Association between Pancreatitis and Pancreatic Cancer

Subjects: Gastroenterology & Hepatology

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Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with poor prognosis, leading to significant cancer-related mortality and an overall five-year survival rate of about nine percent.

acute pancreatitis chronic pancreatitis pancreatic cancer

1. Introduction

Burden of pancreatic ductal adenocarcinoma (PDAC) is well-recognized globally, and it is estimated as the 11th most common cancer in the world based on accumulative data from 2018 [1]. PDAC incidence varies across the world, with higher rates in developed populations from North America (7.4 per 100,000 people) and Western Europe (7.3 per 100,000 people) [1][2]. PDAC is more common in men (4.9 per 100,000) than women (3.6 per 100,000) and increases in both sexes with age [1][2]. Importantly, PDAC annual incidence is increasing by 0.5–1.0% [3], and remains a lethal disease with poor prognosis, leading to significant cancer-related mortality with an overall five-year survival rate of about nine percent [4]. Rapid growth and lack of a reliable screening modality make diagnosing PDAC challenging, which results in disease discovery at advanced incurable stages [4]. By 2030, PDAC is projected to become the second leading cause of cancer-related mortality [3].

PDAC accounts for more than 90% of all pancreatic tumors [5]. Accumulating evidence suggests that pancreatitis is a risk factor for PDAC. Evolving chronic pancreatitis (CP) following recurrent bouts of acute pancreatitis (AP) has been proposed as risk factor for cancer development in the setting of persistent inflammation and ongoing exposure to carcinogens. Virchow's observation of inflammatory cells within neoplastic tissue suggested correlations between inflammation and future dysplasia [6], proven by development of various cancers from sites of chronic irritation and inflammation, including tumors of the lung, GI tract, skin, and urinary bladder.

2. Association between Pancreatitis and Pancreatic Cancer

2.1. Acute Pancreatitis and Pancreatic Cancer

The association between pancreatitis and pancreatic cancer is well-established, and it is mostly driven by CP. Over the past few decades, there has been an ongoing debate on whether AP carries the same risk of developing pancreatic cancer, and multiple studies aimed to quantify such risk. Kirkegard et al. conducted a large nationwide matched cohort study in Denmark, which included 40,000 patients with AP. This work concluded that the risk of

PDAC in patients with AP was two-fold higher compared to that in the general population over a 5–10-year follow-up period [7]. These observations were similar to the findings from US studies utilizing the VA system database [8][9]. Bansal et al. published a case-control study including about 2600 veterans with PDAC and noncancer controls. This work demonstrated higher likelihood of having a history of AP preceding PDAC (OR 1.76; 95% CI: 1.28–2.41) [8]. Another Taiwanese study assessed AP and PDAC association [10] by evaluating 747 hospitalized patients with AP and 5976 controls. This work observed significantly higher five-year risk of developing PDAC in the AP cohort compared to that in controls (HR 9.10; 95% CI: 3.81–21.76). A large population-based study in Sweden reproduced similar conclusions of elevated PDAC risk in patients with AP in the first few years, but interestingly, this decreased over time [11]. Two meta-analyses were conducted to ascertain the effect of AP and PDAC association. Zhang et al. meta-analysis of four cohort studies estimated a pooled relative risk of 8.30 (95% CI: 4.27–16.13) [12]. Another meta-analysis of 11 observational studies, suggested higher PDAC incidence after AP with estimated pooled relative risk of 7.81 (95% CI: 5.00–12.19) [13]. Although these observations highlighted a robust association between AP and PDAC, the question of whether this is a causal effect or if AP is a presenting symptom of PDAC remains unanswered.

2.2. Chronic Pancreatitis and Pancreatic Cancer

Multiple studies have shown that CP is highly associated with PDAC [8][14][15][16][17][18][19][20]. A multicenter, retrospective cohort study conducted by the International Pancreatitis Study Group showed that the cumulative risk of PDAC in patients with CP is 1.8% and 4% at 10 and 20 years, respectively, a rate which is from 15- to 16-fold greater than that of the general population [14]. Importantly, this risk was independent of sex, ethnicity, and type of pancreatitis (alcoholic and nonalcoholic). A single-center prospective cohort study verified these observations, concluding that CP patients have higher 5- and 10-year cumulative incidence of developing PDAC (1.1% and 1.7%) compared to that in age- and sex-matched controls [15]. Most convincingly, a meta-analysis of six cohort studies and one case-control study showed a pooled relative risk estimate of 13.3 for PDAC among patients with CP [16], which suggested that about five percent of patients with CP will develop PDAC within a 20-year follow-up period. These efforts proposed the higher causative association between long-standing CP and future PDAC development.

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