Germline Mutations in Pancreatic Cancer Become Better Defined

Two recent studies have helped to clarify the prevalence of germline mutations in patients with pancreatic adenocarcinoma (PAC). PAC has been linked to certain inherited cancer susceptibility genes and such syndromes as hereditary breast and ovarian cancer syndrome (BRCA1 and BRCA2), familial atypical mole syndrome (p16), Lynch syndrome (MLH1, mutS homolog [MSH]2, MSH6, PMS2, and EPCAM), Peutz-Jeghers syndrome (STK11), and partner and localizer of BRCA2 (PALB2)-associated PAC. However, the prevalence of germline mutations in patients with pancreatic cancer is not well defined. Data that better define the prevalence of particular germline mutations are needed to make evidence-based recommendations and better select patients with pancreatic cancer for genetic testing.

Researchers at Memorial Sloan Kettering Cancer Center (MSKCC) in New York City identified in their database 175 patients with PAC who underwent genetic counseling between January 1, 2011, and December 31, 2014 (Cancer. 2015;121:4382-4388). Forty patients met the criteria for familial PAC, defined as having at least one first-degree relative with pancreatic cancer. Based on their personal and family histories, patients were recommended to undergo certain genetic testing: 166 patients for hereditary breast and ovarian cancer syndrome, 36 patients for Lynch syndrome, 48 patients for PALB2 mutations, and 17 patients for p16 mutations.

A total of 159 patients pursued the recommended genetic testing, and a germline cancer susceptibility mutation was found in 24 patients (15%). Mutations were detected in BRCA2 in 13 patients, BRCA1 in 4 patients, p16 in 2 patients, PALB2 in 1 patient, and the DNA mismatch repair genes related to Lynch syndrome in 4 patients. The mean age of the patients with a pathologic mutation was 58.5 years compared with 64 years for those without mutations. The prevalence of a germline mutation in patients with early-onset PAC (age 50 years or younger; 26 patients) was 28.6% versus a prevalence of 6.5% in those with late-onset PAC (age 70 years or older; 56 patients). When evaluating the 96 patients who were of Ashkenazi Jewish ancestry, 15 had germline mutations, predominantly BRCA (BRCA2 [11 patients], BRCA1 [2 patients]).

“In our study, we found that Ashkenazi Jewish ancestry, early age at pancreas cancer diagnosis, and a family history of certain cancers known to be associated with inherited cancer predisposition syndromes are important characteristics that should prompt referral of pancreas cancer patients for genetic evaluation,” says Zsofia Stadler, MD, corresponding author and assistant

KEY POINTS
- Germline mutations occur in approximately 15% of patients with PAC.
- These 2 studies suggest that genetic counseling and testing are appropriate for patients with early-onset PAC or a family history of PAC, those with one of several associated cancers, and those of Ashkenazi Jewish ancestry.
- Further study and guidelines are needed to integrate genetic testing for PAC into practice.
attending physician in clinical genetics and gastrointestinal oncology at MSKCC. “Specifically, we found a high number of germline BRCA2 mutations, with most BRCA2 carriers diagnosed with pancreatic cancer after the age of 50 years; germline mutations in patients of Ashkenazi Jewish ancestry without any additional family history of cancer; and evidence of patients with early-onset pancreatic adenocarcinoma having a notable likelihood for carrying a germline mutation.”

The researchers at MSKCC say they believe the results of this study suggest that it is reasonable for patients who are diagnosed with PAC at a young age or who are of Ashkenazi Jewish ancestry to be referred for genetic counseling and testing.

“Additionally, it is important [to] advocate for coverage benefits of genetic counseling for patients with pancreatic cancer since many third-party payers primarily only focus on benefits for patients with breast, ovarian, and colorectal cancer,” says Dr. Stadler.

Researchers at the Mayo Clinic in Rochester, Minnesota also conducted a study examining germline mutations in patients with PAC, but with a different approach (Cancer Epidemiol Biomarkers Prev [published online ahead of print October 19, 2015]. pii: cebp.0455.2015). They conducted genetic testing among 96 patients with PAC who were identified through their cancer registry from June 1, 2013, to June 1, 2014. The patients were unselected for family history and all were screened with a 22-gene panel.

Of the 96 patients, 7% had first-degree relatives with PAC, thus meeting the criteria for familial pancreatic cancer, and 10% had second-degree relatives with PAC. Fourteen probably pathologic genetic mutations were found in 13 individuals (14%): 4 in ATM; 2 each in BRCA2, CHEK2, and MSH6; and 1 each in BARD1, BRCA1, FANCM, and NBN. These included 9 mutations (9.4%) in established pancreatic cancer genes. The study authors noted that no mutations in PALB2, a known PAC susceptibility gene, were found. Three mutations were found in patients with a first-degree relative with PAC, and 10 mutations were found in patients with first-degree or second-degree relatives with breast, pancreatic, colorectal, ovarian, or endometrial cancer. There was no difference in age at diagnosis between patients with or without mutations.

“Pancreatic cancer patients with a family history of any of several cancers (breast, ovarian, colorectal, or endometrial cancer), not just those with a family history of pancreatic cancer, have a substantial chance of carrying inherited mutations in cancer predisposition genes,” says Fergus Couch, PhD, corresponding author, professor of medical research, and chair of the division of experimental pathology at the Mayo Clinic in Rochester. Dr. Couch says he believes the study’s weakness is its small size, which can lead to inaccurate estimates of prevalence, but adds that future studies with a larger population are planned. A major strength of the study is that the patients were sequential and that all known predisposition genes were tested, he says.

“We believe that all pancreatic patients with a family history of several cancers should be tested for inherited predisposing mutations, and perhaps more importantly, individuals with no cancer with the same family history of cancer should be tested,” says Dr. Couch.

Clinical Implications

“These studies highlight the growing recognition of germline (inherited) mutations in the development of pancreatic cancer,” says Ralph Hruban, MD, professor of pathology and director of the Sol Goldman Pancreatic Cancer Research Center at Johns Hopkins Medical Center in Baltimore, Maryland. Dr. Hruban was not involved in these studies.

“The findings in these 2 studies are important for 3 reasons: first, members of families in which there is a strong family history of pancreatic cancer can now be tested, and those found to carry a deleterious germline variant will be the first to benefit from new approaches, currently in the research stage, to screen for curable pancreatic neoplasia,” says Dr. Hruban. “Second, almost all of the germline variants that predispose to pancreatic cancer, with the notable exception of PRSS1, also predispose to extrapancreatic tumors. Individuals found to carry a deleterious germline variant can also benefit from screening for early, curable extrapancreatic neoplasms. Finally, many of these genes are therapeutically targetable. As clinical genetic testing becomes less expensive, and the genes responsible for the familial aggregation of pancreatic cancer are defined, we look forward to the growing integration of germline genetic testing in routine patient care,” he says.

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