Familial Pancreatic Adenocarcinoma

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KEYWORDS

• Genetic susceptibility • Familial risk • Genetic testing
• Risk assessment and management

KEY POINTS

- Familial pancreatic cancer (FPC) kindreds have 2 or more first-degree relatives ever diagnosed with pancreatic ductal adenocarcinoma.
- Patients with FPC constitute 8% to 10% of all patients with pancreatic cancer. Positive family history of pancreatic cancer is a consistent risk factor, with twofold increased risk to first-degree relatives.
- Although novel genes that predispose to FPC remain to be discovered, increased risk of pancreatic cancer is now known to be associated with half a dozen inherited syndromes with known germline mutations, including *BRCA1, BRCA2, CDKN2A, PALB2,* ataxia telangiectasia mutated (*ATM*), mismatch repair genes, as well as *PRSS1* and *SPINK2* of hereditary pancreatitis.
- Predisposition genetic testing for individuals in FPC kindreds is feasible and typically consists of sequencing a panel of multiple genes. Cancer risk assessment is less precise, and research into prevention and screening is nascent.
- Guidelines for management of family members at risk for FPC are being developed or disseminated. Owing to limited experience worldwide, guidance is often based on expert opinion. It is agreed that more research is needed to improve the shaping of options.

INTRODUCTION

Pancreatic cancer is a devastating diagnosis for patients and their families, and it is the fourth leading cause of cancer death. Among the major cancers, pancreatic cancer has the worst survival and historically, has been the least studied. Approximately 95% of pancreatic neoplasms are ductal adenocarcinomas. The rapid mortality of patients with pancreatic adenocarcinoma makes this cancer challenging for research into basic, translational, and epidemiologic studies. For genetic or molecular

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investigations that require biospecimens for DNA studies, involving patients who are often too ill to participate and whose disease precludes surgical resection (with consequent lack of tumor tissue) has posed difficulties.

This longstanding dearth of knowledge has resulted in only minimal inroads to improve risk reduction or survival. In the United States, the incidence and mortality rates have remained largely unchanged since 1973. During 2005–2009, the incidence rate for whites and African Americans was 11.6 of 105 and 15.2 of 105, respectively. Mortality rates were 10.7 of 105 for whites and 13.8 of 105 for African Americans.[1] The 5-year survival has been 4% to 6% for decades.[2] The low survival from pancreatic cancer is primarily due to the advanced stage at diagnosis in most cases: by the time of diagnosis, 80% of pancreatic carcinomas are no longer localized to the pancreas. To date, no reliable screening tests or effective cures for pancreatic cancer are available; there are few long-term survivors.

It is crucial to advance the knowledge of etiology to enable evidence-based strategies to decrease incidence and mortality. For years, pancreatic cancer was thought to be a sporadic disease, due in part to the lack of systematic studies and the inherent challenges as described earlier. Over the past 2 decades, however, there has been sustained effort to elucidate its genetics. As demonstrated for a variety of cancers, genetic epidemiology and family-based approaches have led to important breakthroughs in a variety of diseases, and particularly cancer.[3–5] Discerning familial patterns of cancer incidence, combined with detailed studies of clinical and DNA variation, has defined a variety of inherited cancer syndromes and their causal genes. This article reviews the evidence for a genetic component of pancreatic cancer, studies of hereditary syndromes that feature increased risk of pancreatic cancer, and the current status of clinical translation of the findings.

EVIDENCE FOR GENETIC BASIS OF PANCREATIC CANCER

Familial Clustering

Early reports of familial clusters of pancreatic cancer provided the first suggestion that at least a hereditary, but rare form of pancreatic cancer might exist. Reports of clusters included families in which multiple siblings were affected (but not the parents)[6–9] or 1 family in which 3 generations contained an affected member each.[10]

Familial Aggregation Studies and Analysis of Families

More formal study designs that apply epidemiologic and genetic segregation analysis methods are widely accepted standards to uncover existence of genetic basis for a cancer. One conventional approach to investigating potential host susceptibility is to perform case-control comparisons of family history of pancreatic cancer. A comprehensive summary of these studies and estimated risks are listed in **Table 1**. Seven case-control studies, 2 cohort studies, 1 population-based genealogic analysis, and 1 case series that estimated the incidence of pancreatic cancer in relatives have found that first-degree relatives have at least a 2-fold increased risk of developing pancreatic cancer. These findings are remarkably consistent, given that case ascertainment and data collection spanned 30 or more years, multiple countries and cultures, and different methods for estimating risk. A systematic review and meta-analysis by Permuth-Wey and Egan[22] of 1 cohort study and 7 case-control studies totaling 6568 pancreatic cancer cases calculated an overall relative risk of 1.80 (95% confidence interval [CI], 1.48–2.12). The investigators also found that 1.3% of pancreatic cancers in the population is attributable to family history. The risk was consistent for both males and females, and did not differ by early or late