



Patient Report

Very High Risk of Cancer in Familial Peutz-Jeghers Syndrome

An Article Review by
Stephanie Sugars

As most of you know, Dr. Francis Giardiello of Johns Hopkins University and others published an article on risk of cancer in PJS folks in the December 2000 issue of Gastroenterology.¹

As I mentioned in an earlier e-mail, the information presented in this article galvanized me to start this online support group. The news sounded so grim, that I needed to act against the fear it created. I've been struggling for a month about how to share the news without frightening you.

A life with PJS is full of good news/bad news. So is this article. PJS is sometimes like a good news/bad news joke.

Doctor 1: We found out what is wrong with you.

Doctor 2: But we can't pronounce the diagnosis.

Doctor 1: You'll need to have surveillance for cancer and polyps for the rest of your life.

Doctor 2: But the tests will be uncomfortable, inconclusive and possibly cause cancer.

We could go on and on with this gallows humor, each contributing jokes from our own lives. Though this article contains scary information, it is also humorous. The good news is PJS folks are at high risk for a variety of cancers. The bad news is that we don't know how to manage (either prevent or cure) that risk. It makes me wonder just who is behind the wheel and how safe we really are. If I didn't laugh, I'd cry. And sometimes I do.

Let's look at the article. First a little vocabulary.

- Relative Risk (RR) is the ratio of observed to expected cases for cancer. We are 15 times more likely to get cancer than a person in the general population.
- Confidence Limit (CL) the range that those RR figures are drawn from. Example: "breast (15.2; CL 7.6, 27)". This means that based on this meta-analysis women with PJS are 15 times more likely to get breast cancer than a woman in the general population. The RR ranged between 7.6 and 27.
- Cumulative risk is the risk of developing cancer between the ages of 15 and 64, based on this meta-analysis.

From the abstract:

- Background & aims: The Peutz-Jeghers syndrome (PJS) is an autosomal dominant polyposis disorder with increased risk of multiple cancers, but literature estimates of risk vary.
- Methods: We performed an individual patient meta-analysis to determine the relative risk (RR) of cancer in patients with PJS compared with the general population based on 210 individuals described in 6 publications.

- Results: For patients with PJS, the RR for all cancers was 15.2 (95% confidence limits [CL], 2, 19). A statistically significant increase of RR was noted for esophagus (57; CL, 2.5, 557), stomach (213; CL, 96, 368), small intestine (520; CL, 220, 1306), colon (84; CL, 47, 137), pancreas (132; CL, 44, 261), lung (17.0; CL, 5.4, 39), breast (15.2; CL, 7.6, 27), uterus (16.0; CL, 1.9, 56), ovary (27; CL, 7.3, 68), but not testicular or cervical malignancies. Cumulative risk for all cancer was 93% from age 15 to 64 years old.
- Conclusions: Patients with PJS are at very high relative and absolute risk for gastrointestinal and nongastrointestinal cancers.

The first question I ask myself about the article is whether this is news. I am immediately concerned that only 210 individuals are included in the group. Just one patient with one cancer can skew the statistics. If that person is young, the skew is dramatic. For instance the 67 year old gentleman with esophageal cancer in chart 5 can lead to a relative risk of esophageal cancer of 57 for the entire group. The cumulative risk becomes 0.5%. But does this cumulative risk apply to all of us equally? Can a doctor turn around to us and say, "every one of you has a risk of esophageal cancer that is 57 times that of someone in the general population. And a 0.5% risk of getting esophageal cancer between the ages of 15 and 65."? Probably not.

The second question I ask is, what is the source of this information. Table 1 shows the six studies that were used for this meta-analysis. The first thing I notice is the information on the right side of the table. These reflect the frequency of cancer in the study participants. They are:

- Study 1: Giardiello 1987 48%
- Study 2: Spigelman 1989 22%
- Study 3: Westerman 1998 28%
- Study 4: Boardman 1998 53%
- Study 5: Foley 1988 17%
- Study 6: Burdick 1982 25%

The frequency of cancer in these six studies is 17%-53%. How does that become a cumulative risk of cancer of 93% ? I think this may relate to age at diagnosis because cancer usually affects older people.

The mean (average) age of diagnosis of cancer in patients with PJS to be 43 years old. It's implied that people with PJS are diagnosed earlier than expected.

Okay, let's think about this for a minute. Breast cancer risk. Most of us have heard that one in eight women will be diagnosed with breast cancer. But that is a lifetime risk. A woman who lives to age 95 has a 1 in 8 lifetime risk of breast cancer. But the lifetime or cumulative risk at age 25 is 1 in 19,608; age 35 is 1 in 622; age 45 is 1 in 93; age 55 1 in 33; age 65 1 in 17. So if our relative risk for breast cancer is 15, it doesn't mean twice the 1 in 8 figure (two breast cancers per woman). It means that we are likely to get it younger. Sure enough, table 5 shows the mean age of breast cancer diagnosis of 37 years

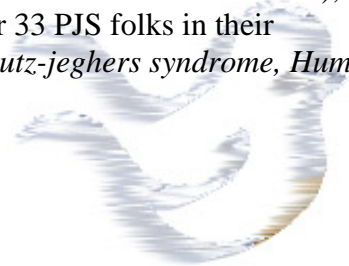
with the age range between 26 and 48. Table 4 shows the cumulative risk for breast cancer as being 54% for ages 15 to 64. In the text the authors say, "Of concern, the absolute risk of breast cancer is similar in magnitude of risk noted in hereditary forms of that tumor caused by germline mutations of BRCA1 or BRCA2 (genes associated with hereditary breast cancer)."

Is this good news or bad news? I want to think about germline mutations for a moment. First off, all cancer is genetic in that it occurs in the genes. In most people cancer is due to a series of events (aging, hormones, environment, etc.). Their good cells must go bad. But people with hereditary cancer have a half bad chromosome to start with. PJS folks have a quirky chromosome (LKB1, STK11, 19p13.3) that is altered in one allele of every cell in our bodies. I strongly suggest reading Hereditary Breast Cancer by Maren Scheuner, M.D., M.P.H. at <http://www.breastdiseases.com/genebr.htm>. The author explains Knudson's 2-hit model of carcinogenesis with illustrations. A while back Leanna asked what would happen if someone were to inherit the PJS gene from both parents. I think it is something like we've experienced with our polyps, spots and cancers. If we have a pair of alleles and one is quirky at birth, then an event happens to inactivate the second allele, something is likely to happen.

Note: Understanding of the PJS gene has advanced since I wrote this. It's been found that one bad copy of the PJS gene is enough to give one spots & polyps. The second hit seems to be implicated in cancer.

Our PJS gene is identified as a tumor suppressor gene whose function is important for controlling cell growth and guaranteeing that aberrant cell division does not occur (usually by inhibiting cell growth or promoting cell death). The loss or malfunction of such a gene would lead to uncontrolled If the normal allele mutates it weakens tumor suppression and possibly leads to benign or malignant growths. How do you know if you are likely to get lose your normal allele (loss of heterozygosity) and what can you do to prevent that from happening? That's a question neither I nor this article can answer.

Chris Amos is working on a genotype/phenotype model for PJS. There are not only different mutations to the PJS gene, but possibly different PJS genes. Though some studies have shown that PJS is on chromosome 19p13.3 (also called STK11 and LKB1), Lisa Boardman et al. of Mayo Clinic found that only 6 of over 33 PJS folks in their registry had the LKB1 mutations. *Genetic heterogeneity in peutz-jeghers syndrome, Hum Mutat 2000;16(1):23-30.*



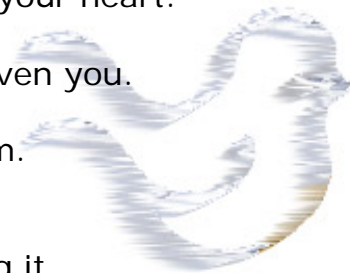
Someday we might have a clear genotype/phenotype model that would act as a crystal ball to forecast our risk of various cancers/PJS complications. Today we don't. And the doctors don't. We are reliant on their studies and interpretations to plan our next move. Do we begin mammograms at the age of 25, knowing that it isn't prevention but a method of early detection? Knowing that younger, firmer breast tissue can lead to inconclusive results or false negatives? Knowing that radiation exposure can lead to cell damage and future cancers? But knowing that breast cancer diagnosed at an early stage has a better cure rate than breast cancer diagnosed at a later stage? These are terrible questions to face.

We can sit down with each of the cancers listed in the article (esophagus, stomach, small intestine, colon, pancreas, lung, testes, breast, uterus, ovary and cervix) and ask similar questions about prevention, early detection, cancer symptoms, non-detection, etc. Reading medical articles, I am constantly reminded that I am not a doctor. I do not think like a doctor, but like a patient. And an impatient patient at that. I am looking for ways to save my life and the lives of others with PJS. The ambiguity of a meta-analysis based on only 210 cases of PJS is difficult for me. I've read four of the six studies that this article is based on and I find them inconclusive too. Why does this article use the word familial in the title when nearly half of the folks (18 of 34) in Boardman's study had sporadic cases of PJS? Are these the same PJS patients from Mayo Clinic that have mutations other than LKB1? What differences are there between familial and sporadic PJS cases? What's happened with Burdick's PJS family in the 18 years since his article was published? How did the frequency of cancer in these six studies (17%-53%) become a cumulative risk of cancer of 93%? If one person can skew the figures for everyone, what could one family (genotype) do to the whole group? And most especially, how do we take this data and move forward with our lives? Will an article like this free us, allow us to move forward with confidence? Or will it cripple us by immobilizing us with fear and worry?

Well, there's good news here and bad news. And sometimes one piece of news is both good and bad. In spite of the humor we can find in this article, living with PJS is no joke. And again I am reminded that there are no easy answers for us. To quote the poet Rilke again:

Be patient toward all that is unresolved in your heart.
And try to love the questions themselves.
Do not seek the answers that cannot be given you.

Because you would not be able to live them.
And the point is to live everything
Live the questions now.
Perhaps you will gradually, without noticing it,
Live along some distant day
into the answer.



I invite comments, criticisms and clarifications. If I have made a medical fool of myself, please correct me. It is hard work for me to think like a doctor and interpret what I read to an audience of patients and family members. I would rather be wrong than to misinform anyone.

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.
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