*Gut*, 1989, **30**, 1588–1590

# Cancer and the Peutz-Jeghers syndrome

A D SPIGELMAN, V MURDAY, AND R K S PHILLIPS

*From St Mark's Hospital, London and the Professorial Surgical Unit, St Bartholomew's Hospital, London*

SUMMARY **Among 72 patients with the Peutz-Jeghers syndrome malignant tumours have developed in 16 (22%) of whom all but one have died. There were nine gastrointestinal and seven non-gastrointestinal tumours. The relative risks of death from gastrointestinal cancer and all cancers were 13 (95% CI 2·7–38·1) and 9 (95% CI 4·2–17·3) respectively. The chance of dying of cancer by the age of 57 was 48%. There is evidence for a hamartoma/carcinoma sequence in the Peutz-Jeghers syndrome, suggesting that the gene locus involved is relevant to the development of malignancy in general.**

The Peutz-Jeghers syndrome is an autosomal dominant condition characterised by mucocutaneous pigmentation and gastrointestinal hamartomas.[1,2] Hamartomas are not generally regarded to be premalignant, but in the Peutz-Jeghers syndrome a number of authors have found an excessive rate of gastrointestinal malignancy.[3–9] Some of this excess may have been caused by overdiagnosis of malignancy in Peutz-Jeghers polyps. This can arise when epithelial displacement beneath the muscularis propria, which is quite commonly seen in the Peutz-Jeghers syndrome, is reported as malignant invasion.[10] In 1987, Giardiello *et al* reported 31 patients with the Peutz-Jeghers syndrome in the United States.[7] They confirmed an excessive risk of gastrointestinal malignancy. In addition, they found an excess of malignancies at a number of other sites. Others have reported associations with bilateral breast cancer,[6] ovarian sex cord tumours (with and without precocious puberty),[11,12] adenoma malignum – which is a rare form of cervical cancer,[12] and feminising Sertoli cell testicular tumours in prepubertal boys.[13,14]

In the gastrointestinal tract malignancy could arise as a consequence of a hamartoma/dysplasia/carcinoma sequence, or may arise in adjacent tissue.

We studied Peutz-Jeghers patients registered with the St Mark's Polyposis Registry to assess the incidence, site and outcome of neoplasia, with a view to establishing guidelines for their follow up.

Address for correspondence: Mr R K S Phillips, FRCS, St Mark's Hospital, City Road, London EC1V 2PS.

Accepted for publication 14 March 1989.

## Methods

### PATIENTS

The St Mark's Polyposis Registry has 72 patients (39 women) registered with the Peutz-Jeghers syndrome of whom 17 are under regular review at St Mark's Hospital. Registration involved review of the clinical information and of the pathology in all cases. Of the patients registered, we have identified six, three of whom have been previously reported,[15,16] because they had developed cancer. We have excluded these six patients from the longterm risk analysis in order to minimise selection bias in our estimate of the cancer risk in this syndrome. Questionnaires were sent to the remaining patients who were not under follow up at this hospital or were administered in outpatients to those that were. Patients were asked to provide details of serious illness or tumours occurring in themselves or in relatives. The relative risk of developing cancer and cumulative survival were calculated using the life table method.[17,18] Relative risk was defined as the ratio of the observed risk in the study group compared with that expected from their age and sex matched equivalents in the overall population of England and Wales.[19] All registered patients participated in the study.

## Results

Malignant tumours have developed in 16 patients (22%, nine women). Of these cancers, 10 were gastrointestinal (one patient had two cancers) and seven developed outside the gastrointestinal tract

Table 1 *Malignant tumours encountered*

| *Gastrointestinal* | | *Non-gastrointestinal* | |
|---|---|---|---|
| Stomach | 3 (f30 m31*, 38) | Unknown primary | 2 (f42 m56) |
| Duodenum | 1 (f57*) | Ovary | 1 (f53) |
| Duodeno-jejunal | | Fallopian tube | 1 (f40) |
| Flexure | 2 (f28*, m38*) | Thyroid | 1 (f30) |
| Jejunum | 1 (f26‡) | Lung | 1 (m33) |
| Colon | 2 (f26‡, m40) | Basal cell carcinoma | |
| Pancreas | 1 (m34) | (Face) | 1 (f39) |

*Carcinoma in hamartoma; ‡Same patient

Table 2 *Relative risks for cancer death*

| | | *Gastrointestinal cancer* | *All cancer* |
|---|---|---|---|
| Years at risk | | 1992 | 1992 |
| Unexpected deaths | E | 0·23 | 0·99 |
| Observed deaths* | O | 3 | 9 |
| Ratio | O/E | 13 | 9 |

*Excludes six patients from Table 1 (see text)

(Table 1). The presence of carcinoma within a hamartoma was reported in four of the eight patients where the cancer arose within the intestinal lumen, and may have been present in a fifth patient. With the exception of one woman patient who developed a basal cell carcinoma on the face at the age of 39, all tumours were lethal, these patients dying at an average age of 38 years. Calculating years at risk using the life table method for 66 patients, the relative risk of death from gastrointestinal cancer was 13 (95% CI 2·7–38·1) and the relative risk of dying from any malignancy was nine (95% CI 4·2–17·3) (Table 2). The chance of dying of cancer by the age of 57 was 48%, and the chance of dying of any cause was 57% (Figure).

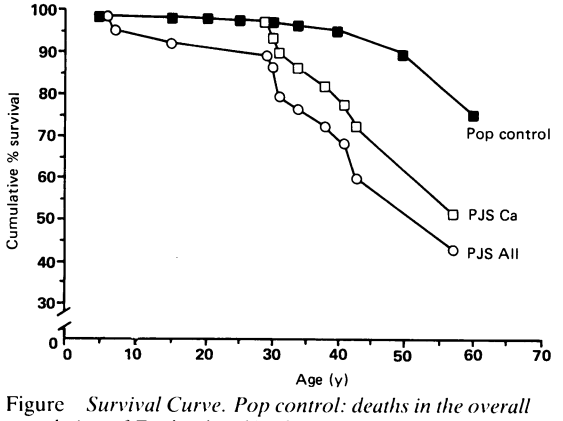


Figure *Survival Curve. Pop control: deaths in the overall population of England and Wales (OPCS); PJS Ca: Cancer specific death in the Peutz-Jeghers syndrome; PJS All: All deaths in the Peutz-Jeghers syndrome.*

## Discussion

There is a significantly increased risk that patients with Peutz-Jeghers syndrome will die of cancer at a young age. Rare cancers occur more commonly in Peutz-Jeghers patients. In addition, common cancers such as lung, breast, and colon, appear at a younger age than expected in the general population. Review of the literature suggests that bilateral breast cancer,[6] gynaecological malignancies[11,12] and testicular cancer in prepubertal boys[13,14] are particularly common. What can be done to prevent death from extra-intestinal cancers in these patients?

In the United Kingdom, screening mammography is available to women over 50 years old. Women at high risk because of genetic factors should have this service made available annually from the age of 40, with a base line mammogram at the age of 25 years. Clinical review should then be yearly. Women with the Peutz-Jeghers syndrome should perhaps be included in this group, and in addition have annual pelvic ultrasound and cervical smears.

Both male and female patients should be encouraged to carry out self examination, and doctors should regard abnormal findings with a high index of suspicion.

The management of the risk of gastrointestinal malignancy ties in closely with the management of polyps in general. A Peutz-Jeghers polyp seen through the intestinal wall at laparotomy shows serosal puckering, probably as a result of the already mentioned epithelial displacement that sometimes leads to confusion over malignancy.[10] These polyps are broadly based and deeply adherent, which makes endoscopic removal difficult, particularly when the polyps are large. It is important when operating on patients with the Peutz-Jeghers syndrome to completely clear the intestine of polyps. This can be achieved by panintestinal endoscopy with the colonoscope passed both from the mouth and from the anus while the abdomen is open. Small polyps can be snared, while larger ones will need an enterotomy for their removal. Thereafter, a policy of two yearly upper gastrointestinal endoscopy and colonoscopy should allow removal of polyps before their size mitigates against this. Polyps outside the reach of endoscopes pose a particular problem. Certainly a small bowel enema will show large ones. We believe that the risk of malignancy should dictate a more aggressive management than heretofore and advocate two yearly small bowel follow through examinations, as proposed by Williams *et al* in 1982.[20] Patients with polyps greater than 1·5 cm diameter, or with smaller polyps but abdominal pain as well, should be advised to undergo laparotomy in the way described above. We hope that thorough attention to the removal of all

small polyps at the time of laparotomy will mean that operations do not have to be undertaken too frequently, although this remains to be seen.

The gene in Peutz-Jeghers syndrome appears to control growth and differentiation in the gastrointestinal tract, as shown by the development of hamartomas. In addition, there is clearly some evidence for a hamartoma/carcinoma sequence, and this has already been suggested for patients with juvenile polyposis.[21,22] The gene is also expressed in other tissues, as shown by the abnormal freckling. The generally increased risk of cancer at a number of other sites suggests that the gene locus involved may be of importance to cancer development in general.

We are grateful to the St Mark's Polyposis Registry, and in particular to Dr H J R Bussey for his meticulous record keeping over the years. Mr Spigelman is supported by the St Mark's Research Foundation, and Dr V Murday, Senior Registrar, Genetics, Royal Free Hospital Medical School, by the Imperial Cancer Research Fund.

## References

1 Peutz JLA. On a very remarkable case of familial polyposis of the mucous membrane of the intestinal tract and nasopharynx accompanied by peculiar pigmentations of the skin and mucous membrane. *Ned Tijdschr Geneeskd* 1921; **10:** 134–46.

2 Jeghers H, McCusick VA, Katz KH. Generalized intestinal polyposis and melanin spots of the oral mucosa, lips and digits: a syndrome of diagnostic significance. *N Engl J Med* 1949; **241:** 1031–6.

3 Utsunomiya J, Gocho H, Miyanaga T, *et al*. Peutz-Jeghers Syndrome: its natural course and management. *Johns Hopkins Med J* 1975; **136:** 71–82.

4 Reid JD. Intestinal carcinoma in the Peutz-Jeghers Syndrome. *JAMA* 1974; **229:** 833–4.

5 Bussey HJR, Veale AMO, Morson BC. Genetics of gastrointestinal polyposis. *Gastroenterology* 1978; **74:** 1325–30.

6 Trau H, Schewach-Millet M, Fisher BK, Tsur H. Peutz-Jeghers Syndrome and bilateral breast carcinoma. *Cancer* 1982; **50:** 788–92.

7 Giardiello FM, Welsh SB, Hamilton SR, *et al*. Increased risk of cancer in Peutz-Jeghers Syndrome. *N Engl J Med* 1987; **316:** 1511–4.

8 Foley TR, McGarrity TJ. Peutz-Jeghers Syndrome: a 38 year follow up of the "Harrisburg Family" [Abstract]. *Gastroenterology* 1988; **94:** A131.

9 Perzin KH, Bridge MF. Adenomatous and carcinomatous changes in hamartomatous polyps of the small intestine (Peutz-Jeghers Syndrome): report of a case and review of the literature. *Cancer* 1982; **49:** 971–83.

10 Shepherd NA, Bussey HJR, Jass JR. Epithelial misplacement in Peutz-Jeghers polyps: a diagnostic pitfall. *Am J Surg Pathol* 1987; **11:** 743–9.

11 Young RH, Dickersin GR, Scully RE. A distinctive ovarian sex cord-stromal tumor causing sexual precocity in the Peutz-Jeghers Syndrome. *Am J Surg Pathol* 1983; **7:** 233–43.

12 Young RH, Welch WR, Dickersin GR, Scully RE. Ovarian sex cord tumor with annular tubules. Review of 74 cases including 27 with Peutz-Jeghers Syndrome and 4 with adenoma malignum of the cervix. *Cancer* 1982; **50:** 1384–402.

13 Cantu JM, Rivera H, Ocampo-Campos R, *et al*. Peutz-Jeghers Syndrome with feminizing Sertoli cell tumor. *Cancer* 1980; **46:** 223–8.

14 Dubois RS, Hoffman WH, Krishnan T, *et al*. Feminizing sex cord tumor with annular tubules in a boy with Peutz-Jeghers Syndrome. *J Pediatr* 1982; **101:** 568–71.

15 Cochet B, Carrel J, Desbaillets L, Widgren S. Peutz-Jeghers Syndrome associated with gastrointestinal carcinoma. Report of two cases in a family. *Gut* 1979; **20:** 169–75.

16 Tweedie JH, McCann BG. Peutz-Jeghers Syndrome and metastasising colonic adenocarcinoma. *Gut* 1984; **25:** 1118–23.

17 Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. *J Chron Dis* 1958; **8:** 699–712.

18 Pocock SJ, Gore SM, Kerr GR. Long term survival analysis: the curability of breast cancer. *Stat Med* 1982; **1:** 93–104.

19 Her Majesty's Stationery Office. Mortality statistics England and Wales. Office of Population Censuses and Surveys. Series DH1+2 1985.

20 Williams CB, Goldblatt M, Delaney PV. "Top and Tail Endoscopy" and follow up in Peutz-Jeghers Syndrome. *Endoscopy* 1982; **14:** 82–4.

21 Jass JR, Williams CB, Morson BC, Bussey HJR. Juvenile polyposis – a precancerous condition [Abstract]. *Gut* 1987; **28:** A1367.

22 Sarles J-C, Consentino B, Leandri R, Dor AM, Navarro PH. Mixed familial polyposis syndromes. *Int J Color Dis* 1987; **2:** 96–9.