 2 of 3: abdominal pain typical for AP; serum amylase and/or lipase greater than or equal to 3 times the upper normal limit; and evidence of AP on imaging (14).
2. CP confirmed diagnosis using imaging demonstrating pancreatic calcification with or without main pancreatic duct dilation, functional studies, or surgical pathology.
3. AIP with known radiological or histological findings diagnostic for AIP (International Consensus Diagnostic Criteria or histology, imaging, serology, other organ involvement, and response to therapy criteria) and/or clinical response to steroids (15,16).
4. Hereditary pancreatitis (HP) with confirmed gene mutation in either *PRSS1*, *SPINK1*, *CFTR*, or *CTRC* genes or with a family history consistent with HP.

Study design

The outcome was a quantitative association between exposure and histologically confirmed PDAC. Case-control, retrospective, or prospective cohort or single-arm cohort studies of any duration or setting studying >10 patients, reporting standardized incidence ratio (SIR), odds ratio (OR), relative risk (RR), and corresponding 95% confidence intervals (CIs) were included.

Exclusion criteria

Conference abstracts, case reports, letters, review articles, editorials, commentaries, qualitative articles, studies with less than 10 subjects, and studies with either patient-reported or *International Classification of Diseases (ICD)* code- based diagnosis of pancreatitis and/or PDAC.

Literature search

A comprehensive search of several databases from each database's inception was conducted, including Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's investigators. Controlled vocabulary supplemented with keywords was used to search for pancreatitis and pancreatic cancer risk in human studies through January 18, 2021, with no language filter. Bibliographies of selected articles were reviewed for additional relevant studies. The detailed search strategy is available in the Appendix (see Supplementary Digital Content 1, http://links.lww.com/CTG/A764).

Data abstraction

Two independent reviewers (S.G. and J.d.l.F.) screened the titles and abstracts of studies based on inclusion and exclusion criteria, followed by a full-text analysis of relevant articles. A third reviewer (S.M.) adjudicated disagreements between the 2 reviewers. Study data were abstracted in duplicate to verify the accuracy of the studies. The following information was abstracted from each study: study type, author, year of publication, population and setting (study site), sample size, number of patients who developed PDAC, method of verification of pancreatitis and PDAC, matched variables, risk estimates, and their corresponding 95% CI. Disagreements were settled by consensus. Data on the cumulative incidence rates (CIRs) of PDAC after CP diagnosis were extracted when available.

Assessment of risk of bias

Risk of bias assessment was analyzed independently for each article by 2 reviewers (S.G. and J.d.l.F.) using the Newcastle-Ottawa Scale for case-control and cohort studies (17) and a modification of the scale for single-arm cohort studies (18). We considered that the follow-up was adequate when patients were followed for more than 2 years after pancreatitis diagnosis and when less than 20% patients were lost to follow-up. The most important factors in assessing the risk of bias in this specific research question were ascertainment of exposure, demonstration that the outcome was not present at the start of the study, assessment of outcome, and adequate length of follow-up in cohort studies. Studies that fulfilled all these criteria were considered to be at low risk of bias. Studies that only fulfilled 1 or none were considered to be at high risk of bias.

Statistical analyses

We meta-analyzed cohort studies (1 case-control study is reported narratively). All the studies reported SIRs except 1 that reported RR. The reported SIR was calculated as the ratio of the observed to expected number of patients with PDAC in the population studied. We conducted meta-analysis with and without the study that reported RR to determine whether the conclusions of the meta-analysis would change by excluding this study.

We pooled SIRs that compared the association between pancreatitis and PDAC risk at a 95% CI, using the random-effects model (19) because of anticipated heterogeneity across study settings and populations. Heterogeneity was assessed using the I^2 statistic, and a value exceeding 50% implied substantial heterogeneity (20). We also conducted a sensitivity analysis on studies that excluded patients who developed PDAC within 2 years of follow-up. SIRs of PDAC in CP in smokers and nonsmokers were pooled when available to evaluate the effect of smoking on PDAC. Publication bias was assessed using the funnel plot.

RESULTS

Study selection

The initial database search identified 882 studies. Eight hundred nine studies were excluded based on title and abstract in the initial review. A full-text review was performed of the remaining 73 studies, and 51 studies were further excluded (Figure 1). Three

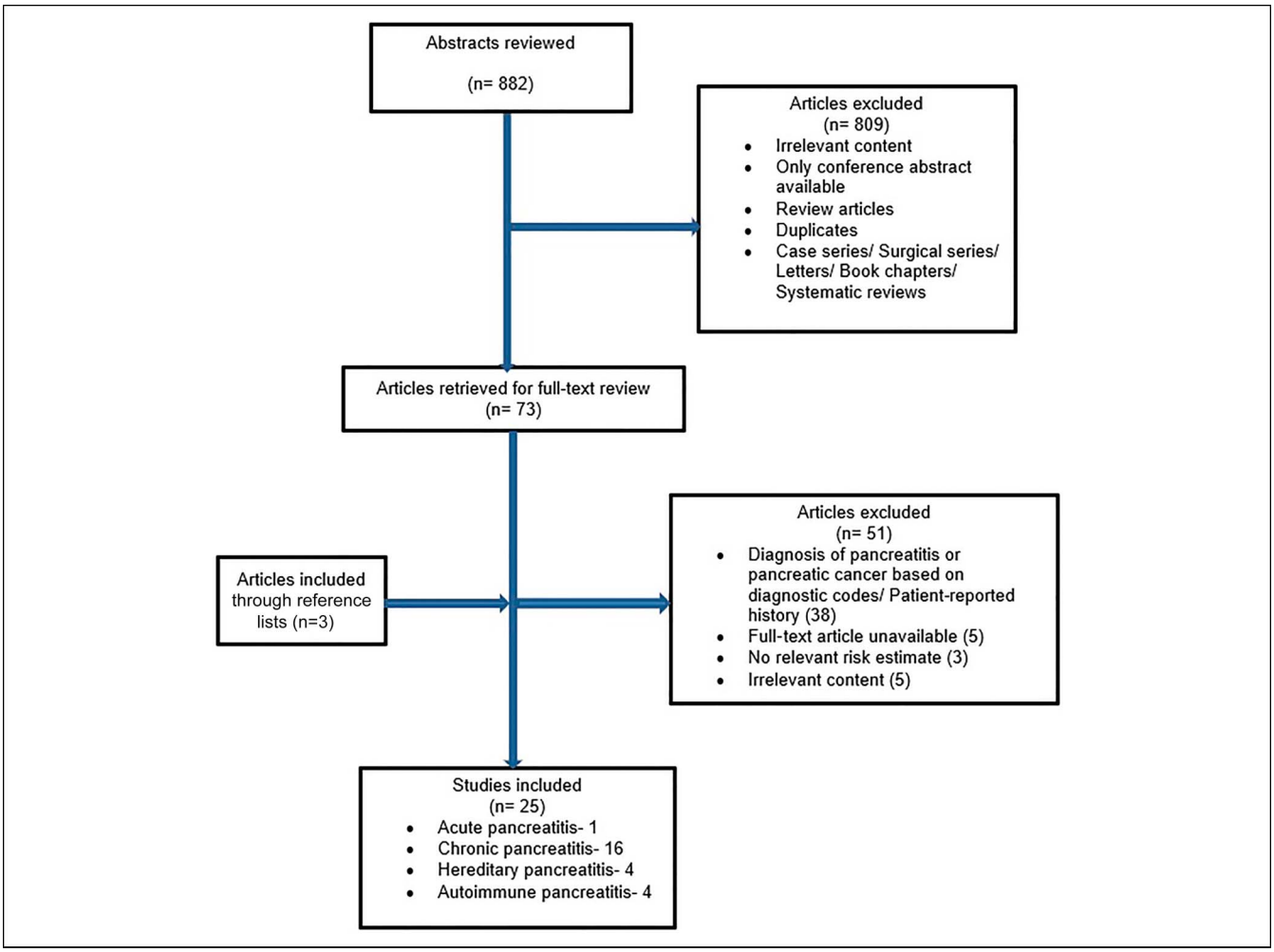

Figure 1. Study flowchart for selection criteria.

additional studies were identified by searching bibliographies of relevant articles.

Study characteristics

We found 25 studies that met our inclusion criteria: 1 for AP and CP, 1 for AIP and CP, 3 for AIP, 4 for HP, and 16 for CP only. Table 1 summarizes the descriptive characteristics of the 17 cohort studies, 7 single-arm cohort studies, and 2 case-control studies (21–45). Midha et al. (23) conducted both case-control and cohort studies and reported their findings in the same article (Midha a: Cohort study; Midha b: Case-control study). Rijkers et al. (38) described the outcomes separately for patients with AP who developed CP (Rijkers a: Outcomes for AP patients and Rijkers b: Outcomes for AP patients who developed CP). Ikeura et al. (42) examined the development of PDAC in both patients with AIP and CP (Ikeura a: Outcomes for AIP patients and Ikeura b: Outcomes for CP patients) (Table 1).

The number of study participants ranged from 61 to 1,766 in cohort studies, 41 to 1,415 in single-arm cohort studies and 116 to 249 cases in case-control studies. The studies differed in populations studied, settings, study periods, and the data sources ranged from single centers to multiple centers. In both case-control studies, cases and controls were matched for age and sex. All cohort studies were standardized by age; all but 5 studies were standardized for sex. Table 1 summarizes the risk estimates of the studies. The risk estimates reported were SIRs in 15 studies, incidence rate in 2 studies, RR in 1 study, and OR in 1 study.

The domains of the Newcastle-Ottawa Scale are listed for each study in Table 2 (21–45). The risk of bias in the included studies was low to moderate because of limitations in demonstration of outcome at the start of the study and adequate length of follow-up.

Meta-analysis

Sixteen studies were included in the meta-analysis (12 studies on CP and 4 studies on HP). Figure 2 depicts forest plots of the association of CP and HP with PDAC.

Meta-analysis of CP studies demonstrated that CP was associated with a statistically significant increased risk of PDAC (SIR: 22.61, 95% CI: 14.42–35.44). Heterogeneity among these studies was high ($I^2 = 83.3\%$, $P < 0.001$). Pooling the risk estimates of 4 HP studies yielded an increased risk of PDAC (SIR: 63.36, 95% CI: 45.39–88.46) compared with the non-HP CP studies. Heterogeneity among the HP studies was low ($I^2 = 37.4\%$, $P = 0.187$). Figure 2 also depicts sensitivity analysis on 7 CP studies that excluded patients diagnosed with PDAC within 2 years of CP

Table 1. Study characteristics of the included studies

Cohort studies									
Study author	**Type of pancreatitis**	**Setting and period**	**Source population**	**Population size/control**	**PDAC cases**	**Pancreatitis verification**	**PDAC verification**	**Adjusted variables**	**EE value and 95% CI**
Jeon	CP	United States 2006–2015	Single-center	1,766	46	Imaging	Pathology/radiology	Age and sex	12 (8.8–16)[a]
Hao	CP	China 2000–2013	Single-center	1,656	21	Imaging or invasive functional testing	Pathology or multidisciplinary evaluation	Age and sex	20.22 (12.53–30.89)[a]
Midha a	CP	India 2004–2009	Single-center	402	5	Imaging and clinical characteristics	Pathology	Age and sex	121 (39.7–295.9)[a]
Ueda	CP	Japan 2009–2010	Muticenter	506	19	Histology/imaging/invasive functional testing	Pathology/radiology	Age and sex	11.8 (7.1–18.4)[a]
Wang	CP	China 1997–2007	Single-center	420	4	Pathology/imaging	Pathology	Age and sex	27.2 (7.4–69.6)[a]
Zheng	CP	China 2009–2017	Single-center	650	12	Pathology	Pathology	Age	68.12 (35.2–118.99)[a]
Talamini	CP	Italy 1971–1995	Single-center	715	14	Imaging/clinical characteristics	Pathology	Age and sex	18.5 (10–30)[a]
Chari	CP	India 1987–1991	Single-center	185	6	Imaging/clinical characteristics	Pathology, operative examination, and clinical characteristics	Age and sex	100 (37–218)[b]
Malka	CP	France 1973–1997	Single-center	373	4	Imaging/pathology	Pathology	Age and sex	26.7 (7.3–68.3)[a]
Lowenfels	CP	Multicountry 1946–1989	Multicenter	1,552	29	Imaging/biochemical testing/clinical evaluation	Pathology/imaging	Age, sex, and center	16.5 (11.1–23.7)[a]
Pedrazzoli	CP	Italy 1970–1999	Single-center	170	2	Pathology	Pathology	Age, sex, and calendar period	2.93 (0.36–10.6)[a]
Rocca	CP	Italy 1970–1984	Single-center	172	2	Pathology/Imaging	Pathology	Age and sex	NA
Hirano	AIP	Japan 1997–2012	Multicenter	95	2	ICDC criteria	Pathology	Age and sex	3.65 (0.42–12.5)[a]
Hamoir	HP	Belgium 1999–2012	Single-center	61	5	AP-Atlanta criteria; CP-imaging; HP-genetic testing/family history	Pathology	Age	26.5 (8.6–61.9)[a]
Rebours	HP	France 2005	Multicenter	200	10	AP-Atlanta criteria; CP-imaging/pathology; HP-genetic testing or family history	Pathology	Age and sex	87 (42–114)[a]
Howes	HP	Multicountry 1997	Multicenter	418	26	AP-Atlanta criteria; CP-imaging/pathology/biochemical studies; HP-or family history	Pathology/imaging	Age, sex, nationality, and surgical intervention	67 (50–82)[a]

Table 1. (*continued*)

Cohort studies

Study author	Type of pancreatitis	Setting and period	Source population	Population size/control	PDAC cases	Pancreatitis verification	PDAC verification	Adjusted variables	EE value and 95% CI
Lowenfels	HP	Multicountry 1995–1996	Multicenter	246	8	AP-Atlanta criteria/HP-family history	Pathology	Age, sex, and country	53 (23–105)[a]

Single-arm cohort studies

Study author	Type of pancreatitis	Setting and period	Source population	Population size/control	PDAC cases	Pancreatitis verification	PDAC verification	EE value and 95% CI
Rijkers a	AP	Netherlands 2004–2011	Multicenter	680	3	Atlanta criteria	Pathology	1.1 (0.3–3.3)[c]
Rijkers b	CP	Netherlands 2004–2011	Multicenter	51	2	Imaging/pathology/ functional testing	Pathology	9.0 (2.3–35.7)[c]
Sakorafas	CP	United States 1976–1997	Single-center	484	14	Pathology	Pathology	NA
Agarwal	CP	India 1998–2019	Single-center	1,415	29	Pathology/imaging	Pathology	NA
Dite	CP	Czech Republic 1992–2003	Unclear	223	13	Imaging/functional test	Pathology	NA
Ikeura	AIP	Japan 2002–2011	Single-center	63	3	ICDC criteria	Pathology	0.92%[d]
Ikeura	CP	Japan 2002–2011	Single-center	41	1	Imaging/pathology/ functional testing	Pathology	0.59%[d]
Gupta	AIP	United States	Single-center	84	2	Pathology	Pathology	
Vujasinovic	CP	Sweden 2003–2019	Single-center	581	6	Imaging/Pathology	Pathology	0.2%[d]

Case-control studies

Study author	Type of pancreatitis	Setting and period	Source population	Control recruitment	Cases/control (n)	Exposed cases/ control	Pancreatitis verification	PDAC verification	Matching/ Adjusted variables	OR (95% CI)
Midha b	CP	India 2004–2009	Single-center	"Healthy" relative of the cases	249/1,000	24/1	Imaging	Pathology/imaging	Age, sex, and socioeconomic status	97.67 (12.69–751.36)
Hart	AIP	United States 1985–2011	Single-center	344 primary care clinic patients	116/344	1/unknown	Pathology, HISORt criteria, and response to steroids	Pathology	Age, sex, and registration date	NA

AP, acute pancreatitis; AIP, autoimmune pancreatitis; CI, confidence interval; CP, chronic pancreatitis; EE, effect estimate; HISORt, histology, imaging, serology, other organ involvement, and response to therapy (criteria for autoimmune pancreatitis); HP, hereditary pancreatitis; ICDC, International Consensus Diagnostic Criteria (for autoimmune pancreatitis); NA, not available; OR, odds ratio; PDAC, pancreatic ductal adenocarcinoma.
[a]Standardized incidence ratio.
[b]Relative risk.
[c]Incidence rate per 1,000 person-years.
[d]Annual incidence rate.

Table 2. Methodological quality assessment of studies using the Newcastle-Ottawa Scale

Cohort studies

Study	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of the exposure	Demonstration that outcome of interest was not present at start of study	Comparability	Assessment of outcome	Follow-up long enough	Follow-up adequacy
Jeon	*Truly representative	*Same community as exposed cohort	*Secure record	No	**Age and sex	*Independent assessment	*Yes	No statement
Hao	*Truly representative	*Same community as exposed cohort	*Secure record	*Yes	**Age and sex	*Independent assessment	*Yes	No statement
Midha a	*Somewhat representative	*Same community as exposed cohort	*Secure record	*Yes	**Age and sex	*Independent assessment	*Yes	*Yes
Ueda	*Truly representative	*Same community as exposed cohort	*Secure record	*Yes	*Age	*Independent assessment	*Yes	No statement
Wang	*Truly representative	*Same community as exposed cohort	*Secure record	*Yes	**Age and sex	*Independent assessment	*Yes	*Yes
Zheng	*Truly representative	*Same community as exposed cohort	*Secure record	*Yes	*Age	*Independent assessment	*Yes	*Yes
Talamini	*Truly representative	*Same community as exposed cohort	*Secure record	*Yes	**Age and sex	*Independent assessment	*Yes	*Yes
Chari	*Truly representative	*Same community as exposed cohort	*Secure record	No	**Age and sex	*Independent assessment	*Yes	*Yes
Malka	*Truly representative	*Same community as exposed cohort	*Secure record	*Yes	**Age and sex	*Independent assessment	*Yes	No
Lowenfels (CP)	*Truly representative	*Same community as exposed cohort	*Secure record	*Yes	**Age and sex	*Independent assessment	*Yes	No
Pedrazzoli	*Somewhat representative	*Same community as exposed cohort	*Secure record	*Yes	*Age	*Independent assessment	*Yes	*Yes
Rocca	*Truly representative	*Same community as exposed cohort	*Secure record	No	**Age and sex	*Independent assessment	*Yes	No statement
Hirano	*Truly representative	*Same community as exposed cohort	*Secure record	*Yes	**Age and sex	*Independent assessment	*Yes	No statement
Hamoir	*Truly representative	*Same community as exposed cohort	*Secure record	No	*Age	*Independent assessment	*Yes	*Yes
Rebours	*Truly representative	*Same community as exposed cohort	*Secure record	No	**Age and sex	*Independent assessment	*Yes	No statement
Howes	*Truly representative	*Same community as exposed cohort	*Secure record	No	**Age and sex	*Independent assessment	*Yes	No statement
Lowenfels (HP)	*Truly representative	*Same community as exposed cohort	*Secure record	*Yes	**Age and sex	*Independent assessment	*Yes	No statement

Single-arm cohort studies

Study	Selection	Adequate ascertainment of exposure	Adequate ascertainment of outcome	Follow-up long enough?	Replication/ Inferences
Rijkers a	*Truly representative	*Yes	No	No	*Yes
Rijkers b	*Truly representative	*Yes	*Yes	*Yes	*Yes
Sakorafas	*Somewhat representative	*Yes	*Yes	No	*Yes
Agarwal	*Truly representative	*Yes	No	*Yes	*Yes
Dite	Unclear	No description	No	*Yes	No
Ikeura	*Truly representative	*Yes	*Yes	*Yes	*Yes

Table 2. (*continued*)

Single-arm cohort studies

Study	Selection	Adequate ascertainment of exposure	Adequate ascertainment of outcome	Follow-up long enough?	Replication/ Inferences
Gupta	*Truly representative	*Yes	*Yes	*Yes	*Yes
Vujasinovic	*Truly representative	*Yes	*Yes	*Yes	*Yes

Case-control studies

Study	Is case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability	Ascertainment of exposure	Same method for ascertainment for cases and controls
Midha b	*Yes, with independent validation	*Consecutive or obviously representative series of cases	*Community controls	No mention	**Age, sex, and socioeconomic status	*Secure record	No
Hart	*Yes, with independent validation	*Consecutive or obviously representative series of cases	*Community controls	No mention	**Age, sex, and registration date	*Secure record	No

CP, chronic pancreatitis; HP, hereditary pancreatitis. *denotes 1 point, and ** denotes 2 points.

diagnosis. The pooled risk ratio did not substantially change (SIR: 21.77, 95% CI: 14.43–32.720), and the heterogeneity among these studies was high ($I^2 = 67.1\%$, $P = 0.006$).

Risk in smokers. Three CP studies compared the risk estimates for PDAC in CP in smokers vs nonsmokers (22,25,26). On pooling the risk estimates, we found no significant difference in SIRs between the 2 groups (Figure 3).

Systematic review of single-arm cohort studies and case-control studies

Acute pancreatitis. Although our eligibility criteria included AP, we identified only 1 study that met our *a priori* inclusion criteria of strict diagnostic ascertainment (38). In this study, the authors concluded that during a median follow-up of 55 months, the risk of future PDAC was significantly higher in patients with AP who eventually developed CP compared with those who did not (incidence rate per 1,000 person-years 9.0 vs 1.1, $P = 0.049$), indicating a possible association with CP and not standalone AP.

Chronic pancreatitis. We identified 4 single-arm cohort studies on CP that could not be included in the meta-analysis. In the study by Agarwal et al. (40), 2% of patients with CP developed PDAC over a median follow-up of 3.5 years, and smoking was a significant risk factor predicting the development of malignancy (hazard ratio 6.48; CI: 2.2–19.0; $P < 0.001$). Vujasinovic et al. (44) reported an annual incidence PDAC rate of 0.2% among patients with CP. About 83.3% of patients with CP who developed PDAC were smokers. In the study by Dite et al. (41), all 13 of 223 patients who developed PDAC over 2–11 years of follow-up were smokers. The interval between CP diagnosis and PDAC was <2 years in 1 patient, 2–5 years in 4 patients, 5–10 years in 5 patients, and >10 years in 3 patients. In the study by Sakorafas et al. (39), PDAC was diagnosed in 2.9% of patients undergoing surgery after a mean duration of follow-up of 3.4 years (2 months–11 years). In 1 case-control study (Midha b), 24 CP cases vs 1 control developed PDAC (OR: 97.67, 95% CI: 12.69–751.36) (23).

Autoimmune pancreatitis. In the case-control study by Hart et al. (45), 1 of 116 AIP cases developed PDAC. The single-arm cohort study by Gupta et al. (43) reported 2 cases of PDAC in 84 patients with AIP after a follow-up period of 6 and 10 years. In another single-arm cohort study by Ikeura et al. (42), 3 of 63 patients with AIP developed PDAC.

Incidence rate of PDAC during CP follow-up

Six studies reported the CIRs of PDAC over time after the diagnosis of CP (21,22,24,25,29,30). Data were insufficient to conduct meta-regression because of the small number of studies, and data for covariates of interest were not consistently available. Figure 4 demonstrates a trend of increasing CIR with increased duration of CP within each individual study. Zheng et al. reported a rising cumulative incidence of PDAC after surgery for CP: 1.48% at 3 years, 2.63% at 6 years, and 3.71% 9 years after the surgery for CP complications. Talamini et al. also described a rising cumulative probability of PDAC occurrence after the onset of CP.

Publication bias

Figure 5 depicts the funnel plot to visualize the effect of publication bias in our study. Presence of asymmetry was considered potentially indicative of bias.

DISCUSSION

Main findings

In this systematic review and meta-analysis, available data confirm higher than average risk of PDAC in patients diagnosed with CP and HP.

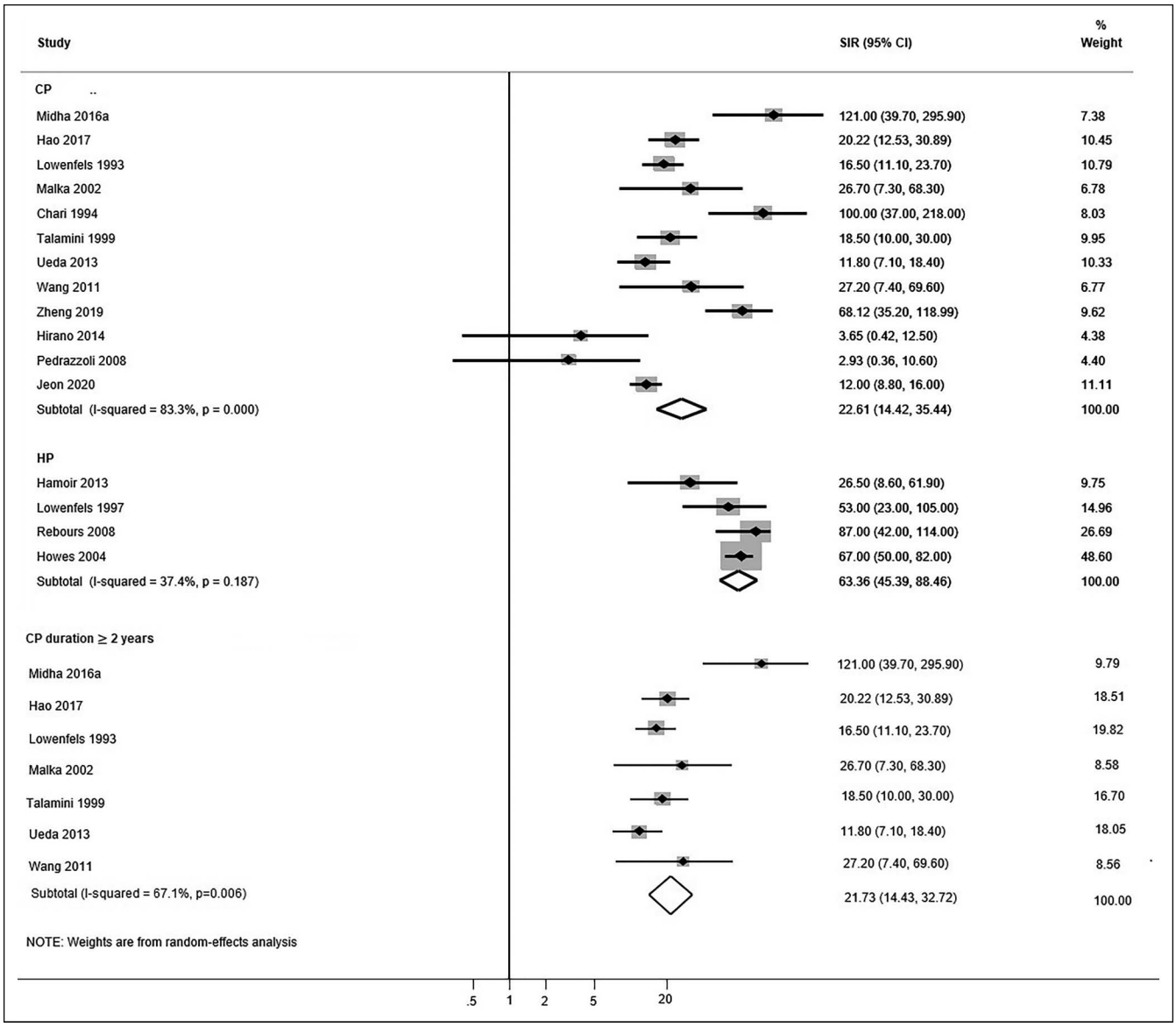

Figure 2. Forest plots of the observational studies examining the association between CP, HP, and PDAC risk. CI, confidence interval; CP, chronic pancreatitis; HP, hereditary pancreatitis; PDAC, pancreatic ductal adenocarcinoma; SIR, standardized incidence ratio.

The elevated risk of PDAC in patients with CP and HP in our meta-analysis is consistent with results reported in previous studies. In a systematic review on CP and pancreatic cancer by Kirkegard et al. (46), the risk estimates at 2, 5, and 9 years after CP diagnosis were 16.16, 95% CI: 12.59–20.73; 7.90, 95% CI: 4.26–14.66; and 3.53, 95% CI: 1.69–7.38, respectively. In a meta-analysis by Raimondi et al. (7), the pooled estimate of 6 CP studies was 13.3, 95% CI: 6.1–28.9 and the pooled estimate of 3 HP studies was 69, 95% CI: 56.4–84.4. In meta-analysis of 6 CP studies by Tong et al. (47), the pooled estimate was 10.35, 95% CI: 9.13–11.75. Using stringent case definitions as is often necessary in clinical practice, we were able to demonstrate and quantify the risk association between CP and PDAC in this meta-analysis. The risk estimates in our study are higher than previously reported estimates. A possible explanation is the inclusion in previously published reports of studies with unverified exposure and outcome (based on self-reported history or *ICD* codes), increasing the risk of misclassification bias. A recent meta-analysis of 11 studies on AP by Liu et al. (48) reported a higher risk of PDAC in patients with AP (RR: 2.07, 95% CI: 1.36–2.78). We were unable to perform a meta-analysis assessing the PDAC risk in AP because only 1 study met our stringent inclusion criteria. It remains unclear whether PDAC is associated with standalone AP or limited to the subset where AP is the first manifestation of underlying CP. Studies that use strict diagnostic criteria for AP and limit inclusion to biopsy-proven PDAC are needed to improve our understanding of accurate risk estimates. Similarly, only 1 AIP study (Hirano) reports SIRs; thus, a separate sensitivity analysis could not be performed. Multicenter prospective cohort studies with long-term follow-up are needed to effectively understand PDAC risk in patients with AIP.

Practice implications

PDAC is a lethal malignancy with an advanced-stage clinical presentation at diagnosis; early detection using surveillance

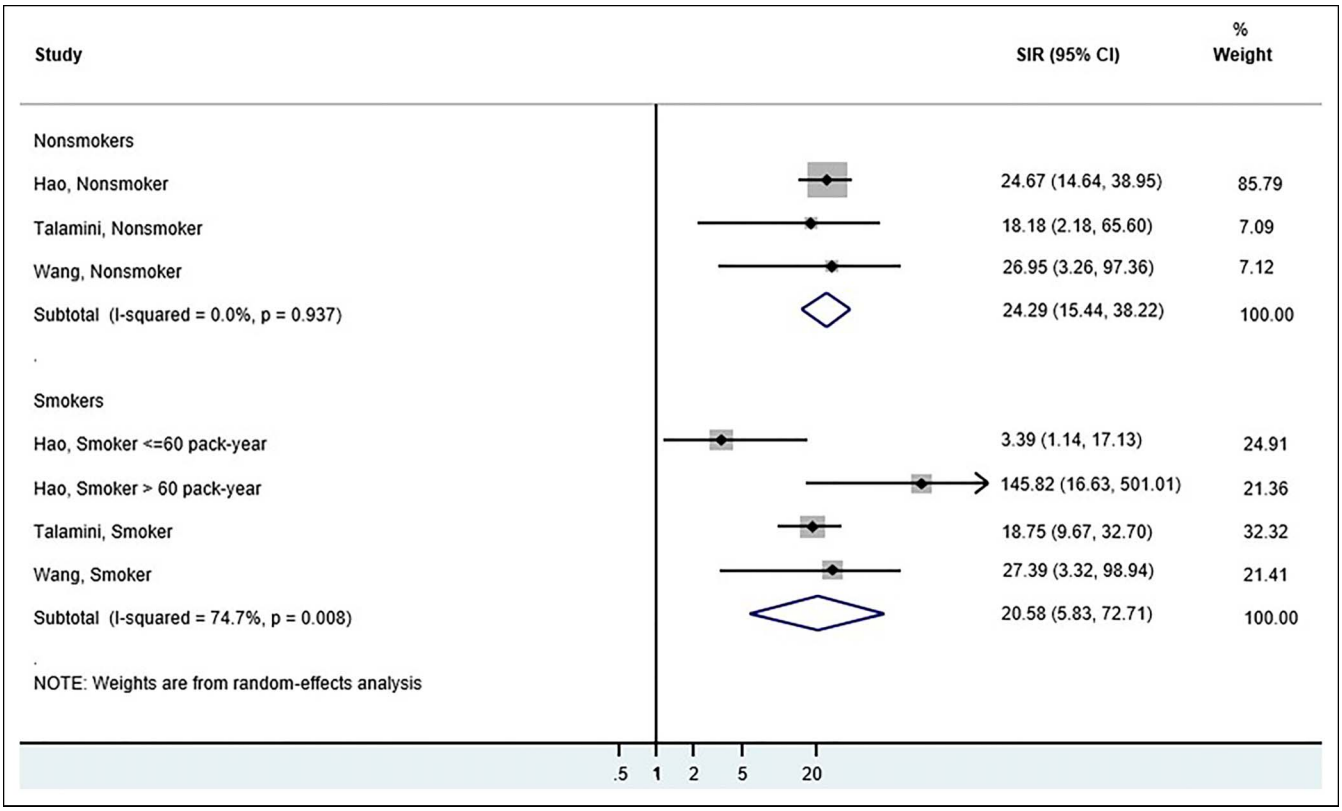

Figure 3. Forest plots of the observational studies comparing the SIR of pancreatic ductal adenocarcinoma in chronic pancreatitis for smokers vs nonsmokers. CI, confidence interval; SIR, standardized incidence ratio.

provides a chance for improving prognosis. The goal of surveillance is to detect and manage precursor lesions of cancer, although the ability to do so is limited in current clinical practice. Because of a substantially increased risk of PDAC in patients with HP, expert consensus supports initiating pancreas surveillance in these patients at age 40 or 20 years after the first pancreatitis attack, irrespective of gene mutation status (49). However, no clear guidelines for screening exist for the patients with CP without an underlying genetic mutation. Our study indicates that PDAC risk increases with duration of CP likely because of chronicity of inflammation-driven carcinogenesis (50). One could envision a pancreas cancer surveillance strategy in patients with CP similar to inflammatory bowel disease, where colon cancer surveillance starts 8–10 years after diagnosis. For a possible surveillance program for these patients, more data are needed on the timing of development of pancreatic cancer after CP diagnosis. Furthermore, screening patients with CP for PDAC requires enrichment strategies by building multivariable models to identify patients with CP at a higher risk of PDAC and concomitant development of novel biomarkers that can accurately detect PDAC in patients with CP with high accuracy (51).

Strengths and limitations

This systematic review has several strengths. It includes an up-to-date quantitative meta-analysis assessing the association of pancreatitis and PDAC using specific diagnostic criteria for both the disease and the outcome. It avoids the use of patient-reported diagnosis and billing codes and its associated pitfalls. This allows for a more reliable risk assessment and minimizes the risk of misclassification of pancreatitis and PDAC, but some degree of misclassification is unavoidable because the clinical diagnosis of CP and other forms of pancreatitis can be challenging. In addition, PDAC diagnosis in CP is challenging and can be delayed because imaging can miss lesions, given the abnormal nature of the pancreatic parenchyma in CP (52). Excluding patients diagnosed within a short interval after CP diagnosis as was performed in the sensitivity analysis in our study is critical for accurate risk estimation. We also specifically report on CIRs of PDAC during CP follow-up, and our data indicate the potential role of pancreatic cancer screening in long-standing CP. Finally, we conducted a comprehensive search of multiple databases; studies were reviewed by independent reviewers, and the study team included experts in pancreatic diseases and research methodology.

This study has some limitations. A high heterogeneity was seen in the overall pooled SIR in CP studies, limiting the interpretation of the summary estimate. Differences in the study population, covariates assessed, and ability to control for confounding by variables such as smoking, alcohol consumption, and diabetes mellitus might account for this heterogeneity. In addition, CP is a heterogeneous disease with no uniform diagnostic criteria which makes pooling studies challenging. Furthermore, there is likely an overlap between HP and CP because a substantial number of studies report idiopathic CP (before routine genetic testing), and some patients might have an undiagnosed genetic mutation. Most HP studies primarily focused on *PRSS1* mutation (3 of the 4 studies), so these data may not represent HP caused by *CTRC, SPINK1* and *CFTR* mutations. There is a risk of selection

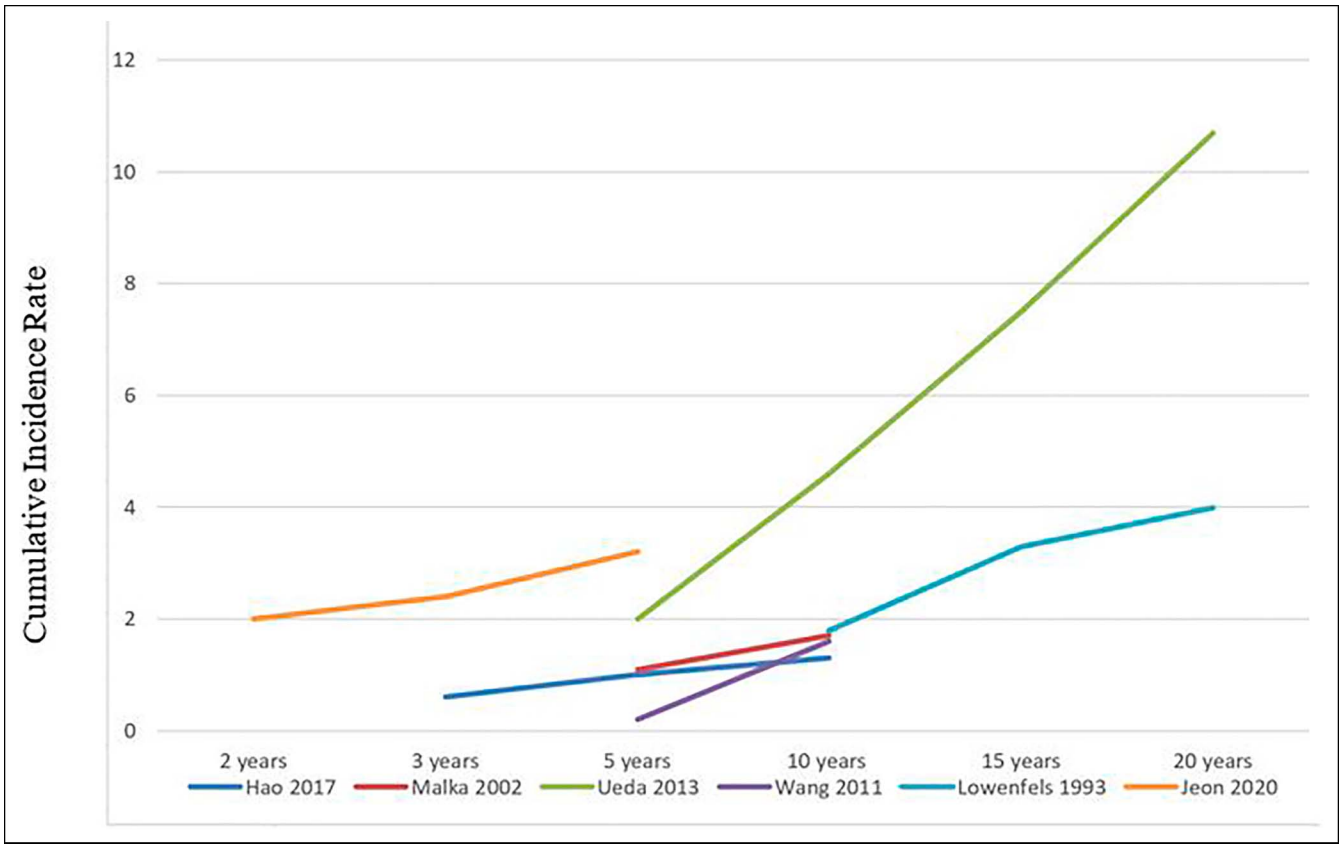

Figure 4. Cumulative incidence rate of pancreatic ductal adenocarcinoma after diagnosis of chronic pancreatitis.

bias in studies because of variable follow-up periods and loss of patients to follow-up. The risk estimates may be inflated and have low precision in studies with very few patients with exposure and outcome and in studies including patients with complicated CP undergoing surgery. Only 3 studies reported risk estimates in smokers vs nonsmokers; thus, we could not evaluate the effect of smoking on PDAC in patients with CP. Moreover, we do not have a good way to statistically assess publication bias because the funnel plot is not reliable when the number of studies is small or when heterogeneity is present.

In summary, CP is associated with an increased risk of PDAC, and the increased risk persists after excluding potentially incident cases in whom PDAC was diagnosed in close temporal proximity to CP diagnosis. Moreover, the risk of PDAC in CP seems to increase with the duration of disease. The risk association between PDAC and AP and AIP remains poorly defined and warrants further study. Future management guidelines should consider incorporating pancreas cancer surveillance in individuals with long-standing CP.

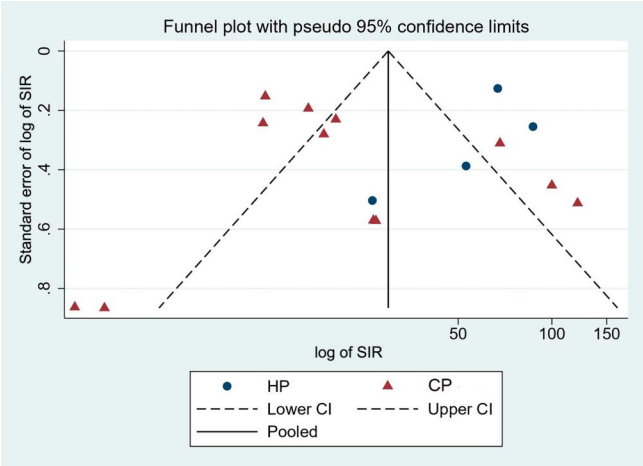

Figure 5. Funnel plot assessing publication bias.

CONFLICTS OF INTEREST

Guarantor of the article: Shounak Majumder, MD.

Specific author contributions: S.G.: study concept and design, acquisition of data, analysis and interpretation of data, and drafting of manuscript. J.d.l.F: study concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, and critical revision of manuscript for important intellectual content. M.H.M.: study concept and design, analysis and interpretation of data, statistical analysis, and critical revision of manuscript for important intellectual content. S.M.: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript for important intellectual content, and study supervision.

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Data, analytic methods, and study materials pertinent to this manuscript may be made available to other researchers on reasonable request.

Study Highlights

WHAT IS KNOWN

- ✓ There is an increased risk of pancreatic ductal adenocarcinoma (PDAC) in patients with pancreatitis, but the magnitude of association, the risk in different forms of pancreatitis, and association with duration of disease is unclear.

WHAT IS NEW HERE

- ✓ This up-to-date systematic review and quantitative meta-analysis including studies with verified diagnosis of pancreatitis and pancreatic cancer suggests an increased risk of PDAC in patients with chronic and hereditary forms of pancreatitis.
- ✓ There are insufficient data to definitively study the risk of PDAC in acute pancreatitis and autoimmune pancreatitis.
- ✓ In chronic pancreatitis, the PDAC incidence rates increase with duration of disease, indicating possible role of pancreatic cancer screening in patients with long-standing chronic pancreatitis.

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