Hereditary Pancreatic Cancer: Part I. The Genetic Profile

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By Michael Goggins, MD [2], Ralph H. Hruban, MD [3], and Scott E. Kern, MD [4]

Adenocarcinoma of the pancreas is the fifth leading cause of cancer death in the United States.[1] It has a lifetime incidence of approximately one in 150 persons in the United States and a male-to-female ratio of approximately 1.3 to 1.[2]

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Most patients present with advanced inoperable disease, and the overall survival is less than 5% at five years.[3] However, for patients presenting early, without clinical evidence of metastasis, pancreaticoduodenectomy can result in a five-year survival of approximately 25%.[4]

Techniques to detect early cancer in at-risk patients, before they develop inoperable disease, could save many lives. Pancreatic cancer has a significant, although generally under-recognized, hereditary predisposition, and patients with this hereditary predisposition constitute an at-risk population to which screening techniques could be applied.

For many hereditary cancers, such as familial polyposis coli, hereditary nonpolyposis colon cancer (HNPCC), or familial breast cancer, a familial tendency toward cancer development can often be easily identified on the basis of a pattern of autosomal dominant inheritance with high penetrance. In contrast, even for patients with pancreatic cancer in whom a hereditary predisposition has been identified, clinical features alone often fail to raise suspicion of hereditary cancer. Despite these difficulties, several genes responsible for at least part of this hereditary predisposition have recently been identified.

Once the genes responsible for an inherited predisposition are characterized, they can be used to identify and manage gene carriers. Indeed, commercial testing for hereditary-cancer-predisposing genes is becoming increasingly available. However, until technologic advances enable routine genetic testing of virtually all cancer patients, the most important task for the clinician considering cancer patients for genetic testing will remain the identification of those patients who carry a hereditary predisposition.

The molecular genetic profile of pancreatic cancer has been relatively well characterized, compared with that of some other cancers. Infiltrating adenocarcinoma of the pancreas has a unique genetic profile, with somatic mutations of the K-ras gene (more than 90% of tumors)[5,6] and the p53 gene (50% to 75%),[7] and genetic inactivation of the p16 gene (approximately 80%)[8] and the DPC4 (SMAD-4) gene (50%).[9]

Unlike colorectal cancers, pancreatic cancers do not have APC mutations.[10,11] Similarly, microsatellite instability suggestive of an inherited defect in one of the mismatch repair genes is an unusual finding in pancreatic cancer.[12]

The genes mutated in sporadic cancers are frequently also responsible for hereditary cancers. Thus, this understanding of the molecular genetics of infiltrating pancreatic cancer provides a foundation for examining the molecular basis for hereditary pancreatic cancer, which will be reviewed in the next article in this series.

References:


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