Familial Pancreatic Cancer: Where Are We in 2003?

Gloria M. Petersen, Ralph H. Hruban

There is a sense of déjà vu for those of us involved in pancreatic cancer research. Many of us have had the opportunity to witness the buildup leading to spectacular discoveries of major genes in studies of hereditary colorectal cancer and breast cancer families. In the same way, we are tackling pancreatic cancer through the use of high-risk pedigrees, a task that is much more difficult with a malignancy that is no more than one-fifth as common as and much more deadly than breast or colorectal cancers (1). Our experiences also parallel those of researchers who are searching for a major hereditary prostate cancer gene but are instead finding that multiple genes, each of modest effect, may tell the story of that disease. In the case of familial pancreatic cancer (FPC), we have not yet identified hypothesized novel major genes, but this research is in its infancy. The study reported by Hahn et al. (2) in this issue of the Journal is an illustration of a critical early strategy that is both logical and possible at this stage of our understanding of FPC. By capitalizing on existing information through studies of plausible candidate genes, we add to our knowledge base and gain more insight into what we do not know, thereby allowing us to design our next moves.

Hahn et al. (2) have provided more evidence that known cancer predisposition genes may comprise a sizable fraction of the entity known as FPC, for which, interestingly, there is no formally agreed-upon definition. To date, the community of researchers who investigate the pedigrees of patients with pancreatic cancer is relatively limited, and the criteria used to identify families eligible for research into this disease can vary depending on the size of the study and the nature of the ascertainment methods. In 1998, we proposed that families that contained two or more first-degree relatives with pancreatic cancer constitute those with FPC (3). Although this arbitrary guideline has generally been used by other researchers, including Hahn et al., we all recognize that some patients with germline mutations in cancer-causing genes do not have a family history of cancer (4). The infrequent occurrence of FPC has mandated the development of patient and family registries to pool scarce study resources. In North America, the National Familial Pancreatic Tumor Registry (NFPTR) (1,3) and collaborations such as the Pancreatic Cancer Genetic Epidemiology Consortium (PACGENE) have been funded by the U.S. National Cancer Institute. In Europe, data from the German Cancer Foundation and the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) form the basis for the study by Hahn et al. (2).

The main finding by this European collaboration is that germ-line BRCA2 mutations may be found in at least 12% (and as much as 19%) of patients with pancreatic adenocarcinoma who have at least one first-degree relative with confirmed pancreatic adenocarcinoma. BRCA2 is an important gene in which mutations are associated with hereditary breast cancer syndrome, and it has long been recognized that pancreatic cancer risk is increased in some families that segregate mutations of BRCA2 (reviewed in (5)). The observation that a substantial portion of pancreatic cancer case patients with a positive family history of the disease may carry BRCA2 mutations is consistent with the results of two previous reports, each of which varied in the way the family sample was constructed. Lal et al. (6) selected 38 of 113 newly diagnosed pancreatic cancer patients for BRCA2 mutation analysis on the basis of suggestive family histories, the age of cancer onset, or the presence of multiple primary cancers. Of the tested sample, two (25%) of eight high-risk/familial case patients were found to carry the germline BRCA2 mutation 6174delT, whereas only one (3%) of the 30 remaining (i.e., “intermediate” risk) case patients also carried this mutation. Murphy et al. (7) analyzed DNA from 29 probands of kindreds in the NFPTR that contained at least three members affected with pancreatic cancer, at least two of which were first-degree relatives, and found that five (17%) probands had germline BRCA2 mutations, of which three were 6174delT. Although in both studies the carriers of this mutation were of Ashkenazi Jewish descent, only families in the former study showed evidence for hereditary breast cancer.

The sample studied by Hahn et al. did not contain subjects known to be of Ashkenazi Jewish descent, and the study was limited to families with two or more histologically confirmed cases of primary ductal adenocarcinoma in the pancreas. Unlike the approaches used in the earlier two studies, this approach would potentially enlarge the pool of eligible families to include those meeting our arbitrary definition of FPC. Hahn et al. identified six BRCA2 mutations in five of the 26 eligible FPC patients; three of the mutations (in 12% of the analyzed sample) are presumably deleterious because they are predicted to result in a truncated Brca2 protein and have not been previously reported in this context. Thus, it is of interest that analysis of a new sample of families with FPC, none of Ashkenazi Jewish origin, but more broadly (yet carefully) defined than the samples in the Lal et al. (6) or Murphy et al. (7) studies, would show that the proportion of BRCA2 mutation carriers is within the same order of magnitude as in those studies. This consistency suggests that BRCA2 is an important gene that must be considered in sorting out the heterogeneity of FPC, but raises further questions. Two will be considered here.

From an etiologic perspective, we still do not know what proportion of FPC is attributable to single major genes or what proportion of these single major genes are known and how they might interact with known environmental risk factors, such as cigarette smoking. A recent segregation analysis among 287 pedigrees by Klein et al. (8) provided the first formal evidence for a rare major gene in the etiology of pancreatic cancer. This gene behaves in an autosomal dominant fashion. However, the role of smoking in the manifestation of the cancer phenotype remains in question. Furthermore, the putative “major gene”

Affiliations of authors: G. M. Petersen, Mayo Clinic, Rochester, MN; R. H. Hruban, Johns Hopkins Medical Institutions, Baltimore, MD.

Correspondence to: Gloria M. Petersen, Ph.D., Dept. of Health Sciences Research, Mayo Clinic, 200 First St. SW, Rochester, MN 55905 (e-mail: peterg@mayo.edu).

Journal of the National Cancer Institute, Vol. 95, No. 3, © Oxford University Press 2003, all rights reserved.
identified by Klein et al. could be, in aggregate, a collection of susceptibility genes, chief among them BRCA2. Other syndromes (1,3,5) that feature pancreatic cancer in the family history have also been implicated in the etiology of FPC. These syndromes (and associated mutant genes) include hereditary pancreatitis (PRSS1), hereditary nonpolyposis colorectal cancer (mismatch repair genes), familial atypical multiple mole melanoma syndrome (CDKN2A/p16), and Peutz-Jeghers syndrome (STK11/LKB1). The contributions of these syndromes to FPC overall may be low, however. Germ-line mutation of the CDKN2A gene has been reported to occur rarely in the FPC setting (9), and a syndrome of pancreatic cancer and pancreatic insufficiency has been reportedly linked to chromosome 4q32–34 (10). We do not yet know what all these disparate threads mean for FPC as a whole.

From a clinical perspective, recommendations for genetic testing for FPC and subsequent screening management of families with FPC are only in the formative stages. Investigators are in general agreement that families with medical histories suggestive of known hereditary cancer syndromes that include pancreatic cancer warrant genetic counseling and should be considered for genetic testing of the genes known to be associated with these diseases (1,6,11). Hahn et al. suggest that BRCA2 gene testing should be considered when a family with two first-degree relatives with ductal adenocarcinoma of the pancreas is identified. Like others (1,6), we would argue that this latter recommendation should be carried out in a research setting until further data are accumulated on the implications of such testing, especially as it relates to cancer screening in those found to carry mutations. In the arena of cancer screening, too, there are initial forays into developing guidelines for managing members of high-risk families that include the use of spiral computed tomography and endoscopic ultrasound (1,11). It will be important to conduct careful studies of larger numbers of asymptomatic gene mutation carriers and at-risk members of FPC kindreds before a comprehensive set of recommendations for genetic testing and management can be widely accepted. Until we accumulate more data, it will be difficult to rationally move our genetic discoveries surrounding FPC into the broader clinical setting.

REFERENCES