Acute pancreatitis as a risk factor of chronic pancreatitis and pancreatic cancer. An overview

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This is an overview of relation between acute and chronic pancreatitis and between acute pancreatitis and pancreatic cancer. Acute pancreatitis and recurrent acute pancreatitis are an etiological factor of chronic pancreatitis. Population-based studies have calculated the risk of acute recurrent pancreatitis after the first attack of acute pancreatitis to be 20% and development of chronic pancreatitis after first attack of acute pancreatitis is 10%. An important risk factor is tobacco smoking. Acute and chronic pancreatitis are risk factors for pancreatic cancer. The risk of acute pancreatitis is related to the number of recurrences of acute pancreatitis, but not the etiology of acute pancreatitis. Acute pancreatitis, as well as chronic pancreatitis, are risk factors for pancreatic cancer. After an attack of acute pancreatitis or recurrent acute pancreatitis a patient should be regarded as a high risk.

Key words: acute pancreatitis, chronic pancreatitis, pancreatic cancer, alcohol, etiology, pancreatic cancer localisation

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INTRODUCTION

Acute pancreatitis is a disease with a high incidence and one of the most common indications for hospitalization for non-cancerous gastrointestinal diseases. A German study from 2011 showed an incidence of acute pancreatitis ranging from 13 to 43 cases per 100.000 inhabitants[1]. Data from 2017 published in Germany indicate a hospitalization rate of 24 patients per 100.000 inhabitants with acute pancreatitis[2]. The activation of inflammatory processes such as trypsinogen activation, the role of nuclear factor kappa beta (NF-κB) in acinar cells causing a strong inflammatory response and local and systemic damage play a major role in the pathogenesis of acute pancreatitis, but other pathological processes such as lysosomal dysfunction, oxidative stress, pH changes or autophagy with endoplasmic reticulum involvement are also important[3].

ACUTE PANCREATITIS AS A RISK FACTOR FOR CHRONIC PANCREATITIS

Acute pancreatitis and acute recurrent pancreatitis are significant risk factors for the development of chronic pancreatitis. Chronic pancreatitis is characterized as a progressive process of inflammation with fibrosis of the pancreatic tissue and scarring. A new definition of chronic pancreatitis, published in 2016, defines the disease as a pathological fibroinflammatory syndrome of the pancreas in the presence of genetic, environmental and/or other risk factors, leading to a pathological reaction with the development of parenchymal damage[4]. The conservative model of the development of chronic pancreatitis includes five stages (A–E). Stage A is a risk, asymptomatic stage, stage C is a stage of early form chronic pancreatitis with positivity of biomarkers, stage D is characterized by clinical features – immune dysregulation, islet dysfunction, acinar dysfunction, pathologic pain, or metaplasia. Last stage E is the end stage of chronic pancreatitis, with fibrosis, exocrine insufficiency diabetes mellitus type 3c, or pancreatic ductal adenocarcinoma. Stage B is a stage, where acute pancreatitis and acute recurrent pancreatitis precede as an initiating phenomenon of this stage – early chronic pancreatitis. This is called the "two-hit" model, when after acute pancreatitis the gland is damaged and then an abnormal inflammatory response occurs, with activation of pancreatic stellate cells. A study evaluating 14 publications (Table 1) with a total of 8,492 patients showed that 10% of patients after the first episode of acute pancreatitis and 36% of patients with recurrent acute pancreatitis were diagnosed with chronic pancreatitis within 12 months of the acute attack[5]. Alcohol and smoking were found to be the most important risk factors for the devel-

opment of chronic pancreatitis, following acute pancreatitis. Similar results were obtained in a retrospective study by Bertilsson et al. evaluating 1457 people after the first attack of acute pancreatitis. Also in this study, alcohol and smoking were risk factors for chronic pancreatitis, as well as the risk of biliary etiology of acute pancreatitis (53%) (ref.[6]). Finally, in a study from 2020, looking at predictors of the onset and development of chronic pancreatitis, idiopathic juvenile and idiopathic senile variants of chronic pancreatitis were shown to be particularly important, in addition to alcohol[7].

In our study from 2020, we confirmed that chronic pancreatitis can occur after the first attack of acute pancreatitis, and that this is significantly potentiated by the presence of a metabolic syndrome (obesity, arterial hypertension, hypertriglyceridemia, type 2 diabetes mellitus). The interval of development of chronic pancreatitis after the first attack of acute pancreatitis was 12 months in persons with presence of metabolic syndrome and an average of 20 months in the group without metabolic syndrome. According to these results, the metabolic syndrome is a factor significantly potentiating or accelerating the development of chronic pancreatitis[8].

ACUTE PANCREATITIS AS A RISK FACTOR FOR PANCREATITIC CANCER

Acute pancreatitis and pancreatic carcinoma are diseases whose association is still a matter of debate[9]. A Danish study involving follow-up of 41.669 people with acute pancreatitis showed that the incidence of pancreatic carcinoma after the diagnosis of acute pancreatitis was higher in the two years following the diagnosis of acute pancreatitis (HR 19.28: 95%CI, 14.62–25.41). In the following years after the first attack of acute pancreatitis, although the incidence of pancreatic cancer decreased, the number of pancreatic cancer diagnoses was still high (HR 2.02: 95%CI, 1.57–2.61). These results suggest that the risk of pancreatic cancer after acute pancreatitis is long-term[10]. A Swedish population-based study published in 2018, similar to the study from Denmark, showed the highest incidence of pancreatic cancer during the first few years after acute pancreatitis, but 10 years after acute pancreatitis, the incidence of cancer was similar to that of the control group[11]. A recent US study compared the risk of pancreatic cancer in 35,500 people with acute pancreatitis versus a control group 3–10 years after acute

Table 1. Characteristics of Included Studies[5].

Study	Year	Country	Study design	Population or hospital based	Study period	Total patients included	Patients followed up, n	Mean follow-up time, mo	Accrual rate per month	Patients with first episode of AP, n (%)	Severity criteria
Madsen and Schmidt	1979	Denmark	Prospective cohort	Hospital	1960–1975	122	112	180	0.7	101 (83)	Not stated
Reid and Kune	1980	Australia	Prospective cohort	Hospital	1968–1975	113	113	Not stated	1.3	113 (100)	Not stated
Angelini et al.	1993	Italy	Prospective cohort	Hospital	1974–1990	300	118	52.8	1.6	Not stated	Not stated
Doepel et al.	1993	Finland	Prospective cohort	Hospital	1974–1988	67	37	74.4	0.4	Not stated	Ranson
Seidensticker et al.	1995	Germany	Prospective cohort	Hospital	1976–1992	38	37	34	0.2	38 (100)	Ranson >4
Lund et al.	2006	Denmark	Retrospective cohort	Hospital	1995–1998	155	138	Not stated	6.5	155 (100)	Ranson >3
Garg et al.	2007	India	Prospective cohort	Hospital	1995–2003	75	75	17.6	0.8	0	Not stated
Yasuda et al.	2008	Japan	Prospective cohort	Hospital	1990–2006	103	45	56	0.5	Not stated	JSS > 2
Lankisch et al.	2009	Germany	Prospective cohort	Hospital	1987–2004	532	501	93.6	2.6	532 (100)	APACHE II >8
Takeyama	2009	Japan	Prospective cohort	Population	1987–2004	717	174	Not stated	4.6	Not stated	JSS>2
Nojgaard et al.	2011	Denmark	Prospective cohort	Population	1977–2008	352	352	158.5	6.2	Not stated	Not stated
Yadav et al.	2012	United States	Retrospective cohort	Population	1996–2007	7456	6010	40	69	7456 (100)	Not stated
Cavestro et al.	2014	Italy	Prospective cohort	Hospital	2002–2011	196	196	52.2	1.9	196 (100)	Revised Atlanta
Nikkola et al.	2014	Finland	Prospective cohort	Hospital	2001–2005	120	79	24 or 84	3	120 (100)	Revised Atlanta

Table 2. Higher risk of pancreatic carcinoma after the diagnosis of acute pancreatitis[14].

Study (Country)	Total patients included	Risk
Denmark	41,669	HR 2.02: 95 %CI, 1.57–2.61
Sweden	49,749	769 individuals developed pancreatic cancer, of whom 536 (69.7%) had a history of acute pancreatitis
US	35,500	HR 1.7, 95 % CI, 1.4–2.0
Rijkers et al.	731	the rate ratio of pancreatic cancer was almost 9 times higher in patients who developed chronic pancreatitis compared with those who did not (P = 0.049).

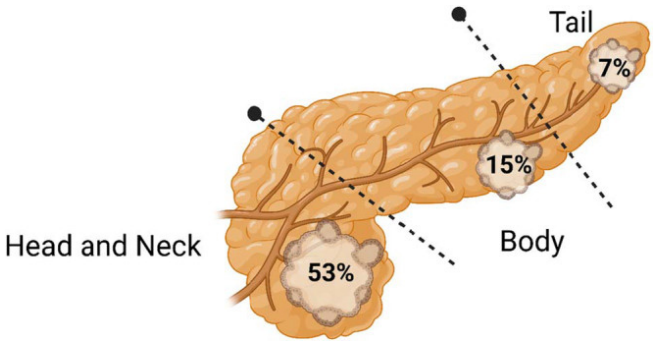

Fig. 1. Image depicting location of pancreatic adenocarcinoma within the pancreas in patients with acute pancreatitis[19].

pancreatitis[12]. The results of this study also confirmed a significantly increased incidence of pancreatic cancer after acute pancreatitis (HR 1.7, 95% CI, 1.4–2.0). As mentioned above, acute pancreatitis can progress to chronic pancreatitis. A study by Rijkers et al. investigating the course of changes after acute pancreatitis found that in a cohort of 731 patients who developed chronic pancreatitis after acute pancreatitis, only two patients out of 51 developed pancreatic cancer[13]. In contrast, the incidence of pancreatic cancer was up to nine times higher in those who did not progress from acute disease to chronic pancreatitis[14] (Table 2). In a population-based study, Park et al. demonstrated that smoking, high BMI and diabetes mellitus are significant risk factors for pancreatic cancer[15].

One of the most common etiological factors of acute pancreatitis is alcohol. Interestingly, alcoholic versus non-alcoholic forms of acute and chronic pancreatitis do not differ in terms of the initiation of pancreatic cancer[16,17]. Alcohol drinking was not identified as a risk factor leading to pancreatic cancer in a study from the United States[18]. Age play an important role in the development of pancreatic cancer following an attack of acute pancreatitis. Compared with the control group, younger individuals with pancreatic cancer after acute pancreatitis have a better prognosis. One of the reasons for this is probably that they are diagnosed at an early stage[12,19]. Risk factors for pancreatic cancer are also overweight, liver cirrhosis, prediabetes/diabetes mellitus, and gallbladder concretions[20]. Gender is also a risk factor, although the findings are inconclusive[21], but women with acute pancreatitis and pancreatic cancer predominate[22].

Regarding the localization of pancreatic adenocarcinoma, the head of the pancreas was the most frequent localisation in subjects after acute pancreatitis (53%) (ref.[19]) (Fig. 1). This localization is one possible explanation for the presence of carcinoma accompanied by simple hyperamylasaemia or acute pancreatitis due to pancreatic ductal permeability[8]. In persons with unclear etiology of acute pancreatitis, the possibility of pancreatic adenocarcinoma should always be considered. In such a case, CEA and CA19-9, which are elevated in pancreatic disease termed APUE (Acute Pancreatitis of Undetermined Etiology) (ref.[23,24]) and may be a marker of the presence of early-stage pancreatic adenocarcinoma, should be investigated. In the study by Singh et al, CEA and CA19-9 levels were lower or less frequently elevated in APUE without the presence of pancreatic adenocarcinoma[19]. A limitation of the investigation is, of course, that CA19-9 and CEA levels may also be elevated in acute biliary pancreatitis or hepatobiliary disease.

CONCLUSION

Acute pancreatitis is one of the risk factors for pancreatic adenocarcinoma. The maximum of this risk is usually within 2 years after acute pancreatitis, which does not change the fact that acute pancreatitis is a long-term risk. Pancreatic adenocarcinoma may also be present after the presentation of acute pancreatitis. Therefore, in the case of APUE the possibility of pancreatic adenocarcinoma should always be considered. In such case, we can diagnose pancreatic adenocarcinoma at an early stage.

Smoking, obesity or diabetes mellitus are significant risk factors for pancreatic cancer but may be unrelated to acute pancreatitis. Acute pancreatitis, including a form of

acute recurrent pancreatitis, is also an etiologic factor in the development of chronic pancreatitis. While opinions on the relationship between acute pancreatitis and pancreatic cancer are not clear-cut, chronic pancreatitis can clearly be considered a significant risk.

Search strategy and selection criteria

MEDLINE, PubMed and EMBASE data were searched for published studies during last seven years-from 2017 to 2023 (except one publication from year 2011) in patients with acute, or chronic pancreatitis, resp. pancreatic adenocarcinoma. The selection criteria were the evaluation of papers in patients with acute pancreatitis, which developed to chronic pancreatitis, and the publications with topic acute pancreatitis and pancreatic cancer, resp. patients with pancreatic cancer and a history of acute pancreatitis. In this overview study the etiology or grading, resp. complications of acute pancreatitis was not evaluated.

Author contributions: PD: study design; DS, MB, PD: data collection; MS, BK: data interpretation; PD, DS: literature search and manuscript writing.
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REFERENCES

1. Phillip V, Huber W, Hagemes F, Lorenz S, Matheis U, Preinfalk S, Schuster T, Lippl F, Saugel B, Schmid RM. Incidence of acute pancreatitis does not increase during Octoberfest, but is higher than previously described in Germany. Clin Gastroenterol Hepatol 2011;9(11):995-1000. doi: 10.1016/j.cgh.2011.06.016
2. Beyer G, Hoffmeister A, Lorenz P, Lynene P, Lerch MM, Mayerle J. Akute und chronische Pankreatitis. In. Beyer G., Hoffmeister A., Lorenz P. et al: Clinical practice guidelines: Acute and chronic pancreatitis. Dtch Arztebl Int 2022;119(29-30):495-501. doi: 10.3238/arztebl.m2022.0223
3. Sah RP, Dawra RK, Saluja AK. New insights into the pathogenesis of pancreatitis. Curr Opin Gastroenterol 2013;29(5):523-30. doi: 10.1097/MOG.0b013e328363e399
4. Whitcomb DC, Frulloni L, Garg P, Greer JB, Schneider A, Yadav D, Shimosegawa T. Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition. Pancreatology 2016;16(2):218-24. doi: 10.1016/j.pan.2016.02.001
5. Sankaran SJ, Xiao AY, Wu LM, Windsor JA, Forsmark ChE, Petrov MS. Frequency and progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology 2015;149(6):1490-500. doi: 10.1053/j.gastro.2015.07.066
6. Bertilsson S, Sward P, Kalaitzakis E. Factors that affect disease progression after first attack of acute pancreatitis. Clin Gastroent Hepatol 2015;13(9):1662-69. doi: 10.1016/j.cgh.2015.04.012
7. Agarwal S, Sharma S, Gunjan D, Singh N, Kaushal K, Poudel S, Anand A, Gopi S, Mohta S, Sonika U, Saray A. Natural course of chronic pancreatitis and predictors of its progression. Pancreatology 2020;20(3):347-55. doi: 10.1016/j.pan.2020.02.004
8. Bojkova M, Dite P, Kunovsky L, Blaho M, Kianicka B, Novotny I, Uvirova M, Dvorackova J, Dolina J, Precechtelova M, maskova H, Prochazka V, Janecek P, Motyka O, Martinek A. The role of metabolic syndrome in the induction of chronic pancreatitis after a first attack of acute pancreatitis-multisite study. Vnitr Lek 2020;66(8):12-6. (in Czech)
9. Gandhi S, de la Fuente I, Murad MH, Majumder S. Chronic pancreatitis is a risk factor for pancreatic cancer, and incidence increases with duration of disease: A systematic review and meta-analysis. Clin Transl Gastroenterol 2022;28;13(3):e00463. doi: 10.14309/ctg.0000000000000463
10. Kirkegard J, Cronin-Fenton D, Heide-Jorgensen U, Mortensen FV. Acute pancreatitis and pancreatic cancer risk: a nationwide matched-cohort study in Denmark. Gastroenterology 2018;154(6):1729-36. doi: 10.1053/j.gastro.2018.02.011
11. Sadr-Azodi, Oskarsson V, Discacciati A, Videhult P, Askling J, Ekbom A. Pancreatic cancer following acute pancreatitis: a population-based matched cohort study. Am J Gastroenterol 2018;113(11):1711-19. doi: 10.1038/s41395-018-0255-9
12. Munigala S, Almaskeen S, Subramaniam DS, BAndi S, Bowe B, Xian H, Sheth SG, Burroughs TE, Agarwal B. Acute pancreatitis recurrences augment long-term pancreatic cancer risk. Am J Gastroenterol 2023;118(4):727-37. doi: 10.14309/ajg.0000000000002081
13. Rijkers AP, Bakker OJ, Ahmed-Ali U, Hagenaars JCJP. Van Santvoort HC, Besselink MG, Bollen TL, van Eijck CH, Dutch Pancreatitits Study Group. Risk of pancreatic cancer after a primary episode of acute pancreatitis. Pancreas 2017;46(8):1018-22. doi: 10.1097/MPA.0000000000000879
14. Liu J, Wang Y, Yu Y. Meta-analysis reveals an association between acute pancreatitis and risk of pancreatic cancer. World J Clin Cases 2020;8(19):4416-30. doi: 10.12998/wjcc.v8.i19.4416
15. Park BK, Seo JH, Chung JB, Choi JK. Lifestyle, body mass index, diabetes, and the risk of pancreatic cancer in a nationwide population-based cohort study with 7.4 million Korean subjects. Br J Cancer 2022;127(3):549-57. doi: 10.1038/s41416-022-01807-5
16. Lowenfels AB, Maissoneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, Dimagno EP, Andrén-Sandberg A, Domellof L. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med 1993;328(20):1433-37. doi: 10.1056/NEJM199305203282001
17. Kudo Y, Kamisawa T, Anjiki H, Takuma K, Egawa N. Incidence of and risk factors for developing of pancreatic cancers in patients with chronic pancreatitis. Hepatogastroenterology 2011;58(106):609-11.
18. Lew D, Kamal F, Phan K., Randhawa K, Cornwell S, Bangolo AI, Weissman S, Pandol SJ. Epidemiologic risk factors for patients admitted with chronic pancreatitis and pancreatic ductal adenocarcinoma in the United States. World J Clin Oncol 2022;13(11):907-17. doi: 10.5306/wjco.v13.i11.907
19. Singh RR, Klein AP, Sharma NR, O´Reilly EM. Does acute pancreatitis herald pancreatic ductal adenocarcinoma? A multicenter electronic health research network study. Cancer Med 2023;12(3):2505-13. doi: 10.1002/cam4.5094
20. Luo J, Iwasaki M, Inoue M, Sasazuki S, Otani T, Ye W, Tsugane S, JPHC Study Group. Body mass index, physical activity and the risk of pancreatic cancer in relation to smoking status and history of diabetes: A large-scale population-based cohort study in Japan-the JPHC study. Cancer Causes Control 2007;18(6):603-12. doi: 10.1007/s10552-007-9002-z
21. Gheorghe G, Ionescu VA, Moldovan H, Diaconu CC. Clinical and biological data in patients with Pancreatic cancer vs. chronic pancreatitis - A single center comparative analysis. Diagnostics (Basel) 2023;13(3):369. doi: 10.3390/diagnostics13030369
22. Ma DM, Dong XW, Han X, Ling Z, Lu GT, Sun YY, Yin XD. Pancreatitis and pancreatic cancer risk. Technol Cancer Res Treat 2023;22:15330338231164875. doi: 10.1177/15330338231164875
23. Topaloglu U, Palchuk MB. Using a federated network of real-world data to optimize clinical trials operations. JCO Clin Cancer Inform 2018;2:1-10. doi: 10.1200/CCI.17.00067
24. Pereira SP, Oldfield L, Ney A, Hart PA, Keane MG, Pandol SJ, Li D, Greenhalf W, Jeon ChY, Koay EJ, Almario ChV, Halloran Ch, Lennon AM, Costello E. Early detection of pancreatic cancer. Lancet Gastroenterol Hepatol 2020;5(7):698-710. doi: 10.1016/S2468-1253(19)30416-9