



# Patient Report

## **Frequency of Peutz-Jeghers Syndrome**

A Literature Review by  
Andrew Wells

## **Abstract**

I have been doing some research into the frequency (or incidence rate, or prevalence rate) of Peutz-Jeghers Syndrome. I have done this by examining the literature, by contacting the authors of the papers involved, and by contacting other doctors and polyposis registries. A very wide range of estimates, from 1 in 8,300 to 1 in 300,000, is available in the literature. I conclude that, although it is clearly very difficult to set a true figure for the incidence, it may be around 1 in 300,000.

## **Introduction**

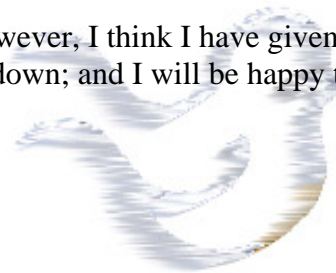
I have been doing some research into the frequency (or incidence rate, or prevalence rate) of Peutz-Jeghers Syndrome. This is the second version of this paper. The first version was originally posted to the PJS online support group (<http://listserv.acor.org/archives/pjs.html>) on 2 September 2003; this second version was originally posted there on 31 December 2003.

First, I'll describe what I've done. I started with a few papers on the cancer risk in PJS sufferers, together with a few more general papers. Where any of those papers gave an incidence rate for PJS (either as "1 in so-many-thousand", or as "X thousand sufferers in this country"; and either as a single figure or as a range); I looked to see where they had got it from. If they gave a source for their figure, I got hold of that source; then got hold of the source that their source used; and so on until I got back to the original appearance in the medical literature (as far as I could tell) of each figure. (The only exceptions to this process have been where the paper was written more than twenty years ago.)

I then emailed the author (or all the authors if there were two or three, or the lead author if there were several) of each paper where an incidence rate made its original appearance, and asked them if they could tell me how it was derived. Many of them have done so, and I would like to express my appreciation to them.

I have also noted which figures are used where. As we shall see, a wide variety of estimates is available for use, and it is interesting to see which figures are actually used by authors.

I have not described the papers with full academic rigour. However, I think I have given enough details for interested readers to be able to track them down; and I will be happy to give full citations to anyone who is interested.



## Papers

This section lists, in alphabetical order of first author's surname, the papers I have used. (In passing, I note that all discrepancies in the names of the authors, and even in the name of the disease, occur in the original papers!)

The *Gene Reviews / Gene Tests* website, in its section on PJS, by Amos, Frazier and McGarrity, last revised in November 2003, says, "Estimates of birth prevalence range widely from 1:25,000 to 1:280,000, but these have not been reliably established. PJS can occur in any racial or ethnic group." (Amos, Frazier and McGarrity have very significantly widened the range of estimates compared to the previous, 2002, version. The paper now reflects much more fully the range of estimates available in the literature.)

Bartholomew et al, in their 1962 paper, "Intestinal polyposis associated with mucocutaneous pigmentation," say that, "174 cases have been reported in the literature." Their paper goes on to describe 8 further cases. They also say how many cases have been reported from each country in the previous three years; the highest number in that period was 15, from France. Later in this paper, they say, "The actual mutation rate is, of course, presently unknown, but considering data from other well studied hereditary diseases, it may be in the range of 1 per 200,000 births."

Boardman et al, in their 1998 paper, *Increased risk for cancer in patients with the Peutz-Jeghers Syndrome*, use Finan & Ray's figures, in saying, "This syndrome occurs in approximately 1 in 8,300 to 1 in 29,000 live births."

However, Boardman, in her 2002 paper, *Heritable colorectal cancer syndromes: recognition and preventive management*, uses Burt's figure in saying, "PJS has an incidence of approximately 1 in 200,000 live births."

Boudeau, Sapkota and Alessi, in their 2003 paper, *LKB1, a protein kinase regulating cell proliferation and polarity*, say quite a lot about this:

- "The reported estimates of the incidence frequency of PJS vary widely."
- "One report estimated the frequency to be 1 in 8,300 live births," - this is the upper end of Mallory and Stough's range
- "while another study put the estimate at 1:120,000." - this is Hemminki's figure
- "In the UK, there are estimated to be around 2,000 people with PJS, indicating the incidence frequency is 1 in 30,000." [they refer to the Association of International Cancer Research for this; this figure may have been derived by applying Mallory & Stough's lower estimate of 1 in 29,000 to the UK population of around 58 million people.]

Burt, in his 2002 paper, *Polyposis Syndromes*, says, "It is estimated to occur in 1 in 200,000 live births." This is taken from Hampel and Pentomaki's 2000 paper, which in turn is taken from Bartholomew's 1962 paper.

The *eMedicine* website, in its section on PJS, by Carethers, last revised in 2003, says, "This [one-tenth the frequency of FAP] would place the frequency from 1 case per 60,000 people to 1 case per 300,000 people."

Dunlop, in his 2002 paper, *Guidance on gastrointestinal surveillance for hereditary non-polyposis colorectal cancer, familial adenomatous polyposis, juvenile polyposis, and Peutz-Jeghers syndrome*, refers to Utsonomiya's paper, and says, "The population prevalence of PJS is probably around 1:50,000."

Eng, Hampel and de la Chapelle, in their 2000 paper, *Genetic testing for Cancer Predisposition*, give an incidence rate of 1 in 200,000.

Finan and Ray, in their 1989 paper, *Gastrointestinal Polyposis Syndromes*, use Mallory & Stough's figure, and say, "The incidence of Peutz-Jeghers Syndrome is approximately 1 in 8,300 to 29,000 births." However, earlier in the same paper, Finan & Ray say, "The incidence of FAP is approximately 1 in 8,300 to 16,000 births." It appears to be generally accepted by other authors that PJS is approximately one-twentieth to one-tenth as common as FAP. If so, and if these FAP figures are correct, that would give PJS figures of 1 in 83,000 to 1 in 320,000. These figures are much more in line with those given elsewhere.

Hampel and Pentomaki, in their 2000 paper, *Hereditary colorectal cancer: risk assessment and management*, use Bartholomew et al's figure, and say, "PJS is a rare condition with an incidence of about 1 in 200,000 live births."

Hemminki, in his 1999 paper, *The molecular basis and clinical aspects of Peutz-Jeghers syndrome*, also uses Mallory & Stough's figure, and says, "An estimate has placed the frequency between 1:8,300 and 1:29,000 births." However, he also uses a previously unpublished figure from Jarvinen, and says, "In Finland it has been estimated to be between 1:50,000 and 1:100,000."

Jishage et al, in their 2002 paper, *Role of LKB1, the causative gene of Peutz-Jegher's syndrome, in embryogenesis and polyposis*, use Linder & Greene's figure, and say, "The incidence of PJS is estimated to be 1 in 120,000 births."

Greene and Lindor, in their 1998 paper, *The concise handbook of family cancer syndromes*, give an incidence rate of 1 in 120,000 births. They do not give any source for of this figure.

Lim et al, in their 2003 paper, *Further observations on LKB1 / STK11 status and cancer risk in Peutz-Jeghers syndrome*, say that 33 index patients were studied.

Loukola, in her 2000 paper, *Molecular diagnosis of hereditary nonpolyposis colorectal cancer (HNPCC)*, uses Spiegelman & Phillips' finding that, "the prevalence of PJS is estimated to be in the order of one twentieth that of FAP."

McGarrity et al, in their 2000 paper, *Peutz-Jeghers syndrome*, use Linder & Greene's figure, and say, "The incidence has been estimated as one in 120,000 births."

Mallory & Stough, in their 1987 paper, *Genodermatoses with malignant potential*, say, "The risk of occurrence is approximately 1 in 8,300 to 1 in 29,000 live births." They do not quote any source for this. Despite later comments that these figures were taken from the literature, I have not found any earlier occurrence of them. (However, they do also say, "The incidence of Gardner's syndrome is approximately 1 in 8,300 to 1 in 16,000 births," and give a source for this; I am trying to acquire a copy of this source, in case it casts any light on the matter.)

Spigelman, Murday and Phillips, in their 1989 paper, *Cancer and the Peutz-Jeghers syndrome*, say that the St. Mark's Polyposis Registry has 72 patients registered with the Peutz-Jeghers syndrome.

Spiegelman and Phillips, in their 1994 chapter on, *Peutz-Jeghers syndrome*, say, "The prevalence of Peutz-Jeghers syndrome is probably of the order of one twentieth that of FAP."

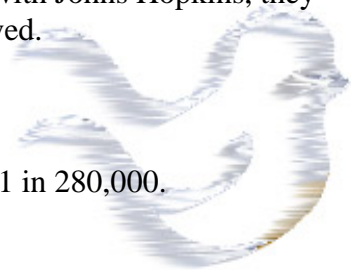
Utsunomiya, Gocho, Miyanga, Hamaguchi, Kashmiure, Aoki and Komatse, in their 1975 paper, *Peutz-Jeghers syndrome: its natural course and management*, say that, "Two hundred and twenty-two patients with Peutz-Jeghers syndrome were ascertained in Japan between 1961 and 1974." However, and contrary to Dunlop, I can find no mention of an incidence rate in this paper.

Ylikorkala, in her 2001 paper, *The LKB1 tumor suppressor*, uses Finan & Ray's and Mallory & Stough's figures, and says, "The incidence of PJS has been estimated to be between 1:8,300 and 1:29,000 live births." She also refers to Spiegelman's and Hemminki's papers, and says, "Some commentators have estimated it to be less common."

*The Johns Hopkins guide for patients and families: Peutz-Jeghers syndrome*, copyright 2001, says, "About 1 in 160,000 to 1 in 280,000 persons will develop PJS." It does not give a source for this figure; although I have been in contact with Johns Hopkins, they have not yet been able to tell me how these figures were derived.

## Different Incidence Rates

- Amos, Frazier & McGarrity, 2002: 1 in 25,000 to 1 in 280,000.
- Bartholomew et al, 1962: 1 in 200,000.
- Carethers, 2003: 1 in 60,000 to 1 in 300,000.
- Dunlop, 2002 (possibly from Utsunomiya, 1975): 1 in 50,000.
- Greene and Lindor, 1998: 1 in 120,000.
- Johns Hopkins, 2001: 1 in 160,000 to 1 in 280,000.
- Mallory & Stough: 1987: 1 in 8,300 to 1 in 29,000.



## Some Comments

Everyone who responded to my requests for further information has said that it is difficult to set a precise figure on the incidence rate for a condition like PJS. This is for several, interlinked, reasons:

- The condition has variable expressibility (meaning that it shows itself in different ways in different people)
- Some sufferers are not diagnosed as having PJS (for example, I was not diagnosed until I was 36 years old)
- There is also a problem of definition of PJS (for example, does someone with hamartomatous polyps, but no lip pigmentation, family history, or discernible LKB1 / STK11 mutation, have PJS?)
- Some sufferers are not reported as such, even when diagnosed correctly the problem of misdiagnosis may be particularly great in under-developed countries
- The problem of under-reporting may be particularly great in countries without efficient centralised registries
- One of the common ways of deriving an incidence rate is by comparison with a more common disease, like FAP, and this method has its own hazards.

The most-quoted figure is 1 in 8,300. As I explain below, I strongly believe that this figure is incorrect. On its first appearance in the literature (as far as I can tell), it was presented with no real justification. Moreover, this is the upper bound given by the original authors; and it is far outside the range of the other figures noted above. I am surprised and disappointed that this dubious figure is used so often; I think it should be recognised as false, and not used in future.

The second most often quoted figures are 1 in 120,000 and 1 in 200,000. These do at least have the virtue of being more in line with the majority. However, the first occurrence of "1 in 200,000" is from the oldest paper considered here; it was presented 41 years ago!; and the author of that paper (Bartholomew) is quite open in presenting no real backing for it. All later uses of this figure refer, directly or indirectly, to that first occurrence.

It does need to be borne in mind that some of these papers give an estimate of "1 in X,000 of the population," while others say, "1 in Y,000 births," and still others say, "1 in Z,000 live births". This does not make the task of comparing these estimate any easier!

## Further Evidence

There were, a few years ago, 73 PJS patients on the polyposis registry at St Marks. I understand that this covers most (but not all) of the UK, and includes some patients from overseas. If we exclude the overseas cases, and suppose that the registry covers two-thirds of the UK, then that means there are about 100 patients recorded in the UK. If even as many as 50% of cases go unreported, that means there are about 200 sufferers in the UK, or 1 in 300,000 of the population. This would mean that an average hospital would only have one case in its area, and that most GPs would not have a case on their books.

In a recent discussion with my consultant surgeon at my local hospital, she confirmed that I am the only patient with PJS that she knows of; and that hospital has a catchment area of around 300,000 people. She also said that it is the sort of condition that most doctors only see once.

I have had some contact with registries in other parts of the world. The evidence is not conclusive. Some states (with efficient, centralised registries), appear to have only around 1 in 600,000 of the population being affected. Other such countries have a higher incidence rate, have around 1 in 150,000 of the population affected. Unfortunately, most of the larger countries, even in the first world, do not have registries like this.

### **Conclusion**

I believe that the higher estimates, particularly the oft-quoted 1 in 8,300 figure, are too high, when compared with the incidence rates for FAP. Also, if there really were that many sufferers, most GPs would have seen a case, and most surgeons would have seen several. I know from my own case that this just isn't so.

Therefore, my own conclusion is that the incidence rate is probably in the region of 1 in 300,000.

We also have to conclude that the published literature contains no authenticated figures for the incidence rate of PJS. I think that someone could do worse than do a detailed examination of the registries (where these exist), and by comparing these to the populations of the areas served by those registries, produce a first estimate (which would also be close to a lower bound) for the incidence rate. They could then, by drawing on their own experience and that of their colleagues, make estimates of the degree of under-reporting etc, and produce a second estimate and an upper bound.

I also think that this does matter. If the incidence rate is 1 in 300,000, then there are about 200 sufferers in the UK. Many hospitals would only have one local patient, and the current spread of knowledge and expertise might be almost enough. Studies that look at a few tens of patients are covering a large proportion of the sufferers in the region the researcher works in.

However, if the incidence rate is 1 in 8,300, there are about 7,000 sufferers in the UK. Most hospitals would have several local patients, and there are several hundred people in reach of each of the big cities (and a few thousand in reach of St Marks). In this case, there should be a dramatic increase in the level of resources available to tackle the problem. And studies that only look at a few tens of patients are covering only a few percent of the sufferers in the region.

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