Hereditary factors in pancreatic cancer

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Abstract The incidence and the mortality rates for pancreatic cancer are the same, indicating its dismal outlook. Its natural history remains elusive. Cigarette smoking appears to be the most significant environmental culprit. Hereditary factors may account for approximately 5% of the total pancreatic cancer burden. However, when its extent heterogeneity and the reduced penetrance of causal germline mutations are considered, the hereditary incidence may significantly exceed this estimate. Even when endoscopic ultrasound (EUS), the gold standard for pancreatic cancer screening, is utilized, early detection with surgical cure has rarely been accomplished. Needed to ameliorate this problem is research into genetic and environmental risk factors and their interaction. The identification of tumor biomarkers which signal early pathogenetic events, thereby enabling pancreatic cancer to be diagnosed at its earliest possible stage before it has spread to regional lymph nodes or to more distant sites, will improve the outlook. We discuss our research approaches to this problem. Members of families with the p16 germline mutation will undergo EUS coupled with the collection of pancreatic juice for the study of a possible gradient for telomerase activity, K-ras mutations, and cytology. If changes in these putative biomarkers are observed, endoscopic retrograde cholangiopancreatography (ERCP) would be the next diagnostic step. We conclude with a discussion of ethical concerns about this research.

Key words Pancreatic cancer · Hereditary cancer · Cancer genetics

Introduction

It was expected that, in the United States during 1999, 28600 new cases of cancer of the pancreas would occur and its mortality would be 28600.¹ Globally, the 1999 figures for pancreatic cancer were projected to be 170000 new cases and 168000 deaths.² A sobering fact is that its mortality approximates its incidence, clearly depicting its dismal outlook. The etiology of pancreatic cancer remains elusive. New clues to its genetic transmission in selected families, and recent molecular genetic discoveries in certain hereditary pancreatic cancer-prone syndromes, may provide elucidation as to its causality and may be translated into improved control measures.

Our purpose is to review current issues in the molecular genetics and the genetic epidemiology of pancreatic cancer.

Natural history

Very little is known about the natural history of pancreatic carcinoma, inclusive of its precursors. In an attempt to gain insight into this problem, Brat et al.³ studied three patients in whom atypical papillary hyperplasia of the pancreas was documented 17 months to 10 years prior to the development of an infiltrating adenocarcinoma of the pancreas. The initial patient was a 70-year-old woman who underwent pancreaticoduodenectomy for adenocarcinoma of the pancreas. Findings disclosed atypical papillary duct hyperplasia extending to the pancreatic neck margin of the resection. Interestingly, the margin was negative for infiltrating carcinoma. Nine years after this resection, an infiltrating adenocarcinoma developed in the remaining pancreas. The second patient was a 58-year-old man who underwent distal pancreatectomy for chronic pancreatitis, at which time histologic examination identified chronic pancreatitis in association with multiple foci of atypical papillary duct hyperplasia. Ten years later, a Whipple procedure was performed for infiltrating adenocarcinoma of the pancreas. The third patient was a 46-year-old woman with a similar history who underwent a Whipple procedure for
recurrent pancreatitis. Histologic findings disclosed atypical papillary duct hyperplasia and chronic pancreatitis, but there was no evidence of infiltrating carcinoma. The tail of the pancreas was radiographically normal. However, 17 months later, postmortem examination showed infiltrating adenocarcinoma in the tail of the pancreas.

These three patients, ‘. . . presented [with] atypical papillary hyperplasia [which] was documented 17 months, 9 years, and 10 years before [our emphasis] the development of infiltrating adenocarcinoma of the pancreas, supporting the concept that there is a progression from intraductal hyperplasia to infiltrating carcinoma of the pancreas, just as there is a progression from adenoma to infiltrating carcinoma of the colorectum. Based on evidence that these intraductal lesions are precursor lesions to infiltrating adenocarcinoma of the pancreas, we suggest the term ‘hyperplasia’ be replaced by the more specific term ‘pancreatic intraepithelial neoplasia.”’

DiGiuseppe et al. studied a pancreas that was prophylactically removed from a patient with a strong family history of pancreatic carcinoma, thereby providing the unique opportunity to investigate early events in the development of familial carcinoma of the pancreas. Pathology examination showed multifocal papillary and nonpapillary mucinous duct hyperplasia of the pancreas. Microdissection was performed on seven foci and they were analyzed for K-ras and p53 mutations. Interestingly, “Five of the seven duct lesions harbored activating point mutations in codon 12 of K-ras; a G-to-A transition was found in four and a G-to-C transversion in one. In contrast, these lesions did not harbor detectable p53 mutations . . . nor was there overexpression of the p53 protein . . .” These authors suggested that, “. . . mutations in K-ras represent an early event in the pathogenesis of pancreatic carcinoma. In addition, monitoring of patients with a strong family history of pancreatic carcinoma for K-ras mutations may identify patients at risk for the development of invasive carcinoma.”

Telomerase activity and pancreatic carcinoma

Kobitsu et al. discussed the role of telomerase activity in primary pancreatic duct carcinomas. While telomerase activity is elevated in 95% of ductal adenocarcinomas of the pancreas, it is important to realize that telomerase activity may also be elevated in carcinomas of the lung, prostate, colon, liver, brain, ovaries, lymphomas, Wilms’ tumors, rhabdomyosarcomas, and leiomyosarcomas.

Suehara et al. described a 61-year-old alcoholic man who had epigastric back pain and who had a diagnosis of groove pancreatitis with inflammation in the pancre-