



Patient Report

The LKB1/Lung Cancer Connection

A Report by
Stephanie Sugars

First off, a disclaimer. There really isn't much incidence in the literature of lung cancer in PJS folks, certainly no where near the numbers of gastrointestinal (GI), pancreatic, breast or reproductive cancers and tumors. Dr. Giardiello wrote about the very high risk of cancer in familial cancer¹ and the absolute risk for lung cancer was 15%, well below the estimated cancer risk for many other organs. I am aware that lung cancer in PJS folks might be under reported in the literature because most authors have focused on GI malignancy to the exclusion of all other types of cancers and tumors. Even reproductive tumors haven't been considered part of the syndrome until recently and some physicians, especially gastroenterologists, still discount the gynecological and testicular problems of PJS folks. All the information isn't in yet.

A report from Johns Hopkins suggests a link between inactivation of LKB1 and sporadic lung adenocarcinomas.² Inactivation of LKB1 occurs when both working copies of the gene are knocked out. This is roughly analogous to loss of heterozygosity (LOH). As I've written before, most people with PJS have one working and one non-working copy of the LKB1 gene, whereas other people have two working copies of the gene. It was thought that when the one working copy lost function through a mutating event that polyps, tumors and cancers arose. Loss of the working copy is called loss of heterozygosity.

Anyway, this report is NOT about people with PJS getting lung cancer, but about lung cancers in the general population or sporadic cancer. The researchers found inactivation of LKB1 in many lung adenocarcinomas. I have to backtrack here with a bit of history. After the genetic locus for PJS was pinpointed in 1997, researchers began testing for inactivation of LKB1 in a variety of cancers associated with PJS including breast, cervical, colon, testicular, gastric and ovarian. (I won't give you footnotes on these, but am happy to dig them up.) Most studies didn't find a connection between inactivated LKB1 and the cancers, which discouraged researchers from looking for connections between LKB1 and cancers less common in PJS.

Research into rare genetic conditions like PJS (LKB1 OR STK11 gene), Familial Adenomatous Polyposis (APC gene), Li-Fraumini syndrome (p53 gene), Cowden syndrome (PTEN gene), BRCA1 and BRCA2 give scientists insight into the mechanisms of cancer. There are basically two main types of hereditary predisposition to cancer -- oncogenes and tumor suppressor genes. Think of them like accelerator and brakes. Oncogenes make cancer go, tumor suppressors make them stop. LKB1 is a tumor suppressor gene, so when both copies are knocked out, then cancer or other tumors are no longer suppressed and can grow. There are many pathways to cancer and many genes involved, some genes involved in carcinogenesis are related to inherited predisposition to cancer syndromes, others aren't.

Dr. Sanchez-Cespedes' group was surprised to find a connection between LAD tumors and mutations that inactivate LKB1 because other researchers had not found a strong link between such mutations and other sporadic (non-inherited) tumors, including breast and colorectal cancer. One-third of the 41 lung adenocarcinomas analyzed showed inactivation of LKB1. This news supports more research into LKB1. Since over 50,000 people in the USA develop lung adenocarcinoma annually, there may be interest and funding for more studies of LKB1 that will ultimately affect us.

As I wrote, I've been collecting lung cancer cases. There are two topics in my mind, one is a group member who's had a lung hamartoma and the second is the connection between cigarette smoke and lung, colon, breast and other cancers.

Following is a table with reports of lung cancer from the literature and outside of the literature.

Report Source	Diagnosis	Age & Gender
Giardiello et al ³	Large cell undifferentiated lung cancer	41, female
	Lung adenocarcinoma	70, female
Spigelman et al ⁴	Lung cancer	33, male
Boardman et al ⁵	Lung cancer (3 patients)	n/a
Burdick & Prior ⁶	Lung adenocarcinoma	63, female
Utsunomiya et al ⁷	Fatal lung cancer (2 patients)	n/a
Dormandy ⁸	Multiple bronchial adenomas	60, female
Boardman et al ⁹	Lung adenocarcinoma	n/a
Dozios et al ¹⁰	Lung adenocarcinoma & bilateral breast tumors	49, male
Hirano et al ¹¹	Metastatic adenocarcinoma	31, male
Massachusetts General Hospital ¹⁶	Fatal lung cancer	31, male
Group member	Lung cancer (2 patients)	female
Non-group member	Fatal lung cancer	male
Group member	Lung cancer	35, female

In March 2003, Dr. Sanchez-Cespedes' group published a new paper on the LKB1-lung cancer pathway.¹² I have only read the abstract, not the article, but the findings are interesting for a couple of reasons. When the researchers introduced overexpressed LKB1 into lung adenocarcinomas cells it led to cell-growth suppression. I assume this is in a laboratory, not a person. They then analyzed the changes in gene expression and found that "growth suppression in A549 cells overexpressing LKB1 may be mediated by p53. In addition, PTEN up-regulation indicates that LKB1 could be involved...". Other researchers have found connections between PJS and p53 and PJS and PTEN.^{13, 14} Remember: p53 mutations cause Li-Fraumeni syndrome and PTEN mutations lead to Cowden syndrome. Interestingly, another study found that LKB1 didn't follow another common cancer pathway (ras).¹⁵

I am not suggesting any screening or prevention for lung cancer, nor have I read that any is suggested by any PJS expert. This patient view isn't meant to depress or scare anyone. As I wrote earlier, lung cancer seems to be the least of our worries. I'm actually encouraged because I hope that research interest and money will continue to flow into PJS so that we get better prevention, screening and treatment.

¹Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, Cruz-Correa M, Offerhaus JA. *Very high risk of cancer in familial Peutz-Jeghers syndrome.* Gastroenterology. 2000 Dec;119(6):1447-53.
PMID: 11113065 [PubMed - indexed for MEDLINE]

²M, Parrella P, Esteller M, Nomoto S, Trink B, Engles JM, Westra WH, Herman JG, Sidransky D. *Inactivation of LKB1/STK11 Is a Common Event in Adenocarcinomas of the Lung.* Cancer Res. 2002 Jul 1;62(13):3659-3662.
PMID: 12097271 [PubMed - as supplied by publisher]

³Giardiello FM, Welsh SB, Hamilton SR, Offerhaus GJ, Gittelsohn AM, Booker SV, Krush AJ, Yardley JH, Luk GD. *Increased risk of cancer in the Peutz-Jeghers syndrome.* N Engl J Med. 1987 Jun 11;316(24):1511-4.
PMID: 3587280 [PubMed - indexed for MEDLINE]

⁴Spigelman AD, Murday V, Phillips RK. *Cancer and the Peutz-Jeghers syndrome.* Gut. 1989 Nov;30(11):1588-90.
PMID: 2599445 [PubMed - indexed for MEDLINE]

⁵Boardman LA, Thibodeau SN, Schaid DJ, Lindor NM, McDonnell SK, Burgart LJ, Ahlquist DA, Podratz KC, Pittelkow M, Hartmann LC. *Increased risk for cancer in patients with the Peutz-Jeghers syndrome.* Ann Intern Med. 1998 Jun 1;128(11):896-9.
PMID: 9634427 [PubMed - indexed for MEDLINE]

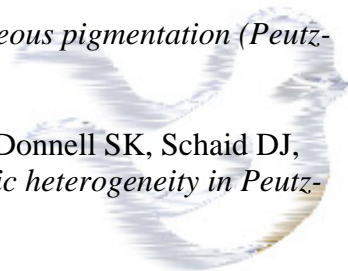
⁶Burdick D, Prior JT. *Peutz-Jeghers syndrome. A clinicopathologic study of a large family with a 27-year follow-up.* Cancer. 1982 Nov 15;50(10):2139-46.
PMID: 7127254 [PubMed - indexed for MEDLINE]

⁷Utsunomiya J, Gocho H, Miyanaga T, Hamaguchi E, Kashimure A. *Peutz-Jeghers syndrome: its natural course and management.* Johns Hopkins Med J. 1975 Feb;136(2):71-82.
PMID: 1117595 [PubMed - indexed for MEDLINE]

⁸Dormandy, Thomas. *Gastrointestinal polyposis with mucocutaneous pigmentation (Peutz-Jeghers syndrome).* NEJM 1957 Jun 6 256(24):1093-1102.

⁹Boardman LA, Couch FJ, Burgart LJ, Schwartz D, Berry R, McDonnell SK, Schaid DJ, Hartmann LC, Schroeder JJ, Stratakis CA, Thibodeau SN. *Genetic heterogeneity in Peutz-Jeghers syndrome.* Hum Mutat. 2000;16(1):23-30.
PMID: 10874301 [PubMed - indexed for MEDLINE]

¹⁰Dozios RR, Judd ES, Dahlin DC, et al. *The Peutz-Jeghers syndrome: Is there a predisposition to the development of intestinal malignancy?* Arch Surg. 1969; 98:509-516



¹¹Hirano S, Takiguchi Y, Igari H, Hiroshima K, Shingyoji M, Watanabe R, Moriya T, Tanabe N, Tatsumi K, Kuriyama T. *A case of pulmonary adenocarcinoma accompanied by superior vena caval thrombosis in a patient with Peutz-Jeghers syndrome.* Jpn J Clin Oncol 2002 Aug;32(8):307-9
PMID: 12411569

¹²Jimenez AI, Fernandez P, Dominguez O, Dopazo A, Sanchez-Cespedes M. *Growth and molecular profile of lung cancer cells expressing ectopic LKB1: down-regulation of the phosphatidylinositol 3'-phosphate kinase/PTEN pathway.* Cancer Res 2003 Mar 15;63(6):1382-8
PMID: 12649203

¹³Karuman P, Gozani O, Odze RD, Zhou XC, Zhu H, Shaw R, Brien TP, Bozzuto CD, Ooi D, Cantley LC, Yuan J. *The Peutz-Jegher gene product LKB1 is a mediator of p53-dependent cell death.* Mol Cell. 2001 Jun;7(6):1307-19.
PMID: 11430832

¹⁴Luukko K, Ylikorkala A, Tiainen M, Makela TP. *Expression of LKB1 and PTEN tumor suppressor genes during mouse embryonic development.* Mech Dev. 1999 May;83(1-2):187-90.
PMID: 10381580

¹⁵Bardeesy N, Sinha M, Hezel AF, Signoretti S, Hathaway NA, Sharpless NE, Loda M, Carrasco DR, DePinho RA. *Loss of the Lkb1 tumour suppressor provokes intestinal polyposis but resistance to transformation.* Nature. 2002 Sep 12;419(6903):162-7.
PMID: 12226664

¹⁶[No authors listed] *Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 24-1975.* N Engl J Med. 1975 Jun 19;292(25):1340-5.
No abstract available. PMID: 1128608

© 2004 by Stephanie Sugars, all rights reserved, used by permission. No part of this article may be reproduced in any form without written permission from the author.

Contact Stephanie Sugars at PJ4Steph@aol.com

