Very High Risk of Cancer in Familial Peutz–Jeghers Syndrome

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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 Peutz–Jeghers syndrome (PJS) is an autosomal dominant disease characterized by hamartomatous polyps in the gastrointestinal tract and by mucocutaneous melanin pigmentation.[1,2] Recently, investigators discovered that germline mutations of the STK 11 (serine threonine kinase 11) gene on chromosome 19p cause this disorder.[3,4]

Patients with PJS are known to be at increased risk for common gastrointestinal and nongastrointestinal cancers.[5–12] Other studies have underscored the unusual types of associated tumors, such as ovarian sex-cord tumor with annular tubules and adenoma malignum of the cervix in females.[13] In addition, testicular tumors of sex cord and Sertoli-cell type have been associated with sexual precocity and gynecomastia in boys with this syndrome.[14]

Although risk of cancer in PJS patients is considered increased, patient management has been hampered by variability in risk estimates and inconsistency in cancer screening/surveillance recommendations.[5,7,8,15] Therefore, we conducted a meta-analysis of existing literature to assess risk of cancer in PJS and to better develop screening and surveillance guidelines.

Materials and Methods

Study Identification and Selection

A systematic search on the MEDLINE from January 1966 to December 1998 and the EMBASE database from 1980 to December 1998 was done to identify all literature under the MESH headings and texts words of "Peutz–Jeghers syndrome" and "melanotic pigmentation." In addition, an extensive manual search was conducted by using references from all retrieved reports, review articles, and chapters from textbooks of gastroenterology.

Studies included in the meta-analysis were those with confirmation of the diagnosis of PJS in affected patients, ability to calculate patient age at diagnosis of cancer, and patient follow-up time. We included studies that had a single or series of pedigrees with PJS regardless of the research question under analysis. Review articles, editorials, and letters to the editor were excluded. Also, case reports of patients with PJS and cancer that would introduce an element of publication bias by increasing estimated cancer risks were not included.

Qualitative Assessment

We evaluated the quality of the articles with regard to (1) definition of the diagnosis of PJS, (2) ability to determine follow-up of patients, and (3) confirmation of the diagnosis of the carcinoma. We abstracted descriptive data to determine which reports could be combined from a clinical perspective. After evaluation, the authors (F.M.G., J.D.B., A.C.T., and J.A.O.) discussed the differences and achieved consensus.

Abbreviations used in this paper: CL, confidence limits; ICD-9, International Classification of Diseases, 9th revision; PJS, Peutz–Jeghers syndrome; RR, relative risk.

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Quantitative Assessment

After qualitative assessment, we extracted the data from the literature reports. Numerical discrepancies were resolved by discussion among the authors. Data extracted included patients' sex, ethnicity, presence or absence of cancer, site of cancer, length of follow-up, and age at diagnosis of cancer. Data from each literature report were extracted together by 2 authors and converted into a common format.

Statistical Analysis

A risk assessment using the International Classification of Diseases, 9th revision (ICD-9), was performed for all cancers (ICD-9) 140.0–208.9, esophageal carcinoma (ICD-9) 150.0–.9, stomach carcinoma (ICD-9) 151.0–.9, small intestinal carcinoma (ICD-9) 152.0–.9, colorectal carcinoma (ICD-9) 153.0–.9, pancreatic carcinoma (ICD-9) 157.0–.9, lung carcinoma (ICD-9) 162.0–.9, testicular carcinoma (ICD-9) 186.0–.9, breast carcinoma (ICD-9) 174.0–175.9, uterine carcinoma (ICD-9) 182.0–.9, ovarian carcinoma (ICD-9) 183.0–.9, and cervical carcinoma (ICD-9) 180.0–.9.

Computation of person-years at risk for cancer started January 1, 1920. Patients were considered at risk from birth until the date of diagnosis of cancer, or the closing date of the study as mentioned in the publication. Patients were censored at age 65.

Person-years at risk were calculated for ages 15-64 years according to sex, race, and age-specific categories during subsequent 5-year calendar time periods of observation using a computer program for cohort analysis.[16] Expected cancer cases were calculated by multiplying the number of person-years for each of 5-year age groups and sex by the corresponding race, age, sex, and calendar time–specific incidence rate for the general U.S. population. For the period 1920–1964, the incidence rates from the state of Connecticut were used; for the period 1965–1998, the Surveillance, Epidemiology and End Results (SEER) data[17] for the U.S. population were used. In the risk analysis for all cancer combined, only the first cancer observed was counted for patients who developed more than one cancer. In the analysis for specific types of cancer, second and third cancers were included. The ratio of observed carcinomas over the expected number was computed with a test of significance and 95% confidence limits (CL) assuming a Poisson distribution. This ratio forms the relative risk (RR) and compares cancer risk in the study population with that in the general population. Using the absolute rates for each 5 year age group, the cumulative risk for ages 15–64 years was calculated according to cumulative risk = 1 − exp (−cumulative rate).[18]

Results

Searches of MEDLINE, EMBASE, and referenced articles yielded 94 articles. Of these, 86 were disqualified because they were either review articles or case reports of 1 or 2 patients with PJS and cancer at young age without pedigree information. Eight publications evaluated the long-term follow-up of PJS patients. Of these 2 studies were excluded because the frequency or RR of cancer in PJS patients could not be calculated from data provided.

The characteristics of the 6 studies included in this analysis are listed in Table 1. All investigators used the usual clinical and histopathologic criteria to establish the diagnosis of PJS, and cancer diagnosis was confirmed histopathologically. Also, none of the pedigrees in this analysis were identified or recruited because of malignancy in the proband. However, variation existed in methodology and endpoints between reports. Formal RR calculations for overall cancer and for specific cancers in patients with PJS were done in 3 studies[5,7,9] (Figure 1), the rate of cancer was calculated in 1 study,[8] and no evaluation was made in 2 others.[10,11] While the risk of cancer in PJS patients from multiple families was the main outcome variable in 4 of these investigations,[5,7–9] the other 2 studies[9,10] reported both benign and malig-

Table 1. Reports on the Frequency or Relative Risk of Cancer in PJS

Study	Site	Eligibility[a]	Sample size/no. of pedigrees	Design	Indices measured
Giardiello et al.[5]	MD, USA	1 or (2/3) of 2,3,4	31/13	RCS	RR all CA, 18 RR of pan CA, 100× Freq of CA, 48%
Spigelman et al.[7]	UK	1 and 2	72/12	RCS	Freq of CA, 22% RR of death from CA, 9 (CL, 4.2–17.3) RR of death GI CA, 13 (CL, 2.2–38.1)
Westerman et al.[8]	Holland	1 and 2 or 3	61/21	RCS	Freq of CA, 28%
Boardman et al.[9]	MN, USA	1 or (2/3) of 2,3,4	34/31	RCS	Freq CA, 53% RR all CA, 9.9 (CL, 5.7–16.2) RR GI CA, 50.5 (CL, 18.5–109.9) RR of breast and gyn CA, 20.3 (CL, 7.4–44.2)
Foley et al.[10]	PA, USA	2 or 1 and 3	12/1	RCS	Freq CA, 17%
Burdick et al.[11]	NY, USA	1 and 3	8/1	RCS	Freq CA, 25%

RCS, retrospective cohort study; CA, cancer; pan, pancreatic; Freq, frequency; CL, confidence limits; GI, gastrointestinal.
[a]1, Hamartomatous polyps; 2, labial melanin deposits; 3, family history of PJS; 4, small bowel polyposis.

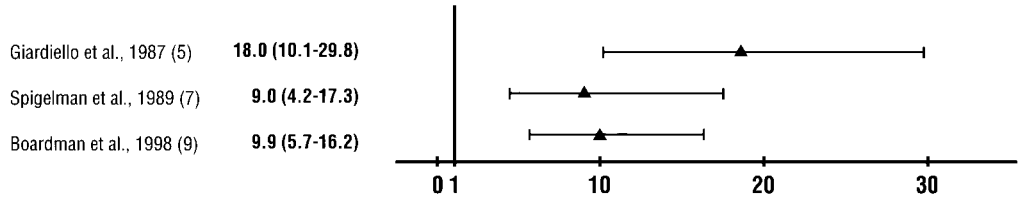

Figure 1. RR and CL of overall cancer in literature reports of patients with PJS.

nant events. Four studies evaluated PJS patients from multiple families,[5,7–9] and 2 studies assessed single pedigrees.[9,10] These single pedigree studies are the only 2 such reports in the literature.[9,10] They were included in the analysis because they provided the longest term follow-up (27 and 49 years, respectively) of the 2 largest pedigrees reported and RR could be calculated from data provided.

The study population consisted of 107 white male and 106 white female patients from 79 families with PJS. Of these, 1 male and 2 females were excluded from analysis because they were younger than 15 years by the closing date of the study. Hence, the analysis included 210 patients with PJS contributing 5059.11 person-years of follow-up. The features of the study population and follow-up times are shown in Table 2. Multiple cancers developed in 3 male and 7 female patients. For testicular cancer risk analysis, 106 males contributed 2552.05 person-years. For breast, cervical, uterine, and ovarian cancer, 104 females contributed 2507.05 person-years.

The RR for all cancers in PJS patients aged 15–64 years was 15.2 (CL, 12.0%, 19.0%), and the absolute rate was 1304.6 per 100,000 person years (1.3%/yr). No difference in RR of all cancers was noted between male (RR, 15.5; 95% CL, 10.5%, 22%) and female (RR, 14.8; CL, 10%, 21%) patients. The mean age (±SD) at first diagnosis of cancer was 42.9 ±10.2 years (Figure 2).

Table 3 shows the risk analysis for cancers in patients with PJS. A high statistically significant RR for all cancers—esophageal, stomach, small intestinal, colon, pancreas, lung, breast, uterine, and ovarian—was observed. No statistically significant RR for testicular or cervical cancer was found.

The absolute rate of cancer in patients with PJS is shown in Table 4. Risk from age 15 to 64 years for developing cancer of any site in PJS patients was 93%. Patients have the highest cumulative risks for breast (54%), colon (39%), pancreatic cancer (36%), stomach (29%), and ovarian (21%) cancer.

Literature case reports of malignant and nonmalignant tumors not included in the meta-analysis in PJS are summarized in Table 5.

Table 2. Characteristics of Patients With PJS

Patients with PJS, n	210
Sex [M/F (% male)]	106/104 (50)
Race, white [n (%)]	210 (100)
Age at diagnosis of cancer (*yr*, mean ± SD)	42.9 ± 10.2
Age at last follow-up (*yr*, mean ± SD)	38.7 ± 8.5

	Distribution of follow-up	
Decade	(n)	Person years
0–14	0	0
15–24	210	2072
25–34	205	1987
35–44	191	742
45–54	37	185
55–65	13	73

Discussion

This meta-analysis agrees with the high increased RR and young age of onset of cancer in patients with PJS previously described.[5,7–9] The magnitude of cancer risk in this study was similar to that recently reported.[9] However, unlike Boardman et al.,[9] this investigation found no significant difference in overall cancer risk between genders. RR was increased for a wide variety of gastrointestinal and nongastrointestinal malignancies in PJS patients over the general population. Of note, this

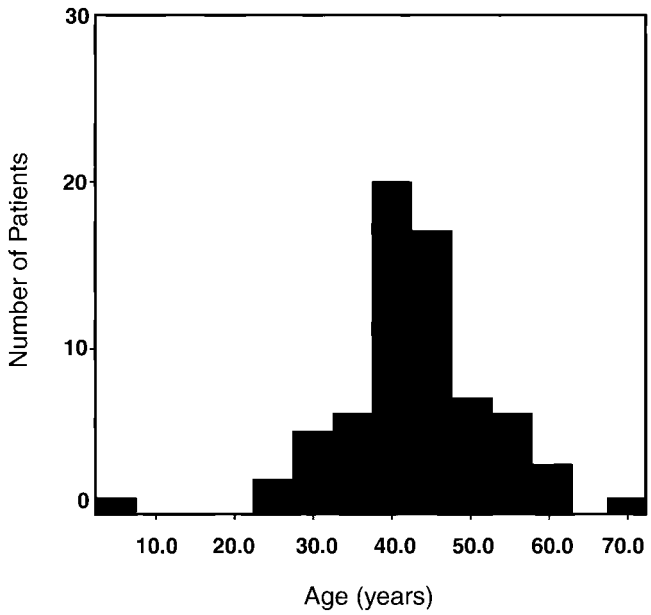

Figure 2. Age of diagnosis of first cancer in patients with PJS.

Table 3. Risk Analysis of Cancers in Patients Aged 15–64 Years With PJS

Site, ICD-9	Observed	RR (O/E)	95% CL	*P* value, 2-sided
All cancers 140.0–208.9	66	15.2	12, 19	<0.001
Esophagus 150.0–.9	1	57	2.5, 557	0.036
Stomach 151.0–.9	10	213	96, 368	<0.001
Small intestine 152.0–.9	6	520	220, 1306	<0.001
Colon 153.0–.9	15	84	47, 137	<0.001
Pancreas 157.0–.9	6	132	44, 261	<0.001
Lung 162.0–.9	5	17	5.4, 39	<0.001
Testes 186.0–.9	1	4.5	0.12, 25	0.396
Breast 174.0–175.9	11	15.2	7.6, 27	<0.001
Uterus 182.0–.9	2	16.0	1.9, 56	0.014
Ovary 183.0–.9	4	27	7.3, 68	<0.001
Cervix 180.0–.9	3	1.5	0.31, 4.4	0.63

O/E, observed/expected.

Table 4. Absolute Rate of Cancer in Patients With PJS From Ages 15 to 64 Years

Site	Rate/100,000 person-years	Cumulative risk from age 15 to 64
All cancers	1304.6	93%
Esophagus	19.8	0.5%
Stomach	197.7	29%
Small intestine	118.6	13%
Colon	296.5	39%
Pancreas	118.6	36%
Lung	98.8	15%
Testes	39.2	9%
Breast	438.8	54%
Uterus	79.8	9%
Ovary	159.6	21%
Cervix	119.7	10%

study confirms the previously reported increased risk of pancreatic cancer, particularly in men and the risk of breast and gynecological tumors noted in women.[9]

We found an overall cumulative risk for cancer of >90% in patients with PJS. Of concern, the absolute risk of breast cancer is similar to the magnitude of risk noted in hereditary forms of that tumor caused by germline mutations of BRCA1 or BRCA2 (genes associated with hereditary breast cancer).

The findings in this investigation are limited by the small number of families analyzed. Also, because we evaluated patients with familial PJS, the data may not be applicable to sporadic cases. This highlights the need for a more extensive cohort study using data from multiple Peutz–Jeghers registries to better estimate cancer risk. Although mutation of STK 11 gene has been identified in most PJS families evaluated, differences may exist between site and type of mutation and cancer risk. The pedigrees in this study were not recruited because of malignancy in the proband, but preferential publication of families with high cancer rates, causing exaggeration of the estimated risk, cannot be eliminated. However, even if this factor elevated the risk, it seems unlikely to fully account for the magnitude of cumulative risk noted; these patients would still merit attention to surveillance and close follow-up even if the risks were substantially lower than those reported by us.

Germline mutations in the STK 11 gene were described in patients with PJS by 2 independent groups.[3,4] Investigators found that truncating germline mutations in the STK 11 gene appear necessary and sufficient to cause PJS.[3,4,19] Gruber et al.[19] reported evidence in PJS that STK 11 acts as a tumor-suppressor gene potentially involved in the earliest steps of pathogenesis of hamartomas into adenocarcinomas. The confirmation of the wide variety and striking risk of malignancy in PJS

Table 5. Case Reports of Malignant and Nonmalignant Tumors in PJS

Site	No. of cases	Sex (M/F) (*% male*)	Age at diagnosis (mean ± SD)	95% CL	Range	Comments	Study (references)
Esophagus	1	1/0 (100)	67	—	—		21
Stomach	8	5/3 (63)	30.1 ± 16.7	16.1, 44.1	10–61		22–29
Small intestine	16	7/9 (44)	41.7 ± 17.5	32.0, 51.4	21–84		22,28–43
Colorectal	9	7/2 (78)	45.8 ± 17.3	32.4, 59.0	27–71		44–50
Pancreas	6	4/2 (67)	40.8 ± 16.2	23.9, 57.8	16–60		33,50–54
Breast	9	0/9 (100)	37.0 ± 11.4	28.2, 45.8	19–48	3 Cases bilateral	47,55–57
Cervix	28	0/28 (100)	34.3 ± 7.8	30.8, 37.7	23–54	22 Adenoma malignum	50,55,57–68
Ovarian	53	0/53 (100)	28.0 ± 12.5	24.4, 31.5	4–57	49/53 Sex cord tumors[a]	47,55,57,60,61, 63,65,68–78
Testes	9	9/0 (100)	8.6 ± 5.4	4.3, 12.7	3–20	All Sertoli cell tumor	79–85

[a]Concomitant breast cancer in 3 patients, breast cancer and cervical adenoma malignum in 3, breast and ovarian cancer in 1, cervical adenoma malignum in 10, ovarian adenocarcinoma in 1, ovarian and cervical adenoma malignum in 5, and Sertoli cell tumor in 3.

should stimulate research into the molecular mechanism and role of STK11 gene mutations in carcinogenesis of sporadic cancer. Of note, STK11 mutations were found in sporadic pancreatic cancers.[20] Also, genotype/phenotypic studies are needed to attempt to stratify risk in PJS patients.

Several investigators have made suggestions for cancer surveillance in patients with PJS.[5,7,8,15] However, patient management has been impeded by variability in risk estimates by individual reports. The results of this study place the risk of breast, gynecological, colorectal, stomach, and pancreatic cancer in the range of risk at which surveillance programs have been advocated in other conditions. Recommendations for cancer surveillance in PJS might be modeled after guidelines developed for disorders with similar cancer risks. Future studies based on pooled registry data are needed to confirm the risk estimates cited in the present study. In addition, formal evaluation will be necessary to assess the impact of surveillance regimens on morbidity and mortality in patients with PJS.

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