Screening for Pancreatic Cancer in High-risk Populations

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KEYWORDS

• Pancreatic cancer • Hereditary • Screening • Peutz-Jeghers • BRCA
• Lynch syndrome • IPMN • PanIN

KEY POINTS

- Approximately 10% of pancreatic cancer cases are estimated to have an underlying hereditary basis. Of these, only 20% are caused by a known genetic syndrome. Most are caused by nonsyndromic aggregation of pancreatic cancer cases or familial pancreatic cancer.
- Assessment of family cancer history is essential to identify individuals who may benefit from genetic evaluation, testing for underlying cancer susceptibility genes, and screening for pancreatic cancer.
- Screening aims to identify preinvasive lesions with high-grade neoplastic changes that are significantly associated with an increased risk for invasive pancreatic cancer (pancreatic intraepithelial neoplasia-3 and intraductal papillary mucinous neoplasm with high-grade dysplasia).
- Endoscopic ultrasonography and MRI/magnetic resonance cholangiopancreatography can detect pancreatic cancer precursor lesions in high-risk individuals but have limitations.
- Novel biomarkers have the potential to inform the diagnosis and management of pancreatic cancer precursor lesions detected on imaging.

INTRODUCTION

Pancreatic adenocarcinoma is the fourth leading cause of cancer-related death in the United States and the eighth leading cause worldwide.[1] Surgical resection is the only potentially curative treatment of exocrine pancreatic cancer. However, because of the late presentation at diagnosis, only 15% to 20% of patients are candidates for surgery.

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Early detection of pancreatic cancer with curative resection can improve survival.[2,3] Population-based screening for pancreatic cancer is not cost-effective given the low incidence of pancreatic cancer and the low positive predictive value of current screening modalities. However, individuals at increased risk for pancreatic cancer may benefit from screening to detect early pancreatic neoplasia and screening may be cost-effective.[4,5]

EPIDEMIOLOGY

Approximately 10% of pancreatic cancer cases are estimated to have an underlying hereditary basis.[6] Of these, only 20% are caused by a known genetic syndrome (**Table 1**).[7]

Familial Pancreatic Cancer

Familial pancreatic cancer (FPC) has been defined by consensus opinion as affecting families with at least 2 first-degree relatives (FDRs) with pancreatic cancer without a known pancreatic cancer–associated hereditary syndrome.

The risk of pancreatic cancer in FPC families increases with the number of affected FDRs. Other important determinants of pancreatic cancer risk in FPC families include the age at pancreatic cancer diagnosis, the family size, and the number of first-degree relatives with pancreatic cancer in the family. Genetic anticipation has been noted in 65% to 80% of individuals from FPC families.[8] In one prospective study that included 838 FPC kindreds, individuals with 1 affected FDR had a 4.5-fold increased risk compared with the general population.[9] Those with 2 and 3 or more affected FDRs with pancreatic cancer had a 6.4-fold and 32-fold increased risk of developing pancreatic cancer, respectively.

Table 1
Syndromes associated with increased risk of pancreatic cancer

Syndrome	Gene	Estimated Lifetime Risk of Pancreatic Cancer (%)
Peutz-Jeghers syndrome	*STK11*	11–36
FAMMM	*p16/CDKN2A*	10–17
Hereditary breast and ovarian cancer	*BRCA2* *BRCA1*	5 3.6
Fanconi anemia, breast cancer	*PALB2*	Unknown
Lynch syndrome	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	3.7
Li-Fraumeni syndrome	*p53*	Unknown
Familial adenomatous polyposis	*APC*	2
Ataxia-telangiectasia	*ATM*	Unknown
Hereditary pancreatitis	*PRSS1*	40
Familial pancreatic cancer 1 FDR 2 FDR ≥3 FDR	Majority unknown	 6 8–12 40

Abbreviations: FAMMM, familial atypical multiple mole and melanoma; FDR, first-degree relative.