



Patient Report

Cancer Risks in PJS Sufferers

A Literature Review by
Andrew Wells

If cancer risks scare you, you might want to skip this paper, or at least to read it while sitting down with a nice drink of tea, whisky, whatever. You might then want to talk to others on the group, or to your family, or to your doctor about the risks involved.

Difficulties of Measuring Cancer Risks

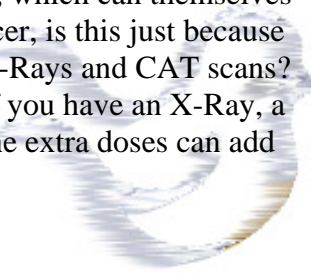
The first difficulty lies in the problems associated with defining, and diagnosing, PJS. I have PJS - I have lots of spots on my lips (and a few on other parts of my body), and I had 15 hamartomatous polyps. But what about my mother (who had spots as a child, but who has no polyps in her stomach or her large intestine)? What about my sister (who has spots, but who has not yet had any GI scans)? What about someone with spots and GI problems, but with no family history of PJS?

A separate problem is this. Many people are diagnosed with PJS fairly late in life. For example, I was diagnosed at 36. My mother has not yet been formally diagnosed, but she has now had breast cancer twice. Even if she is later diagnosed as having PJS, her inclusion in the statistics as, "A PJS sufferer with breast cancer," might skew the results, because the breast cancer was diagnosed first. And what about someone who has breast cancer, then is diagnosed with PJS, then has breast cancer again - should they be counted, or not?

Another difficulty is that in the old days - and by that, I mean anything up to about twenty years ago - hardly anybody recognised that PJS could cause cancer, and certainly not cancer outside the GI system. So, no-one looked very hard for cancers in PJS sufferers, and probably didn't make a special note if they were diagnosed.

And that brings me on to another problem, and probably one of the biggest we have to deal with. These days, most diagnosed PJS sufferers have more screening than the typical non-PJS sufferer. Whether it is just a triennial endoscopy, colonoscopy and barium meal; or whether it is the full set of annual endoscopy, colonoscopy, barium meal and capsule endoscopy, plus mammograms, vaginal / testicular ultrasound, endoscopic ultrasound, whatever; we undergo more tests than most "normal, healthy" people. So, if we have cancer, it will be picked up more quickly.

Indeed, some of the tests we undergo involve doses of radiation, which can themselves cause cancer. So, even if PJS sufferers are at greater risk of cancer, is this just because we've got PJS, or might it also be because we've had so many X-Rays and CAT scans? (The extra risk from each dose is very, very small indeed. But if you have an X-Ray, a barium meal and a CAT scan every year throughout your life, the extra doses can add up).



In fact, we might be more health conscious than most people, and our doctors might also be more health-conscious on our behalf. My GI surgeon has specifically told me that if I have a worrying lump, bump or whatever, to get it taken off - it's simpler & quicker than getting it biopsied, then getting it taken off later. So, if I have a malignant melanoma (say), it might get picked up more quickly than it would one someone else. (But, what if it's removed while it's still in a pre-cancerous phase? That might not count as a cancer at all, whereas someone who waits a year would have it counted as a cancer).

There are some difficulties which are associated with PJS in very specific ways:

- The cancer risk associated with familial PJS might be different from the risk associated with sporadic PJS;
- The cancer risk associated with an LKB1 / STK11 mutation might be different from the risk associated with the mutation in some other gene; and
- The cancer risks may differ between men and women.

Separately to all this are three problems with measuring cancer risks in the general population:

- Cancer risks increase as you get older, and people are living longer than ever before, so there are more cancer sufferers;
- Cancer risks also change over time in other ways; and
- Ways of identifying cancer improve over time.

There aren't many of us PJS sufferers around, and this gives its own problems. Very few hospitals have more than 50 or so patients on their books, and very few studies include more than 50 or so cases. This can give rise to significant errors in statistical sampling. A good experimental design can minimise these problems, but not remove them altogether.

Moving on from this, say you've studied 50 patients for ten years, and that these patients are spread out over the age range 15 - 75. That only gives you ten "patient-years" for each age that you are interested in. So you aren't studying 50 cases altogether - you're only studying 10 at each age. (Also, many reports involve some sort of mathematical model, and these can be hard for non-mathematicians to get to grips with - especially if we're also non-medicos trying to understand a report written by a team of specialist doctors).

What do we do with the results? If cancer of the thumb is fatal in 20% of cases, I'd be scared about getting it, and I'd want to be screened. But if there's no reliable way of screening yet, or if the screening involves a massive radiation dose, then maybe I don't want screening. Even if screening means three hospital appointments every year, and unpleasant things involving needles and pain, I might not want screening, if the risk of getting cancer of the thumb is small enough.

Some cancers are very rare. Say that cancer of the big toe only occurs in 0.001% (1 in 100,000) of people each year. Then a study of 50 PJS sufferers over ten years probably won't have a single case of cancer of the big toe, even if it's twenty times as likely among PJS sufferers as it is in the general population. And if the study does find one case, does that mean it's twenty times as common among PJS folk, or does it just mean that the researchers were (un)lucky enough to get one case?

And if cancer of the big toe is twenty times as common among PJS folk, but we still only have a one in five thousand chance of getting it, we probably shouldn't worry too much about it. But if cancer of the little toe affects one person in ten, I'd be worried, even if there's no additional risk for PJS sufferers.

Unfortunately, some of the cancer risks that affect us are a bit like this - okay, they don't affect our thumbs or our toes very often, but they can affect some other parts of our bodies.

Literature Review

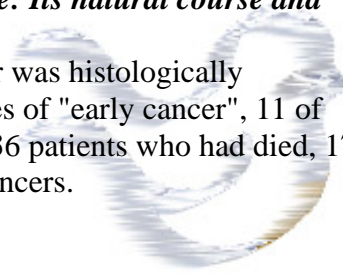
I'm going to look at some papers on cancer risks among PJS sufferers. These cover all the papers I know of that have specifically looked at this subject (except for one that I haven't yet been able to obtain), and some of the major general papers on the subject. In each case, I will give brief details of the author(s), title and publication date; I'll be happy to give fuller citations to anyone who is interested.

- **Bartholomew et al, 1962, *Intestinal polyposis associated with mucocutaneous pigmentation.***

This paper is a broad overview of the original Harrisburg family, and the current state of knowledge of PJS. It talks at some length about whether the intestinal polyps can become malignant, and it casts some doubt on this. I do not know enough about medical matters to be able to evaluate their comments properly, but they are interesting. The authors do not appear to discuss extra-GI cancers, and in their conclusion, they say, "Evidence presented seems to favor the view that the disease is benign."

- **Utsunomiya et al, 1974, *Peutz-Jeghers Syndrome: Its natural course and management.***

This is a study of 222 Japanese patients. GI cancer was histologically confirmed in 28 cases. These included 15 examples of "early cancer", 11 of "advanced cancer", and two "personal cases". Of 36 patients who had died, 17 were due to cancer, and 8 of these were non-GI cancers.



- **Burdick & Prior, 1982, *Peutz-Jeghers Syndrome: A clinicopathologic study of a large family with a 27-year follow-up.***

This does what it says on the tin: it is a study of one large family over a 27 year period. Some quotes from the discussion:

- "At the time of our original study of this family [in 1963] these authors took the position that the Peutz-Jeghers polyp did not have a malignant potential ..."
- "We based this belief on the fact that the polyps were hamartomatous in nature, that there had been no reported deaths from carcinoma in these patients up to that time, the ten-year follow-up which revealed no intestinal malignancies, and the fact that all reported cases of intestinal carcinoma up to that time were not convincing."
- "Reports of metastasizing intestinal cancers began appearing in 1965. Since that time, there have been over three dozen acceptable cases of metastasizing intestinal carcinomas in Peutz-Jeghers syndrome."
- "Some authorities place the incidence rate of cancer in Peutz-Jeghers syndrome as high as 3%."
- "We have corroborated the reported increased incidence of ovarian and breast neoplasms ..."

- **Mallory and Stough, 1987, *Genodermatoses with malignant potential.***

This is a report on several different conditions, including PJS. Here, they say: "There is some debate with regard to the actual incidence of malignancy in Peutz-Jeghers syndrome. Estimates for gastrointestinal malignancies range from 2% to 3% in one source to 12.6% in another." They also list some of the other malignancies that have occurred in sufferers, including in the gonads, the cervix and the breasts.

- **Giardiello et al, 1987, *Increased risk of cancer in the Peutz-Jeghers Syndrome.***

This is a study of 31 patients from 13 unrelated families. In total, these 31 patients were studied for 622 patient-years, ie for an average of just over 20 years each. 15, or 48%, of these patients developed cancer during the period covered by the study. Four were cases of GI cancer. The relative risk for the development of cancer was found to be 18. For women, the relative risk was 16. For men, the relative risk was 22.

- **Foley, McGarrity & Abt, 1988, *Peutz-Jeghers Syndrome: A clinicopathologic survey of the 'Harrisburg Family' with a 49-year follow-up.***

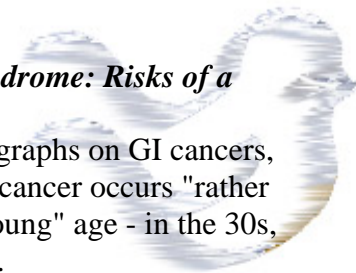
Again, this does what it says on the tin. Some quotes from the discussion:

- "The incidence of gastrointestinal malignancy appears to be increased in PJS."
- "PJS patients appear to be at an increased risk of extraintestinal malignancy."

- **Spigelman et al, 1989, *Cancer and the Peutz-Jeghers Syndrome.***
This is a study of the 72 PJS patients on the St Marks, London, registry. Malignant tumours had developed in 16 of these (22%). Of these cancers, 10 were gastrointestinal, and 7 were not - one patient had two cancers. All but one of these tumours were lethal.

Using a mathematical model, the chance of dying of cancer by age 57 was found to be 48%, and the chance of dying of any cause was 57%. The relative risk of death from GI cancer was 13 (95% CI: 2.7 - 38.1), and from all cancers was nine (95% CI: 4.2 - 17.3).

- **Spigelman & Phillips, 1994, *Peutz-Jeghers syndrome.***
This is a chapter of a textbook. It has a broad review of all features of PJS. In the section on cancer risks, it reviews all the papers mentioned above, and some others. Interestingly, this section opens by saying: "Reports of Peutz-Jeghers syndrome in connection with gastrointestinal and extraintestinal cancers have led to a re-assessment of the management of patients with this condition." In their conclusion, they say: "There seems to be a real risk for gastrointestinal and for non-gastrointestinal cancer in patients with Peutz-Jeghers syndrome."
- **Boardman et al, 1998, *Increased risk for cancer in patients with the Peutz-Jeghers Syndrome.***
This is a retrospective study of 34 patients from 31 families. In total, these patients were studied for 425 patient-years, ie for an average of just under 14 years each. 18, or 53%, of these patients developed a total of 26 cases of cancer during the period covered by the study. Ten were cases of GI cancer. The relative risk for the development of cancer was found to be 9.9, with the 95% CI (confidence interval) being 5.7 to 16.2. For women, the relative risk was 18.5 (CI, 8.5 to 35.2). For men, the relative risk was 6.2 (CI, 2.5 to 12.8). They say, "In conclusion, our study confirms that the Peutz-Jeghers syndrome is associated with a significantly increased risk for both intestinal and extraintestinal cancer."
- **Westerman & Wilson, 1999, *Peutz-Jeghers Syndrome: Risks of a hereditary condition.***
This is a broad study of PJS. It has two brief paragraphs on GI cancers, although it does highlight the fact that pancreatic cancer occurs "rather frequently" in PJS patients, and at a "strikingly young" age - in the 30s, compared to close to 60 in the general population.



- **Westerman et al, 1999, *Peutz-Jeghers syndrome: 78-year follow-up of the original family.***
Again, this is a follow-up of a single extended family. They say: "Although PJS polyps are hamartomas, frequent association of this syndrome with both gastrointestinal and non-gastrointestinal tumours has led to reassessment of the cancer risk in this hereditary disorder. Seven out of the 22 (32%) affected family members developed cancer, five of which occurred in the gastrointestinal tract. This proportion does not necessarily reflect the risk of cancer in present generations, because there have been syndrome associated competing causes of death in the earlier generations. The young age at which cancer death occurred in this family was striking, with a mean of 50 years. All cancers had metastasised at the time of death, and therefore represented true cases of cancer."

- **McGarrity et al, 2000, *Clinical reviews: Peutz-Jeghers Syndrome.***
This is a broad overview of the condition, which covers many aspects, including that of cancer.

There is a long discussion of the relationship between PJS and GI malignancy. In the conclusion of this discussion, the authors say, "There is little doubt regarding the increased risk of GI malignancy in PJS. However, the origin of cancer within the GI tract of PJS patients is debated."

There is a discussion of genital tract tumours. This opens by saying, "Unusual and common genital tract neoplasms and nonneoplastic lesions have been reported at an increased frequency in female and occasionally in male patients with PJS."

There is also a discussion of other malignancies. This covers the studies on cancer risks discussed above, and also mentions some reports of specific cancers that have been found in PJS sufferers.

- **Giardiello et al, 2000, *Very high risk of cancer in familial Peutz-Jeghers Syndrome.***
This is a meta-analysis. That means that they did not investigate one group of patients directly. Instead, they looked at six earlier studies, and combined all their data. This has the advantage that they had much more data to work on than previous researches did, which means that their results are much more credible than those of previous researchers. However, it has the disadvantage that some inconsistencies could have crept in between different studies.

Another difference is that previous studies only looked at cancers which developed during the period of the study. This meta-analysis did this as well, but then went on to build a mathematical model of how many more cancers might develop in later years. This does allow more information to be gained from the data, but on the other hand, the model might not accurately reflect what actually happens.

Overall, these six studies covered 210 individuals. This meta-analysis concludes that:

- The chance of a PJS sufferer getting cancer between ages 15 and 64 is 93%
- The relative risk is 15.2, so PJS sufferers have a 15.2 times higher chance of getting cancer than "normal" people, with a 95% confidence interval of 12.0 to 19.0
- The relative risk is 15.5 for males and 14.8 for females
- The mean (average) age at first diagnosis of cancer was 42.9 years.

- **Lim et al, 2003, *Further observations on LKB1/STK11 status and cancer risk in Peutz-Jeghers syndrome.***

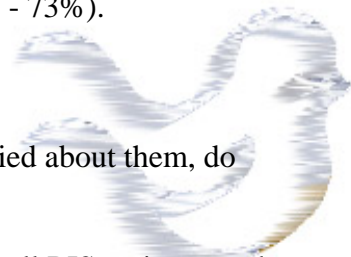
This is an investigation of cancer risks in PJS sufferers, and of whether these sufferers have a known mutation in the LKB1 / STK11 gene. It looked at 33 index patients (ie with no more than one patient from each family). Of these cases, 13 were familial and 20 were sporadic. Of the 33 cases, 17 had identified LKB1 / STK11 mutations.

The study also looked at a wider range of patients, including other family members. This gave a total of 70 people, who were studied for 2,120 patient years, or just over 30 years each. As with Giardiello's meta-analysis, this study also appears to have developed a mathematical model to predict the risk of cancer developing by age 65. They found that this risk was 37% across all patients in the study (95% CI: 21% - 61%). For patients with an LKB1 / STK11 mutation, the risk was 47% (95% CI: 27% - 73%).

Comment

Now, these are some scary numbers. Before you get too worried about them, do remember these points:

- They are all based on a sample of PJS patients, not on all PJS patients, and so there will be some sampling error;
- Some of them are based on a mathematical model, and this might not accurately reflect what actually happens;



- Some of the numbers are for familial PJS, and some are for risks in people with an identified LKB1 / STK11 mutation, and not everyone falls into these groups; and
- Not all current PJS doctors and researchers agree that the cancer risk is as high as some of these papers put it.

However, it is clear that there is a cancer risk - my own GI surgeon has said that his rule of thumb is that roughly half of PJS patients will get cancer, and that roughly half of the cases will be in the GI tract. If you've got any questions on this report, do ask me. But, if you need more information on the cancer risks and how they apply to you, you should talk to your own doctor.

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