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Advances in Pancreatic Cancer, Intraductal Papillary Mucinous Neoplasms, and Pancreatitis

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Abstract

According to the theme of the Golden Jubilee Issue of our journal, we present a commentary on landmark contributions reported in the journal on pancreatic cancer, pancreatic cysts, and intraductal papillary mucinous neoplasms (IPMN) and pancreatitis.

Graphical Abstract

Diabetes and Pancreatic Cancer

Associations between diabetes and pancreatic ductal adenocarcinoma (also known as pancreatic cancer) have long been recognized. Two highly cited articles in *Gastroenterology* have furthered understanding of these associations.[1,2] Chari et al[1] performed a population-based study to determine the number of patients who develop pancreatic cancer within a 3-year period after a new diagnosis of diabetes after age 50. This population-based study of residents of Rochester, Minnesota, who first met criteria for diabetes after age 50 was designed to determine the observed rates of pancreatic cancer. Of 2122 patients meeting criteria for diabetes, 18 (0.85%) were diagnosed with pancreatic cancer during the 3-year period, and 10 of these within 6 months. The importance of this study is that it confirmed the relationship between a late onset of diabetes (after the age of 50 years) and the diagnosis of pancreatic cancer and suggested that late-onset diabetes is a biomarker that could be used for early diagnosis of pancreatic cancer. The association of diabetes after the age of 50 years with pancreatic cancer is a cornerstone of current activity to develop early diagnostic biomarkers for pancreatic cancer.

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Conflicts of interest

The author discloses no conflicts.

In the other highly cited article related to the associations between diabetes and pancreatic cancer in *Gastroenterology*, Li et al[2] reported a hospital-based case-control study to determine the frequencies of use of insulin, insulin secretagogues, metformin, and other antidiabetic medications among patients with diabetes who developed pancreatic cancer compared with controls. The major observation was that patients with diabetes who ever used metformin, especially those with 5 years of use, had a calculated 60% decrease in the incidence of pancreatic cancer compared with never users. Although limited by numbers, there may have been an increased incidence in those using insulin. Observations of the association of metformin use and decreased pancreatic cancer incidence have held up in a meta-analysis of 13 studies (10 cohort and 3 case control).[3]

Importantly, in another highly cited article in *Gastroenterology*, Schneider et al[4] tested the effects of metformin on pancreatic cancer development in a preclinical model of high fat–fed hamsters given the pancreatic carcinogen *N*-nitrosobis-(2oxopropyl) amine. The results showed that none of the metformin-treated hamsters developed malignant pancreatic lesions, whereas 50% of those not treated with metformin developed malignant lesions.

Pancreatic Cancer Microenvironment

The microenvironment of the pancreatic cancer tumor is highly desmoplastic. Two highly cited articles in *Gastroenterology*[5,6] address the source of the desmoplasia[5] and review the roles of pancreatic stellate cells in desmoplasia and the promotion of pancreatic cancer.[6] In their normal physiologic state (quiescent), pancreatic stellate cells provide extracellular matrix for tissue organization and function.[6] The article by Bachem et al[5] using immunostaining methods showed high numbers of stellate cells converted to an activated state as measured by alpha smooth muscle actin. This article further reports experiments to show that pancreatic cancer cells release several factors (fibroblast growth factor 2, transforming growth factor 1, and platelet-derived growth factor) significantly that stimulated proliferation, collagen type I and c-fibronectin synthesis by pancreatic stellate cells. In addition, the report shows that the inclusion of pancreatic stellate cells with cancer cells in animal subcutaneous tissue induced a faster growing tumor with desmoplasia and morphology similar to human pancreatic cancer. A highly cited review by Apte et al[6] addresses additional reports about the roles of activated pancreatic stellate cells in promotion of pancreatic cancer summarizing that they stimulate cancer cell proliferation; inhibit cancer cell apoptosis; and promote metastasis. Further, activated pancreatic stellate cells are present in pre-malignant lesions, namely pancreatic intraepithelial neoplasia, indicating their involvement in all stages of malignant transformation. It should be noted that the involvement of pancreatic stellate cells in the promotion of pancreatic cancer may be more complex and emerging information suggests that tumor-associated stellate cells seem to be heterogeneous and may play diverse roles in either promoting or containing the cancer's progression.[7–9]

Pancreatic Cancer Treatment

Pancreatic cancer remains one of the most lethal of human cancers with poor responses to chemotherapies. A highly cited report in *Gastroenterology* by Farrell et al[10] demonstrated an

association between the expression of human equilibrative nucleoside transporter and outcome of treatment to gemcitabine but not to 5-fluoruracil by measurement of the amount of transporter in surgical specimens prior to initiation of a randomized controlled trial of these 2 agents in the adjuvant setting. These findings have spurred current trends in finding predictive molecular markers for identification of subgroups of patients likely to respond to a particular therapy.

Pancreatic Cysts and IPMN

Pancreatic cysts (most of them are IPMN) are very common incidental findings in patients undergoing abdominal imaging for a variety of symptoms and can be seen in ≤25% to 30% of patients >60 years of age.[11] Current or future pancreatic cancer is a concern in these cysts and hence the current practice of repeated surveillance imaging; use of invasive tests like endoscopic ultrasound examination, fine needle aspiration cytology, and even pancreatic resection in worrisome cases. Originally described in 1982 from Japan, one of the earlier surgical series in *Gastroenterology* by Loftus et al[12] reported 15 patients and recommended surgical resection for all due to the inability to distinguish invasive from noninvasive lesions preoperatively. However, a subsequent larger resected series, describing 113 patients (both main duct and side branch types) from the same institution demonstrated that only 5 of 60 noninvasive IPMNs (8%; including carcinoma in situ, which is currently termed high-grade dysplasia) recurred after partial pancreatectomy and 91% of these recurrences occurred within 3 years.[13] The recurrence rate in invasive cancers was 65%. Most recently, a thorough technical review[11] and grade-based set of guidelines by American Gastroenterological Association (AGA)[14] emphasized the rarity of pancreatic cancer in asymptomatic pancreatic cysts, most of which are side branch IPMNs. The guidelines scaled down the recommendations for frequency of radiologic surveillance, use of endoscopic ultrasound examination with fine needle aspiration cytology, and surgical resection based on the exhaustive technical review findings. This approach has been congratulated by the high-value care groups, pointing out the reduced harm (unnecessary invasive testing and subsequent resections with significant morbidity and some mortality) and great decrease in the health care costs.[15] However, there have been several strong criticisms citing missed cancers by this approach.[16–18] Although one of these groups[17] agreed with many AGA recommendations, the other 2 criticized them citing much smaller studies, although the AGA technical review and guidelines reviewed all the available literature comprising of nearly 10,000 patients with IPMN to estimate the risk of malignancy. In addition to the large number of patients, grade methodology was used for AGA recommendations.[19] Further, none of the studies discuss the total number of patients with pancreatic cysts screened (denominator) to identify cancers, the cost involved, the complications owing to invasive testing and surgery, and the fact that <20% of such highly selected patients with resections had invasive cancer. Some pancreatic cancers will be missed regardless of the intensity of surveillance. “More is not better” and potential harms besides the costs are very important considerations in the surveillance of these cysts, as in any other disease. What is urgently needed is natural history studies of incidentally discovered pancreas cysts (many of them will be side branch IPMNs) and newer molecular markers of cyst fluid with good positive predictive value to identify the rare pancreatic cancer found in these cysts.

Pancreatitis

Walled off necrosis (formerly known as organized pancreatic necrosis) is a cause for significant morbidity and some mortality after acute necrotizing pancreatitis owing to resultant complications like infected necrosis and obstruction of the gastroduodenal area and the bile duct. Novel endoscopic approaches to drain/debride such collections was first described in the journal by Baron et al.[20] In a series of 11 patients with necrosis, endoscopic transgastric or transduodenal drainage was performed along with additional nasobiliary catheter lavage in 8 of these 11 patients. Complete resolution was achieved in 9 with complications in 5. This pioneering work caused much enthusiasm, which led to minimally invasive methods of drainage and even debridement (necrosectomy) of such collections replacing the time-honored standard of care, open surgical necrosectomy. An international consensus conference subsequently endorsed such minimally invasive treatment as standard of care.[21] Further, such endoscopic therapy has been reported to be superior to surgical necrosectomy in a randomized, controlled trial[22] and the same workers in another recent randomized controlled trial confirmed the noninferiority of endoscopic step-up approach for walled off necrosis when compared with other minimally invasive percutaneous method followed by videoassisted retroperitoneal debridement.[23] Thus, the current management of walled off necrosis has evolved from the original contribution in 1996 in *Gastroenterology*.

On a different note, genetic alterations are being increasingly reported in both acute and chronic pancreatitis. The most well-characterized genetic form of chronic pancreatitis is hereditary pancreatitis which is autosomal dominant and results in recurrent acute and subsequent chronic pancreatitis with frequent progression to pancreatic cancer. This condition was first described in the journal as early as 1952 by Comfort et al.[24] Yet another landmark contribution appeared in the journal in 1996, where Whitcomb et al[25] mapped the gene for hereditary pancreatitis to chromosome 7q35. A genome-wide search strategy was employed in a 36 member subset from a pedigree of 500 members of a kindred US family. *Gastroenterology* has continued to publish on this topic when a second mutation in the cationic trypsinogen was identified at position 21 (N21I).[26] Thus, significant contributions to understanding of the molecular genetics in pancreatitis appeared in *Gastroenterology*.

References

1. Chari ST, Leibson CL, Rabe KG, et al. Probability of pancreatic cancer following diabetes: a population-based study. Gastroenterology 2005;129:504–511. [PubMed: 16083707]
2. Li D, Yeung SC, Hassan MM, et al. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology 2009; 137:482–488. [PubMed: 19375425]
3. Wang Z, Lai ST, Xie L, et al. Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Res Clin Pract 2014;106:19–26. [PubMed: 24837144]
4. Schneider MB, Matsuzaki H, Haorah J, et al. Prevention of pancreatic cancer induction in hamsters by metformin. Gastroenterology 2001;120:1263–1270. [PubMed: 11266389]
5. Bachem MG, Schunemann M, Ramadani M, et al. Pancreatic carcinoma cells induce fibrosis by stimulating proliferation and matrix synthesis of stellate cells. Gastroenterology 2005;128:907–921. [PubMed: 15825074]
6. Apte MV, Wilson JS, Lugea A, et al. A starring role for stellate cells in the pancreatic cancer microenvironment. Gastroenterology 2013;144:1210–1219. [PubMed: 23622130]

7. Özdemir BC, Pentcheva-Hoang T, Carstens JL, et al. Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. Cancer Cell 2014;25:719–734. [PubMed: 24856586]
8. Rhim AD, Oberstein PE, Thomas DH, et al. Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma. Cancer Cell 2014;25:735–747. [PubMed: 24856585]
9. Öhlund D, Handly-Santana A, Biffi G, et al. Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer. J Exp Med 2017;214:579–596. [PubMed: 28232471]
10. Farrell JJ, Elsaleh H, Garcia M, et al. Human equilibrative nucleoside transporter 1 levels predict response to gemcitabine in patients with pancreatic cancer. Gastroenterology 2009;136:187–195. [PubMed: 18992248]
11. Scheiman JM, Hwang JH, Moayyedi P. American Gastroenterological Association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology 2015;148:824–848 e22. [PubMed: 25805376]
12. Loftus EV Jr, Olivares-Pakzad BA, Batts KP, et al. Intraductal papillary-mucinous tumors of the pancreas: clinicopathologic features, outcome, and nomenclature. Members of the Pancreas Clinic, and Pancreatic Surgeons of Mayo Clinic. Gastroenterology 1996;110:1909–1918. [PubMed: 8964418]
13. Chari ST. Intraductal papillary mucinous neoplasm. Curr Treat Options Gastroenterol 2002;5:339–344. [PubMed: 12207857]
14. Vege SS, Ziring B, Jain R, et al. American gastroentero-logical association institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology 2015;148:819–822; quiz e12–3. [PubMed: 25805375]
15. Harris RP. Incidental findings in the pancreas (and elsewhere): putting our patients (and ourselves) in a difficult situation. Ann Intern Med 2015;162:787–789. [PubMed: 25807075]
16. Fernandez-del-castillo C, Tanaka M. Management of pancreatic cysts: the evidence is not here yet. Gastroenterology 2015;148:685–687. [PubMed: 25724457]
17. Canto MI, Hruban RH. Managing pancreatic cysts: Less is more? Gastroenterology 2015;148:688–691. [PubMed: 25724460]
18. Singhi AD, Zeh HJ, Brand RE, et al. American Gastroenterological Association guidelines are inaccurate in detecting pancreatic cysts with advanced neoplasia: a clinico-pathologic study of 225 patients with supporting molecular data. Gastrointest Endosc 2016;83:1107–1117. [PubMed: 26709110]
19. Moayyedi P, Weinberg DS, Schunemann H, Chak A. Management of pancreatic cysts in an evidence-based world. Gastroenterology 2015;148:692–695. [PubMed: 25724461]
20. Baron TH, Thaggard WG, Morgan DE, et al. Endoscopic therapy for organized pancreatic necrosis. Gastroenterology 1996;111:755–764. [PubMed: 8780582]
21. Freeman ML, Werner J, van Santvoort HC, et al. Interventions for necrotizing pancreatitis: summary of a multidisciplinary consensus conference. Pancreas 2012; 41:1176–1194. [PubMed: 23086243]
22. Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA 2012;307:1053–1061. [PubMed: 22416101]
23. van Brunschot S, van Grinsven J, van Santvoort HC, et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. Lancet 2018;391:51–58. [PubMed: 29108721]
24. Comfort MW, Steinberg AG. Pedigree of a family with hereditary chronic relapsing pancreatitis. Gastroenterology 1952;21:54–63. [PubMed: 14926813]
25. Whitcomb DC, Preston RA, Aston CE, et al. A gene for hereditary pancreatitis maps to chromosome 7q35. Gastroenterology 1996;110:1975–1980. [PubMed: 8964426]
26. Gorry MC, Gabbaizedeh D, Furey W, et al. Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. Gastroenterology 1997;113:1063–1068. [PubMed: 9322498]