Screening and Surgical Outcomes of Familial Pancreatic Cancer

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KEYWORDS

- Familial pancreatic cancer • Peutz-Jeghers syndrome
- Pancreatic intraepithelial neoplasia • Intraductal papillary mucinous neoplasm
- Mucinous cystic neoplasm

KEY POINTS

- Ten percent of pancreatic cancers have familial inheritance; most of the susceptibility genes for familial pancreatic cancer (FPC) have yet to be determined.
- Utility analysis suggests that pancreatic cancer screening is most cost-effective in individuals whose lifetime risk of pancreatic cancer is 16% or greater.
- Intraductal papillary mucinous neoplasm and pancreatic intraepithelial neoplasia are precursor lesions for FPC; these lesions are higher grade, more common, and multifocal in individuals with FPC compared with patients with sporadic adenocarcinoma and are rarely found in individuals with no history of pancreatic disease.
- High-risk individuals for pancreatic cancer can have abnormal findings on endoscopic ultrasound and magnetic resonance imaging/magnetic resonance cholangiopancreatography including cysts, chronic inflammatory changes, and solid lesions.
- Screening of high-risk individuals, combined with appropriate surgical management, can detect and remove precursor lesions and early pancreatic adenocarcinoma.

INTRODUCTION

Pancreatic cancer remains a lethal disease. In the United States there were 43,920 estimated new cases of pancreatic cancer and almost as many deaths (37,390) in 2012. Although pancreatic cancer accounts for only a small percentage of cancer cases diagnosed in the US, it is the fourth leading cause of cancer death. Unlike breast, colorectal, and prostate cancer, death rates have not declined appreciably in the last 20 years despite advancements in chemotherapy, diagnostic imaging,

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and the understanding of genetic risk factors. Pancreatic cancer, like ovarian cancer, continues to be diagnosed late in progression, often with metastatic disease. Five-year survival correspondingly remains low at only 5%.[1] Early detection of stage 1 disease with curative resection can improve 5-year survival rates upwards of 60%.[2,3] However, detection of asymptomatic early stage disease in the general population has remained elusive.

Although it remains cost-prohibitive to screen the general population for pancreatic cancer, models show that screening of high-risk individuals less than the age of 70 years and who have a lifetime risk of pancreatic cancer greater than or equal to 16% is cost-effective.[4] Approximately 10% of pancreatic cancer is estimated to have familial inheritance.[5,6] Depending on the penetrance of the gene, the risk of cancer in any one individual in these families developing pancreatic cancer can be upwards of 38% by age 70 years.[7] As such, several centers have implemented screening programs for individuals at high risk for developing pancreatic cancer and offer surgical management for concerning precursor findings.

Familial Pancreatic Cancer

Formally defined, familial pancreatic cancer (FPC) is a heterogenous syndrome characterized by a family with 2 or more first-degree relatives with pancreatic cancer, not associated with another described familial hereditary cancer syndrome. Extensive study of familial pancreatic kindreds is ongoing with national and international tumor registries including the North American National Familial Pancreatic Tumor Registry (NFPTR), the German National Case Collection of Familial Pancreatic Cancer (FaPaCa), and the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC).[8–10] Klein and colleagues[7] performed the largest prospective analysis of 5179 individuals from 838 kindreds with FPC. Patients with a single first-degree relative (FDR) affected with pancreatic cancer had a 4.5-fold increased risk of developing pancreatic cancer, 2 FDRs increased the risk to 6.4-fold, and 3 FDRs increased the risk to 32-fold. These numbers have held true in other population analyses.[9,11]

Modeling suggests that unidentified genetic factor(s) drive this familial clustering.[12] At least in European registries, 50% to 80% of families have a pattern of autosomal dominant inheritance.[9,10] Genome-wide association studies suggest susceptibility loci of sporadic pancreatic cancer located at 1p32, 5p15, and 13q22.[13] Large genomic studies are underway to identify the main genetic causes of FPC. An inherited mutation in the highly conserved region of 90-kD palladin (PALLD), an embryonic protein involved in cell motility and invasion, led to highly penetrant FPC associated with prodromal diabetes in one family.[14] To date, this is the only gene indentified in a family with FPC.

Anticipation, the phenomenon whereby successive generations develop the disease at an earlier age than the parent generation, has been shown to affect ~60% to 85% of FPC families in some registries.[8,15] Age of onset in a family member does not seem to affect risk in sporadic pancreatic cancer; however, an early age of onset in an FPC family member (age 40 years) has a marked increase in cumulative risk (19.2%–40%).[16]

Extrapancreatic malignancies are associated with FPC, and it has been hypothesized that there are pure pancreatic cancer families without associated tumors and families with associated tumors. In a Swedish registry, pancreatic cancer was associated with lung, rectal, and endometrial cancer, and melanoma.[17] A German study of 94 histologically confirmed FPC families had increased incidence of breast, colon, and lung cancer.[8] The NFPTR reported an increased risk of death from breast, ovarian, colon, and bile duct cancer.[18]