



Patient Report

PJS & Pancreatic Cancer

A Report by
Stephanie Sugars

A recent article on PJS and pancreatic cancer[†] is a must read for the researchers, genetic counselors and doctors in this group. Patients and family members, especially those whose lives have been touched by pancreatic cancer, may want to read it too. This very thorough article reviews the reported cases of pancreatic cancer in PJS people, illustrates and explains the roles of the PJS gene (STK11/LKB1) and suggests directions for research and treatment.

The authors are from University of Pennsylvania School of Medicine in Philadelphia, PA, USA. UPENN is well known by cancer patients for the patient-friendly website Oncolink at <http://oncolink.upenn.edu/disease/>. Less well known are the authors. None have ever published a PJS article before, and I didn't find biographies for them online, though Dr. Yee's credentials are at <http://nsyee.ascomd.org/>. Dr. Yee kindly corresponded with me, sharing the article and telling me that "My current research involves zebrafish as an experimental model for pancreatic development and cancer." If you'd like to write to him about your experiences with PJS and pancreatic cancer, his work or for a copy of the article, his address is nsyee@mail.med.upenn.edu.

The authors' interest in pancreatic cancer in PJS folks seems to have been sparked by their 71 year-old patient who presented with both pancreatic and colon cancer. They describe her case and in Table 2, review most of the reported cases of pancreatic cancer in PJS people. I won't report the contents of Table 2, but here's some interesting commentary:

“The demographic factors of PJS patients with pancreatic tumors are somewhat different from those of patients who develop sporadic ductal adenocarcinomas. Pancreatic tumors in PJS patients are generally diagnosed at an early age (mean 46.3 year-old), as compared to patients with sporadic pancreatic ductal adenocarcinomas (mean 64.6 year-old). The early age onset is consistent with the notion that PJS predisposes to pancreatic malignancies. There is a strong male preponderance for PJS patients with pancreatic tumors (75%), in contrast to patients with sporadic pancreatic adenocarcinomas (54%).

“Variable presentations have been described for the PJS patients with pancreatic tumors. In several cases including the patient in this report, there were no specific signs or symptoms. The PJS pancreatic tumors were incidentally found during evaluation of coexisting medical conditions or on routine screening radiographic image. Other tumors were discovered during post-mortem examination. Occasionally PJS patients presented with tumor-related abdominal pain, bowel obstruction or back pain. In comparison, patients with sporadic pancreatic ductal adenocarcinomas commonly present with gastrointestinal symptoms such as jaundice, abdominal pain, nausea and vomiting.

“For these reasons, health practitioners should be aware of the fact that pancreatic tumors may develop at a relatively early age in PJS patients and surveillance for this disease should be considered. Current tests available for the detection of pancreatic tumors include computed tomography, magnetic resonance pancreatography, endoscopic ultrasonography, endoscopic retrograde cholangiopancreatography, and serum/stool test for tumor markers including CA19-9, ras and p53 mutations, cytokeratins and CEA. However, these tests have limited sensitivity and specificity and some are too invasive for routine screening. Thus, more effective screening tests for early detection of pancreatic

cancer are needed in genetically predisposed individuals and the general population. For this purpose a thorough understanding of the molecular mechanisms underlying the initiation and progression of premalignant pancreatic lesions will be crucial.”

To find out more about these tests, visit MEDLINEplus at <http://www.nlm.nih.gov/medlineplus/>. Also, a couple of months ago a group member and I had a long discussion about pancreatic cancer screening for PJS folks and why it's not recommended in the UK, but is in the USA. You can search our archives for the topic. And Johns Hopkins in Maryland, USA, has a study on pancreatic cancer screening for PJS folks. Here's the study information:

- Pancreatic Cancer Screening Study -- Canto -- Johns Hopkins
Includes an endoscopic ultrasound examination and abdominal CT testing with a one-year-follow-up.
Contact: Brenda Ridgeway at bridgewa@jhmi.edu
Telephone: 410-955-3821.
Study open only until July 2003. *May still be open.*

The article contains several pages of well-written, well-footnoted text on the molecular genetics of PJS-related pancreatic tumors, developmental roles of STK11/LKB1 (the PJS gene), the tumor suppressor function of STK11/LKB1 and STK11/LKB1 as potential target for treatment and prevention of pancreatic cancer. I'll not report on most of that here, but if these topics interest you, read the article. Two very interesting topics were introduced in the section *STK11/LKB1 as potential target for treatment and prevention of pancreatic cancer*:

“Since STK11/LKB1 is ubiquitously expressed and PJS patients can develop malignancy in a variety of organs, any therapeutic preventive strategy for PJS-associated pancreatic cancer may be applicable to other cancers in these individuals. The findings of biallelic inactivation of STK11/LKB1 in PJS cancer cells and cancer of heterozygous STK11/LKB1 mutant mice suggest that the replacement of wild-type STK11/LKB1 gene either alone or in combination with other therapeutic regimens such as chemotherapy, may be useful for treatment of advanced or recurrent cancer. Alternatively, transfection of either the kinase domain of STK11/LKB1 or a modified gene in which the threonine-189 residue that negatively regulates STK11/LKB1 kinase activity or the threonine-335 residue is mutated, might be more effective in inducing apoptosis and growth suppression in tumor cells. Potential chemopreventive agents may be developed with the aim of restoring normal STK11/LKB1 expression levels, kinase activity, or subcellular compartmentalization. Upregulation of cyclooxygenase-2 (COX-2) in murine (mouse) LKB1^{+/-} mediated polyposis and human PJS polyps suggests that COX-2 is a potential target for prevention and treatment of hamartomatous polyps and possibly cancers in patients with PJS, as in familial adenomatous polyposis and colorectal cancer. In this regard, model organisms such as the zebrafish can potentially be used for high throughput screens for compounds that augment STK11/LKB1 activity or inhibit COX-2 mediated pathways leading to carcinogenesis.”

The interesting ideas are replacing the missing gene product STK11/LKB1, using COX-2 inhibitors (which we already know about) and using zebrafish to investigate PJS, pancreatic cancer and possible treatments. So far, published accounts of PJS animal experiments have been limited to mice and flies, though the PJS gene is expressed in many animals including frogs and worms. I'll be very interested in future reports and studies by Dr. Yee and his coauthors. They bring a fresh view to the subjects of PJS and pancreatic cancer.

† Yee NS, Furth EE, Pack M. *Clinicopathologic and Molecular Features of Pancreatic Adenocarcinoma Associated with Peutz-Jeghers Syndrome*. *Cancer Biol Ther*. 2003 Jan-Feb;2(1):38-47.
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Contact Stephanie Sugars at PJ4Steph@aol.com

