Hereditary Pancreatic Cancer: Part II. Candidate Genes

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This special series on cancer and genetics is compiled and edited by Henry T. Lynch, MD, director of the Hereditary Cancer Institute, professor of medicine, and chairman of the Department of Preventive Medicine and Public Health, Creighton University School of Medicine, and director of the Creighton Cancer Center, Omaha, Nebraska. Part I of this three-part series on pancreatic cancer appeared in June 1997. Part II (below) reviews the gene mutations thought to contribute to the development of hereditary pancreatic cancer, and Part III will explores the clinical recognition of a hereditary predisposition to pancreatic cancer.

Before the genetic basis for a familial predisposition to a cancer can be examined, it must first be established that such a predisposition exists. This has been done for pancreatic cancer. It has been estimated that 5% to 10% of patients with pancreatic carcinoma have a hereditary susceptibility for the disease,[1-7] and a Canadian population-based epidemiologic study found that approximately 8% of pancreatic cancer patients have a first-degree relative with pancreatic cancer.[3]

In addition, patients suffering from a number of inherited syndromes are thought to be at increased risk of pancreatic cancer. These syndromes include von Hippel-Lindau disease, HNPCC (hereditary nonpolyposis colorectal cancer) due to germline defects in mismatch repair genes[4], the Peutz-Jeghers syndrome,[7] hereditary relapsing acute pancreatitis,[8] and the Li-Fraumeni syndrome.[9] These well-characterized syndromes, however, probably account for only a small proportion of the familial pancreatic carcinoma burden.[1-7]

Since most familial clusters of pancreatic cancer are not associated with a recognized syndrome, interest has therefore shifted to a "candidate gene" approach. In this approach, patients with a familial clustering of pancreatic cancer, but without a recognized cancer syndrome, are examined for germline mutations in genes found to be mutated in sporadic pancreatic cancer (see Part I, June 1997).

Mutations of p16

The p16 gene (CDKN2) is frequently inactivated in sporadic pancreatic cancer. It was the first gene identified for which germline mutations could be associated with an increased risk of developing pancreatic cancer.[10] These p16 mutations were first identified as predisposing to a high risk of melanoma,[11,12] but carriers of germline p16 mutations also have a 13-fold increased risk of developing pancreatic cancer.[10] Such mutations appear to account for only a small percentage of all familial pancreatic cancers,[13] and they should be suspected in a patient with pancreatic cancer and a strong family history of melanoma.[13]

Role of BRCA2

The search for the BRCA2 gene was aided by the identification of a homozygous deletion in a sporadic pancreatic cancer. Germline BRCA2 mutations also contribute to the hereditary predisposition to pancreatic cancer. For example, in our recent examination of a large series of unselected patients with pancreatic cancer, we found that 7% had germline BRCA2 mutations.[14]
Remarkably, this hereditary risk for cancer could not have been predicted from the patients’ clinical histories. Of four BRCA2 mutation carriers, none had a family history of pancreatic cancer, and only one had a first-degree relative with breast cancer.[14] Of interest, pancreatic cancer in these patients with germline BRCA2 mutations does not usually present at an early age.[14,15] The contribution of germline BRCA2 mutations to pancreatic cancer may account for previous epidemiologic data that identified an increased prevalence of pancreatic cancer in families of patients with breast and ovarian cancer.

For example, breast cancer families with germline BRCA2 mutations have a higher than expected number of members with pancreatic cancer,[15,16] and Tulinius et al found an increased relative risk of pancreatic cancer in male first-degree relatives of breast cancer patients.[17] Furthermore, in their analysis of the Utah Population Database, Kerber and Slattery found that a family history of pancreatic cancer is significantly associated with an increased risk of ovarian cancer.[18] The increased risk of developing pancreatic and breast cancer associated with germline BRCA2 mutations is particularly noteworthy because of the widespread availability of clinical testing for these mutations.

Based on the relative risk of breast cancer in Ashkenazi Jewish BRCA1 or BRCA2 mutation carriers, the penetrance of early-onset breast cancer in BRCA2 mutant carriers is approximately one third that of their BRCA1 counterparts.[19] The lifetime risk of breast cancer in BRCA2 mutant carriers is less certain, but is probably significantly less than the 80% to 90% risk for BRCA1 mutation carriers, and may be on the order of 25% to 35%.[19,20]

**Low Penetrance of BRCA2**

Penetrance will vary within individual families depending on additional factors, including the type of mutation, its position within the gene, the inheritance of unknown modifier genes, and environmental factors. For example, the cancer risk of most missense mutations will be difficult to predict, as their effects on protein function are generally unknown.

Most of the known mutations of BRCA2, including those found commonly in the Ashkenazi population, would generate truncated proteins. However, not all truncating mutations of the BRCA2 gene would necessarily have an equivalent effect.

For example, mutations in certain regions of the BRCA1 and BRCA2 genes might be more likely to cause ovarian cancer than would other mutations.[21,22] Similarly, it is possible that mutations of certain regions of the BRCA2 gene might, in particular, predispose carriers to the development of pancreatic cancer.

The exact risk of pancreatic cancer in a carrier of a germline BRCA2 mutation is not known at present, but an approximation may be constructed from the currently available data. Among 21 BRCA2 families, Thorlacius et al observed 100 patients with breast cancer and 11 with pancreatic cancer.[23] Similarly, in a report of eight families with germline mutations of BRCA2, Phelan et al found four patients with pancreatic cancer and 48 with breast cancer.[15] In contrast, Couch et al found no pancreatic cancers in 11 families with 36 breast cancers.[24] As these families were recruited to help identify the BRCA2 gene, there was clearly a selection bias toward those families with breast as opposed to pancreatic cancer. However, these data suggest that, in a carrier of a germline BRCA2 mutation, pancreatic cancer may be approximately one tenth as common as breast cancer. Thus, the lifetime risk of pancreatic cancer in BRCA2 mutant carriers is probably in the range of 5%.

This low penetrance at which germline BRCA2 mutations result in pancreatic cancer may explain the previously described observation that 7% of apparently sporadic pancreatic cancer patients have germline mutations in BRCA2.

This figure compares well with the rates seen for "apparently sporadic" breast cancers (less than 4%) and ovarian cancers (less than 4%).[25-29] Thus, even apparently sporadic cancers may, in fact, be caused by germline mutations if these mutations have a low penetrance.

**Other Genes**

Of the other genes found to be somatically inactivated in pancreatic cancer, none has been found in the germline of pancreatic cancer patients.

Hahn et al identified the DPC4 tumor suppressor gene and demonstrated that it is somatically inactivated in 50% of pancreatic cancers.[30] Apart from colon cancer, where DPC4 is somatically
inactivated in approximately 20% of cancers.[31] Most tumor types are rarely associated with inactivation of this gene.[32] Moskaluk et al screened 18 families that had two or more members with pancreatic cancer and found no germline DPC4 mutations.[33]

Patients with Li-Fraumeni syndrome due to germline mutations of the p53 gene have only a 1.2% risk of pancreatic cancer.[9] Similarly, an association between hereditary pancreatic cancer and germline K-ras mutations has never been documented in the human germline. It seems likely that one or more additional genes for hereditary pancreatic cancer-specific susceptibility exist but have yet to be identified. This suspicion is based on the identification of many pancreatic cancer families whose pedigrees do not suggest a BRCA2 or p16 family. Such families have been reported by Lynch and coworkers.[1,2]

**Johns Hopkins Registry**

Pancreatic cancer families that lack a BRCA2 or p16 pedigree are typical of most families in the National Familial Pancreatic Tumor Registry (NFPTTR) at Johns Hopkins.[34] The registry has already enrolled more than 70 families in which more than one first-degree relative has pancreatic cancer. Appropriate families are screened initially for germline mutations in "candidate genes."

**Familial Pancreatic Cancer Registry**

To register a family or an individual with a history of pancreatic cancer, write to the National Familial Pancreatic Tumor Registry, The Johns Hopkins Hospital, Meyer 7-181, Department of Pathology, 600 Wolfe St., Baltimore, MD 21287, or visit the Registry's web site at http://www.path.jhu.edu/pancreas.

Although linkage analysis has historically been used to establish the loci of most of the inherited tumor suppressor genes in other tumor types, the detection of a familial pancreatic cancer gene by use of a linkage analysis approach will be difficult. The small number of affected members in most families, the short life expectancy of most pancreatic cancer patients, and concerns about low penetrance would mandate that a large number of pancreatic cancer families be studied in order for this approach to be successful. The NFPTTR is therefore actively trying to identify and register additional families in which there is an aggregate of pancreatic cancer (see box ).

**References:**


8. Whitcomb DC, Gorry MC, Preston RA, et al: Hereditary pancreatitis is caused by a mutation in the


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