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EDITORIAL

Chronic pancreatitis as a driving factor for pancreatic cancer: An epidemiological understanding

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Abstract

The retrospective study by Lew *et al* (2022) examined the rising hospitalization rates for chronic pancreatitis (CP) and its association with pancreatic ductal adenocarcinoma (PDAC), revealing significant ethno-racial disparities and risk factors. Overweight black men aged 40-59 years and white men over 40 years with higher incomes showed an elevated risk of PDAC among CP patients. The study, which included 14.2 million admissions from 2016-2017, found that 2.6% of adult patients were diagnosed with CP, with white males being the majority. Multivariate regression analysis identified men, black individuals, those aged 40-59 years, and individuals with a body mass index (BMI) between 25 and 29.9 as having an increased risk for CP. Moreover, 0.78% of CP patients also had PDAC, with older age and BMI being significant risk factors for developing PDAC in CP patients. The study also highlighted disparities in healthcare access and utilization among different socioeconomic and ethno-racial groups, which may impact the risk and outcomes of CP and PDAC.

Key Words: Pancreatic ductal adenocarcinoma; Chronic pancreatitis; Acute pancreatitis; Epidemiological study, Pancreatic cancer

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Core Tip: The United States has a high incidence of pancreatic cancer (PanCa) cases that result from chronic pancreatitis (CP). This link between diseases is well-established in many scientific studies and clinical practices. In CP, the chronic inflammation of the pancreas causes DNA mutations and cellular changes that may make one prone to cancerous tumors. The CP is responsible for the persistent damage and fibrosis as a consequence of continuous inflammation of the organ over time. Such chronic inflammation promotes DNA mutations and oxidative stress, and damages cells thus leading to an increased risk of carcinogenesis. On a long-term basis, these alterations can cause the development of pancreatic intraepithelial neoplasia, a precancerous stage prior to pancreatic ductal adenocarcinoma (PDAC), which is another name for PDAC; it's also regarded as the most prevalent type of this ailment. An example is that hereditary pancreatitis patients have up to 40% lifetime risk by age 70 years. Non-genetic CP also increases risks, although not very greatly. Development of PanCa is partly associated with CP risk factors like genetic mutations such as protease serine 1, serine protease inhibitor kazal type 1, cystic fibrosis transmembrane conductance regulator, heavy alcohol use, and smoking.

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INTRODUCTION

Our editorial addresses the retrospective study published by Lew *et al*[1] in 2022 which demonstrated an extensive nationwide study indicating a significant rising pattern in hospitalization rates for chronic pancreatitis (CP), particularly affecting overweight black men aged 40-59 years. Additionally, white men over 40 years who were overweight and had higher incomes showed an elevated risk of pancreatic ductal adenocarcinoma (PDAC) among CP patients. The primary objectives of the study included examining the ethno-racial disparities in hospital admissions for CP compared to the general population and between CP and PDAC. Additionally, the secondary outcome focused on assessing associations between ethnicity/race and hospitalization outcomes (mortality, length of stay, and expenses) among CP and PDAC patients. In their study sample covering the years 2016-2017, comprising 14.2 million admissions, 371275 adult patients (2.6%) were diagnosed with CP with the majority being white (64.8%) and male (55.7%). Interestingly, in multivariate regression analysis, certain demographic factors and health indicators exhibit associations with the likelihood of developing CP. Men [adjusted odds ratio (aOR) = 1.35], black individuals (aOR = 1.13), those aged 40-59 years (aOR = 2.60), and individuals with a body mass index (BMI) between 25 and 29.9 (aOR = 1.34), demonstrated an increased risk for CP. Furthermore, it was also observed that 0.78% of the adult patients admitted with CP, also had PDAC and the subsequent multivariate regression analysis revealed significant risk factors for developing PDAC in patients with CP, such as older age (> 40 years, aOR = 1.05) and BMI (between 25 and 29.9, aOR = 2.40). Contrary to the risk factors, certain demographics were found to be associated with a decreased likelihood of PDAC in CP patients: (1) Women (aOR = 0.77); (2) Blacks (aOR = 0.77); and (3) Hispanics (aOR = 0.66) respectively, highlighting the associations between sex as well as ethnicity/race and disease outcomes. Additionally, the study revealed that patients with CP and PDAC were significantly more likely to have higher median incomes, lower rates of being uninsured, and high rates of being admitted to large urban teaching hospitals when compared to CP patients alone. These findings suggest disparities in healthcare access and utilization among different socioeconomic and ethno-racial groups, which may impact the risk and outcomes of CP and PDAC[1]. One of the main risk categories for pancreatic cancer (PanCa) is people with CP, and research suggests that these patients may have a relative risk of PanCa of up to 7.6-68.1 times. Research on the incidence of PanCa in CP patients has mostly focused on Western nations, where estimates of the disease's frequency range from 1.0% to 2.6%. The incidence of PanCa was reported to be 0.9%-2.9% in a few research conducted in Asia.

CP SERVES AS A WELL-ESTABLISHED RISK FACTOR FOR PDAC

In contrast to the 9-fold to 16-fold increased risk reported in a recent cohort study, their finding of a average increase of PanCa among patients with pancreatitis-especially the chronic or recurrent forms-supports some previous clinical and case-control studies. There is no evidence of a heightened risk for pancreatitis 10 years or longer after the initial discharge, which contradicts a clear-cut causal relationship. Given the short time between pancreatitis and PanCa diagnosis, there's a chance that some types of pancreatitis precede PanCa or that common risk factors (like smoking cigarettes) could also be at play[2]. Several studies have proposed that risk factors associated with CP comprise newly diagnosed hyperglycemia, obesity, old age, smoking habits, alcohol consumption, physical inactiveness and diet to name a few[3]. Hence further validation of these risk factors is necessary, and identification of patient subgroups with CP for surveillance should be based on the risk factors for PDAC. Traditionally, CP and PDAC were considered distinct diseases originating from separate pancreatic cell types, acinar and ductal cells, respectively. However recent studies involving rodent models suggest a shared origin in acinar cells[4]. It has been observed that prolonged inflammation in CP leads to increased cell turnover and stellate cell proliferation, fostering a microenvironment conducive to carcinogenesis and inflammatory

mediators like Cyclooxygenase-2 (Cox-2), NF-κB, and signal transducer and activator of transcription 3 (STAT3) play crucial roles, as sustained inflammation can trigger oxidative damage, exacerbating inflammatory infiltration and acinar cell injury[5,6]. While most PDAC patients exhibit constitutive activation of STAT3, which suggests that STAT3 may be a viable therapeutic target in this malignancy, STAT3 is not necessary for normal development. In PDAC, COX-2 is overexpressed. It's unclear, yet, how COX-2 encourages the development of PDAC. While prior research has assessed the effectiveness of COX-2 inhibition in PDAC models through the use of nonsteroidal anti-inflammatory drugs or the COX-2 inhibitor celecoxib, no study has examined the roles that COX-2 plays in modulating PDAC initiation and progression on a cell intrinsic versus microenvironment level[7].

In a recent study involving 1538 PanCa patients and 15380 controls, Ma *et al*[8] demonstrated that pancreatitis significantly raises the risk of PDAC, which escalates with the age of pancreatitis as well as the age of the individuals, with the highest risk observed in the age group between 61-70 years. Interestingly, the PanCa risk is significantly elevated within the first 3 years, but surprisingly the risk correlation diminishes after 10 years. Similarly, Kim *et al*[3], reported that, compared to individuals without PanCa, patients with CP showed an enhanced risk of PanCa development at older ages (60 years or older). Studies from Han *et al*[9] (2022) and Park *et al*[10] (2023) added some insights on the association of CP with the risk of PanCa in the Korean population. Han *et al*[9], observed that patients with CP posed a greater risk for both incidence and mortality of all cancers, particularly the pancreatic and esophageal cancers, compared with the sex- and age-matched control groups. Park *et al*[10], utilized Korean population-based data to identify 225811 patients with acute pancreatitis (AP) and 225685 with CP, each comprising 50.0% of the sample. Matching them with 4514960 age-matched and sex-matched controls, they analyzed PanCa incidence and adjusted hazard ratios in patients followed for over 2 years or 5 years. Additionally, they assessed risk changes over time in subgroups of AP, recurrent AP (RAP), CP with AP, and CP without AP groups, for both sexes. They observed that although the likelihood of PanCa diminished with time, it remained heightened in individuals with RAP and CP with AP for over 8 years. Female patients with RAP, severe AP (SAP), and CP with AP faced greater PanCa risks compared to men. Patients with RAP and CP with AP experienced prolonged and increased PanCa risks in contrast to those with SAP or CP without AP[10]. These studies added important insights into the age, sex, and ethnicity-related demographic factors, associated with the risk of PanCa for the Asian population, as a very limited number of studies were performed in this area.

CONCLUSION

Hence the findings revealed specific demographic and ethno-racial factors associated with an increased risk for admission with CP and PDAC, shedding light on potential disparities and risk factors for these conditions. The study also highlighted limitations, such as being limited to inpatient encounters and the inability to identify individual patients or the etiology of CP. Despite these limitations, the study provides valuable insights into the epidemiologic risk factors associated with CP and its association with PDAC, emphasizing the importance of understanding the prevalence and outcomes of these conditions.

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FOOTNOTES

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