CME

REVIEW

High Cancer Risk in Peutz–Jeghers Syndrome: A Systematic Review and Surveillance Recommendations

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OBJECTIVES: **Peutz–Jeghers syndrome (PJS) is an autosomal dominant inherited disorder associated with increased cancer risk. Surveillance and patient management are, however, hampered by a wide range in cancer risk estimates. We therefore performed a systematic review to assess cancer risks in PJS patients and used these data to develop a surveillance recommendation.**

METHODS: **A systematic PubMed search was performed up to February 2009, and all original articles dealing with PJS patients with confirmed cancer diagnoses were included. Data involving cancer frequencies, mean ages at cancer diagnosis, relative risks (RRs), and cumulative risks were collected.**

RESULTS: **Twenty-one original articles, 20 cohort studies, and one meta-analysis fulfilled the inclusion criteria. The cohort studies showed some overlap in the patient population and included a total of 1,644 patients; 349 of them developed 384 malignancies at an average age of 42 years. The most common malignancy was colorectal cancer, followed by breast, small bowel, gastric, and pancreatic cancers. The reported lifetime risk for any cancer varied between 37 and 93%, with RRs ranging from 9.9 to 18 in comparison with the general population. Age-related cumulative risks were given for any cancer and gastrointestinal, gynecological, colorectal, pancreatic, and lung cancers.**

CONCLUSIONS: **PJS patients are markedly at risk for several malignancies, in particular gastrointestinal cancers and breast cancer. On the basis of these elevated risks, a surveillance recommendation is developed to detect malignancies in an early phase and to remove polyps that may be premalignant and may cause complications, so as to improve the outcome.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Peutz–Jeghers Syndrome (PJS) is a rare autosomal dominant inherited disorder, characterized by gastrointestinal hamartomas and mucocutaneous pigmentations. The incidence has been estimated between 1:8,300 and 1:200,000 births (1–4). Jan Peutz, a Dutch physician, was the first to recognize the combination of intestinal polyposis, mucocutaneous pigmentation, and heredity in 1921 (5). Thereafter, Jeghers published a description of the syndrome in 1949 (6), leading to the eponym "Peutz–Jeghers syndrome" (7).

In 1998, investigators discovered that germline mutations in the serine threonine kinase 11 gene (*STK11*, also known as *LKB1* gene) cause PJS (8,9). *STK11* is a serine threonine kinase localized on chromosome19p13.3 and is designated as a tumor suppressor gene (10). Genetic testing for clinical practice is widely available, and with the currently available techniques, an *STK11* germ-line mutation can be found in ~80% of clinically affected PJS families (11). Nevertheless, a second gene locus might still exist (12,13).

Although the mechanism of carcinogenesis remains debatable, PJS patients carry a considerably increased risk for the development of both gastrointestinal and extra-gastrointestinal malignancies, as summarized in a previous meta-analysis (14). Several surveillance recommendations have been published (2,4,15–22). However, the clinical management of patients is still hampered by the wide range in reported cancer risk estimates, and in our

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clinical practice, cancer risks seem lower than reported in the meta-analysis (14). Recently, international collaborations have led to publications on larger cohorts of PJS patients with a focus on their increased cancer risks (23,24). We therefore reviewed literature to assess the risk and onset of malignancies in PJS patients. On the basis of this risk profile, we developed a Dutch surveillance recommendation in collaboration with a national working group.

METHODS

We performed a systematic search on PubMed until February 2009 to identify all English and Dutch literature under the MESH headings and text words of "Peutz–Jeghers syndrome or Peutz" and "neoplasms or neoplasm*or cancer or tumour*or tumor or tumors or carcinom*." One reviewer (M.G.F.vL.) inspected the title and abstract of each electronic citation to identify those manuscripts suitable for this review. The full texts were obtained, and an extensive manual search was conducted using references from all retrieved reports and review articles.

Cohort studies and meta-analyses reporting cancer risks in PJS were considered eligible, and case reports, review articles, and editorials were excluded. Original manuscripts were included regardless of their research question, if cancer risks could be estimated in patients with Peutz–Jeghers syndrome by fulfilling the following inclusion criteria: (i) PJS diagnosis (either on the basis of clinical criteria or an *STK11* mutation), and (ii) confirmation of cancer diagnoses.

The quality of the included articles was assessed by evaluating the diagnosis of PJS (based on either clinical criteria such as family history, hamartomas, small-bowel polyposis, and pigmentations or based on an *STK11* mutation), and the diagnosis of cancer (e.g., by histological confirmation). Two reviewers (M.G.F.vL. and A.W.) abstracted detailed data from the articles that fulfilled our inclusion criteria, and discrepancies were resolved by consensus of the study group. Data extracted included diagnosis of PJS, number of included PJS patients, number of PJS families, sex, age at the end of follow-up, cancer diagnosis, age at cancer diagnosis, outcome measures such as relative cancer risks and cumulative cancer risks, and study design and location of study. We pooled data to calculate cancer frequencies, mean ages at cancer diagnosis, relative risks (RRs), and cumulative risks. We registered those cases in which several publications derived from the same data set. Overlap in patient population was assumed if patients from a single medical center were included in more than one article.

RESULTS

Our search through PubMed identified 1,049 articles. This search in combination with an extensive manual search yielded 21 original articles that met the inclusion criteria (3,14,23–41). These studies, 20 cohort studies, and 1 meta-analysis (14), were published between 1975 and 2007 and are summarized in **Supplementary Table 1** online. This table shows that there was considerable overlap in patient populations, caused by two large collaborative studies (23,24) and the meta-analysis (14). Despite the overlap, we chose to report all studies meeting the inclusion criteria as the smaller cohort studies reported on different outcome measures or contained more detailed data than the large collaborative studies and the meta-analysis.

Table 1. Reported cancers and age at diagnosis in 1,644 Peutz–Jeghers syndrome patients from 20 cohort studies (3, 23–41)

Cancer	No. cancers	Mean age in years
Gastrointestinal	198	42 (n=69)
Colorectum	80	43 (n=23)
Small intestine (including duodenum)	41	37 (n=18)
Stomach	35	40 (n=14)
Esophagus	3	33 (n=1)
Pancreas	32	52 (n=12)
Biliary tract	7	32 (n=1)
Extragastrointestinal		
Breast	59	44 (n=23)
Uterus	10	43 (n=1)
Ovary	16	35 (n=8) (including one Sertoli tumor at age 6)
Cervix	14	36 (n=5)
Testes	3	6 (n=1)
Lung	25	47 (n=8)
Other[a]	44	45 (n=9)
Unknown	15	50 (n=7)
Total	384	42 (n=131)

CRC, colorectal cancer.
[a]Other includes multiple myeloma, leukemia, and thyroid, prostate, liver, gall bladder, kidney, adrenal, nasopharyngeal, bone, and skin cancers.
Hearle *et al.* (23) and Lim *et al.* (28): gastroesophageal cancers classified as gastric cancer. Scott *et al.* (30): bowel cancer classified as CRC. Utsunomiya *et al.* (3): cancer deaths instead of cancer incidence. Spigelman *et al.* (37): ovarian cancers include one adnexal carcinoma.

The definitions for PJS and the methods to confirm the diagnosis of cancer varied between the publications, and *STK11* mutation analysis had been performed in only 10 of the 21 studies. In the 20 cohort studies, a total of 1,644 patients were evaluated, and 349 of them developed 384 malignancies at an average age of 42 years. In **Table 1** the absolute number of diagnosed cancer cases and the average ages at cancer diagnosis are shown (excluding the meta-analysis). The most frequently reported cancers were colorectal cancer (n = 80) and breast cancer (n = 59), followed by small bowel, stomach, and pancreatic cancer.

Between the studies, there was some variation in outcome measures. Relative cancer risks were reported in only four publications (14,32,35,39), summarized in **Table 2**. In these four studies, the RR of any cancer varied between 9.9 and 18. In addition, the RR of any cancer could be calculated from two collaborative studies (23,24), and these RRs at age 60 were 7.3 and 4.8 compared with the general population. RRs of cancer at specific sites were reported in only

Table 2. Relative cancer risks

Site	RR	Reference(s)
Any cancer	9.9–18	(14,32,35,39)
Males	6.2–22	(35,39)
Females	16–18.5	(35,39)
GI cancer	50.5	(35)
Males	30.3	(35)
Females	150.9	(35)
Gynecological cancer and breast cancer (females)	20.3	(35)

GI, gastrointestinal (colorectal, small intestinal, gastric, and esophageal cancers); RR, relative risk.

Table 3. Cumulative cancer risks (approaching lifetime risks)

Site	Age (years)	CR	Reference(s)
Any cancer	60–70	37–93%	(14,23,24,28,29,34)
GI cancer	60–70	38–66%	(23,24,28,34)
Gynecological cancer	60–70	13–18%	(23,28)
Per origin			
Stomach	65	29%	(14)
Small bowel	65	13%	(14)
Colorectum	65	39–39%	(14,23)
Pancreas	65–70	11–36%	(14,23)
Lung	65–70	7–17%	(14,23,28)
Breast	60–70	32–54%	(14,23,28)
Uterus	65	9%	(14)
Ovary	65	21%	(14)
Cervix	65	10%	(14)
Testes	65	9%	(14)

CR, cumulative risk; GI, gastrointestinal (colorectal, small intestinal, gastric, esophageal, and pancreatic cancers).
Westerman *et al.* (34): GI cancer does not include pancreatic cancer.

one study (14). Compared with the general population, the RRs were significantly increased for the following malignancies: small intestinal (RR520), gastric (RR213), pancreatic (RR132), colorectal (RR84), ovarian (RR27), lung (RR17), endometrial (RR16), and breast cancer (RR15). In a previous study, Giardiello *et al.* found a similar RR for pancreatic cancer of 132. They also defined the RRs for any cancer according to age; the relative cancer risk was 5 for PJS patients <40 years and 23 for patients ≥40 years (39). In one study, the RRs of cancer mortality were determined on the basis of 66 PJS patients (37). The RR of death from any cancer was 9 (95% CI 4.2–17.3), and the RR of gastrointestinal cancer death was 13 (95% CI 2.7–38). In another study, standardized mortality ratios were determined on the basis of 70 PJS patients, and by the age of 65 years the standardized mortality ratio for all cancers was 9.9 (95% CI 0.4–20.4) and 24.8 (95% CI 0.7–63.6) for gastrointestinal cancer (29).

Cumulative risks for any cancer were calculated in six studies up to age 60, 65, or 70 (**Table 3**) (14,23,24,28,29,34). The lowest cumulative cancer risk was reported to be 37% (95% CI 21–61) at age 65 (29), although the same authors reported a cumulative risk for any cancer in PJS at the age of 70 years of 81% in a large collaborative study (28). The percentage of 37% was based on 70 clinical PJS patients regardless of their *STK11* mutation status. When only *STK11* mutation carriers were taken into account, the cumulative cancer risk was higher: 47% (95% CI 27–73) at the age of 65 years (29). However, in a larger study, cumulative cancer risks were evaluated in patients with and without an *STK11* mutation, and there was no statistically significant difference between the two groups (23).

Four studies reported age-related cumulative cancer risks (any cancer, gastrointestinal cancer, and gynecological cancer), as shown graphically in **Figure 1** (23,24,28,34). Cumulative risks for breast cancer ranged from 5 to 8% at age 40, increasing to 45% at 70 years (23,24,28). Two studies reported age-related cumulative risks for colorectal cancer (CRC), pancreatic cancer, and lung cancer, graphically shown in **Figure 2** (23,28). One study evaluated differences in cumulative risks between males and females for any cancer, showing that at the age of 70 years males and females carry similar risks for the development of a malignancy (55 and 59%, respectively) (24).

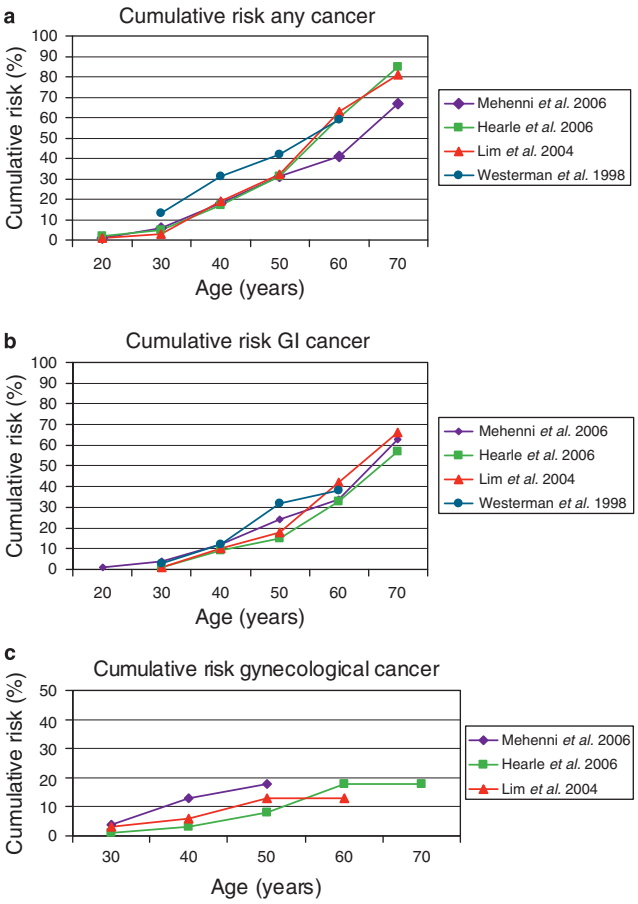

Figure 1. Cumulative cancer risks according to age. (**a**) Cumulative risk of any cancer (23,24,28,34). (**b**) Cumulative risk of gastrointestinal cancers (23,24,28,34). (**c**) Cumulative risk of gynecological cancers (23,24,28).

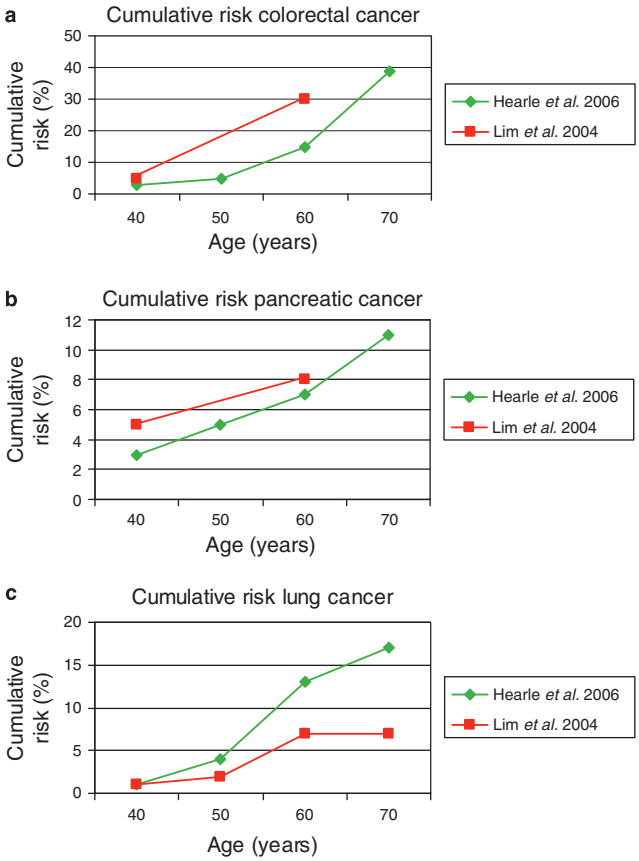

Figure 2. Cumulative cancer risks according to age and origin. (**a**) Cumulative colorectal cancer risks according to age (23,24). (**b**) Cumulative pancreatic cancer risks according to age (23,24). (**c**) Cumulative lung cancer risks according to age (23,24).

DISCUSSION

This systematic review confirms that PJS patients carry a high cancer risk already at a young age (14,25,29), which is consistent with the identification of the *STK11* gene as a tumor suppressor gene (10). Twenty cohort studies reported on 1,644 patients; 349 of them developed 384 malignancies at an average age of 42 years. The overall risk was most markedly increased for colorectal, breast, small bowel, gastric, and pancreatic cancer. There was overlap in patient populations because of two large collaborative studies (23,24). This might have overestimated the cancer risks. However, when we excluded the cohorts already represented in two collaborative studies, we found similar results (757 different patients; 148 of them developed 163 malignancies at an average age of 42 years). As the exclusion of overlapping studies led to loss of interesting data, we chose to report on all studies fulfilling the inclusion criteria.

The relative cancer risks varied between 4.8 and 18 compared with the general population, with lifetime cumulative cancer risks up to 93%. The upper limit of these RRs approached the high relative cancer risk reported in the meta-analysis published in 2000, and the upper limit of cumulative risks (93%) was derived from Giardiello's meta-analysis (14). Although the largest included cohort study showed no statistically significant difference in cumulative cancer risk between patients with and without an *STK11* mutation (23), the cancer risk did seem higher for *STK11* mutation carriers compared with patients without a mutation in another study (29). In the future, it would be interesting to gain more insight into genotype–phenotype correlations and to investigate whether differences in *STK11* mutation types are related to cancer proneness.

There are some limitations to this systematic review that need to be addressed. First of all, the included studies may be hampered by selection bias; only patients with the most severe phenotypes might have been included, thereby overestimating cancer risk. However, the patients described in the cohort studies were selected systematically and were not recruited because of cancer in the proband; only one proband presented with cancer at the first consultation (36). Moreover, referral bias might have led to overestimation of cancer risks. Only patients with a severe phenotypic expression of the disease (including cancers) might have been referred to specialized centers that subsequently report their data. On the other hand, cancer risks may have been underestimated as they partly depend on the duration of follow-up; some studies reported on relatively young patients at the end of follow-up (27) in whom cancer may still develop. Other studies displayed no data on the age of the included patients or the duration of follow-up (3,23,24). Finally, there were some difficulties in pooling data as different definitions and different end points were used. For example, pancreatic cancer was considered as extra-gastrointestinal cancer in one study (34) but as gastrointestinal cancer in other studies (23,28).

Assessment of the cancer risk in PJS is difficult for several other reasons; the true incidence of PJS is not known and some cases with an uncomplicated syndrome (e.g., patients without cancer) remain unpublished (publication bias). Furthermore, pseudo-carcinomatous invasion of epithelial cells into the muscularis propria and serosa may be mistaken for an invasive carcinoma, overestimating cancer incidence (42,43). Pseudo-invasion can be distinguished from invasive carcinoma by the lack of cytological atypia. This phenomenon occurs predominantly in the small bowel as it is caused by torsion and infarction of the polyps during bowel obstruction; pseudo-invasion was observed in ~10% of small-bowel polyps in one study (44).

Nevertheless, cancer risks in PJS patients are very high and come close to other high-risk conditions in which surveillance has been recommended. The upper confidence limit of the breast cancer risk in PJS has, for example, been shown to be as high as the breast cancer risk in patients with *BRCA1* or *BRCA2* mutations (28). The high cancer risks justify surveillance of PJS patients. However, the optimal surveillance strategy remains to be established, and the wide spectrum of PJS-associated cancers as well as other complications caused by polyposis, such as intussusception, have to be taken into account.

On the basis of risks of intussusception (45,46) and other polyp-related complications, such as bleeding or anemia early in life, and on the basis of increased cancer risks later in life described in this review, we proposed a new Dutch surveillance recommendation in collaboration with a national working group (**Table 4**). In this working group, gastroenterologists, internists, clinical geneticists, pediatricians, and gynecologists from the Netherlands are

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Table 4. Dutch surveillance recommendations for Peutz–Jeghers syndrome patients

Examination[a]	Starting age	Interval
History, physical examination (including testicular palpation), and hemoglobin analysis	10 Years	1 Year (pediatrician)
Video capsule endoscopy (VCE) and/or MRI enteroclysis[b]	10 Years	2–3 Years
Gastroduodenoscopy	20 Years	2–5 Years (depending on findings)
Colonoscopy	25–30 Years	2–5 Years (depending on findings)
MRI and endoscopic ultrasonography (EUS) pancreas	30 Years	1 Year, only in a prospective ongoing trial (61)
Breast exam and breast MRI	25 Years	1 Year
Mammography and breast MRI	30 Years	1 Year[c]
Pelvix exam, cervical smear, transvaginal ultrasonography, and CA-125	25–30 Years	1 Year

MRI, magnetic resonance imaging.
[a]Earlier and/or more frequently in symptomatic patients/if clinically indicated.
[b]If VCE shows polyps, it is recommended to perform an MRI enteroclysis to determine the exact localization and size of the polyps. Polyps >1 cm in diameter are an indication for double-balloon enteroscopy (DBE) with polypectomy. In addition, we recommend intra-operative enteroscopy with polyp removal in every indicated laparotomy, to avoid re-laparotomies. If surgery is indicated a laparoscopic approach is preferred when possible.
[c]Mammography and MRI alternately performed every 6 months.

represented. The recommendation was developed on the basis of the literature reviewed here and clinical experience, and solely reflects expert opinion as no controlled trials have been published on the effectiveness of surveillance in PJS. With respect to uncontrolled data, German investigators recently reported that a similar surveillance strategy, as proposed by us, led to the early detection of 50% of all cancers (5/10) diagnosed in 31 PJS patients (47).

New surveillance and treatment techniques such as video capsule endoscopy, magnetic resonance imaging (MRI) enteroclysis, and double-balloon enteroscopy, which have become widely available, are incorporated into this new surveillance recommendation. This is the main difference between the surveillance recommendations proposed here compared with previously published surveillance guidelines (2,4,15–22). It has been shown that video-capsule-endoscopy and/or MRI are good alternatives to small-bowel follow-through for the detection of small-bowel polyps (48,49), and that double-balloon enteroscopy is clinically useful and safe for therapy of small-bowel polyps in PJS patients (50).

Another difference between the recommendations presented here and the guideline published by Giardiello *et al.* in 2006 (22), the latest guideline in print, is that we advocate starting small bowel surveillance at a more regular basis already at a young age (starting at age 10 with 2–3 year intervals, compared with a starting age of 18 years and a baseline examination at age 8). It is generally accepted that surveillance for gastrointestinal cancer is not indicated before the age of 20–25 years (28). However, we recommend starting small intestinal surveillance at a younger age in view of the morbidity caused by the hamartomas (45,46). "Benign" complications of the polyps, such as bleeding and intussusception, predominate in the first three decades of life, whereas malignant complications become more common thereafter (3). By the removal of large polyps, bleeding and intussusception might be prevented. There is no consensus on the management of small-bowel polyps. In general, polypectomy has been recommended for polyps >1–1.5 cm and symptomatic small-bowel polyps (2,22,51,52). Furthermore, we propose colonoscopic surveillance from a later starting age than Giardiello *et al.* (22) (30 years vs. 18 years, respectively) do, as the colorectal cancer risk is low under the age of 30 years (**Figure 2**).

A point of discussion is whether the malignancies in the gastrointestinal tract originate from the hamartomas or from coexisting adenomas or normal mucosa (53,54). The location of the gastrointestinal malignancies in PJS patients did not always correlate with the location of the hamartomatous polyps (54). However, a metastasizing duodenal carcinoma arising in a hamartoma was first reported in 1965 (55), and ever since several studies have reported a hamartoma–adenoma–carcinoma sequence (36,56–58). The latter suggests that endoscopic polyp removal could potentially decrease the risk for malignancies. To answer the question whether or not hamartomas are premalignant, further basal research is required and prospective studies should show whether or not the incidence of gastrointestinal malignancies decreases with endoscopic polypectomy. For now, the mechanism of carcinogenesis remains unknown and the primary aim of cancer surveillance is the early detection of malignancies, thereby improving outcome, and perhaps removal of premalignant polyps decreasing the gastrointestinal cancer risk.

Pancreatic screening seems promising (59–61), but in the Netherlands it is nowadays only performed in light of an ongoing prospective trial (61) as there are still many unanswered questions regarding pancreatic screening. These include whether early detection of (precursor) lesions leads to an improved patient outcome, and also focus on the best way to manage detected lesions. In contrast, the beneficial effect of breast cancer surveillance in high-risk individuals has been established. As breast cancer risk in PJS approaches breast cancer risk in patients with *BRCA1* or *BRCA2* mutations, breast cancer surveillance is similar (62).

In addition to ovarian carcinomas, mucinous neoplasms of the ovary and ovarian sex-cord tumors with annular tubules occur frequently in women with PJS (63,64). The latter may cause sexual precocity and infertility and are generally considered benign, but may become malignant. The gynecological surveillance recommendation is therefore also directed at early detection of these lesions. Although the risk for a testicular tumor was not established in this review, annual testicular palpation is recommended in boys as testicular Sertoli cell tumors occur more frequently in PJS and may cause precocious puberty and gynecomasty (65). Annual physical examination of children and hemoglobin analysis may furthermore reveal anemia, raising the suspicion of gastrointestinal hamartomas.

In conclusion, PJS patients carry a markedly elevated cancer risk concerning mainly gastrointestinal carcinomas and breast cancer. However, cancer risks may be lower than in a previously published

meta-analysis (14). Although the benefits of surveillance remain to be established, surveillance seems justified and therefore we made surveillance and treatment recommendations. The effect of such a surveillance program on cancer incidence, survival as well as cost-effectiveness will have to be established in prospective trials.

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CONFLICT OF INTEREST

Guarantor of the article: M.G.F. van Lier, MD.

Specific author contributions: Data collection (identification of manuscripts suitable for this review, PubMed search and manual search, and data abstraction from the articles), draft writing, and final approval: M.G.F. van Lier, member of the National Peutz–Jeghers Working Group; data collection (data abstraction from the articles), revising article, and final approval: A. Wagner, member of the National Peutz–Jeghers Working Group; revising article and final approval: E.M.H. Mathus-Vliegen, member of the National Peutz–Jeghers Working Group; study design, revising article, and final approval: E.J. Kuipers; data analysis/interpretation, revising article, and final approval: E.W. Steyerberg; study design, revising article, and final approval: M.E. van Leerdam, member of the National Peutz–Jeghers Working Group.

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