# Peutz-Jeghers Polyposis Associated with Carcinoma of the Digestive Organs

## Report of Three Cases and Review of the Literature

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**Three cases of Peutz-Jeghers polyposis with carcinoma of the digestive organs are studied. Although mucocutaneous pigmentation was not present in two of the three patients, the features of intestinal polyposis are consistent with those of Peutz-Jeghers syndrome. One patient had a carcinoma of the pancreas and the other two had carcinomas with colonic Peutz-Jeghers polyps. Previous reports on carcinomas associated with Peutz-Jeghers syndrome are reviewed. An unusual location in the gastrointestinal tract, together with occurrence at an early age, characterize the carcinoma in Peutz-Jeghers syndrome. In Japanese patients, the large bowel is the site of the greatest number of carcinomas. On the other hand, Western patients showed a relatively even distribution. A possible surveillance protocol for early detection of gastrointestinal carcinoma in patients with Peutz-Jeghers syndrome is discussed. [Key words: Peutz-Jeghers syndrome; Carcinoma]**

PEUTZ-JEGHERS SYNDROME is a specific type of intestinal polyposis, usually associated with mucocutaneous pigmentation. The intestinal polyps in this syndrome are considered to be hamartomatous,[1] so the risk of developing cancer is thought to be small. Some reviews of reported cases of cancer-associated Peutz-Jeghers syndrome, however, have suggested an increased cancer risk in this syndrome.[2-4] Although it is not possible to clarify exactly how much the risk is increased, an extensive review of the literature should clarify some important aspects of this subject. This paper reports three cases of Peutz-Jeghers polyposis associated with malignancies, and analyzes the results of an extensive review of the previously reported cases.

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### Report of Cases

**Patient 1:** In May 1981, a 49-year-old woman was admitted to a local hospital because of abdominal distention, nausea, and vomiting suggestive of bowel obstruction. Upper gastrointestinal endoscopy showed two polyps in the stomach; multiple polyps were found on colonoscopy. There was pigmentation on her lips and on the fingers of both hands. The symptoms of bowel obstruction disappeared spontaneously. The family history was negative for any major illnesses. Peutz-Jeghers syndrome was suspected and she was referred to the surgical department.

Barium-enema examination showed several polyps in the left side of the large bowel. In July 1981, colonoscopy revealed five polyps in the descending and sigmoid colon. These polyps were pedunculated, coarsely lobulated structures with a smooth surface; all five polyps were removed by colonoscopic polypectomy. Each polyp showed the typical histologic features of a Peutz-Jeghers polyp. The largest polyp, removed from the descending colon, showed a focus of adenocarcinoma limited to the mucosa (Figs. 1 and 2). The patient refused x-ray examination of small bowel. Since then she has been followed for five years and reports no particular symptoms.

**Patient 2:** In 1983, gastroduodenoscopy was performed on a 57-year-old man complaining of epigastric discomfort; one small duodenal polyp was found. There was no skin pigmentation, and no family members had features of Peutz-Jeghers syndrome.

In August 1985, the patient complained of anal bleeding and a prolapse of a "hemorrhoid." At hemorrhoidectomy two rectal polyps were resected through the transanal approach, both showing typical histologic features of Peutz-Jeghers polyps; one polyp had adenoma-

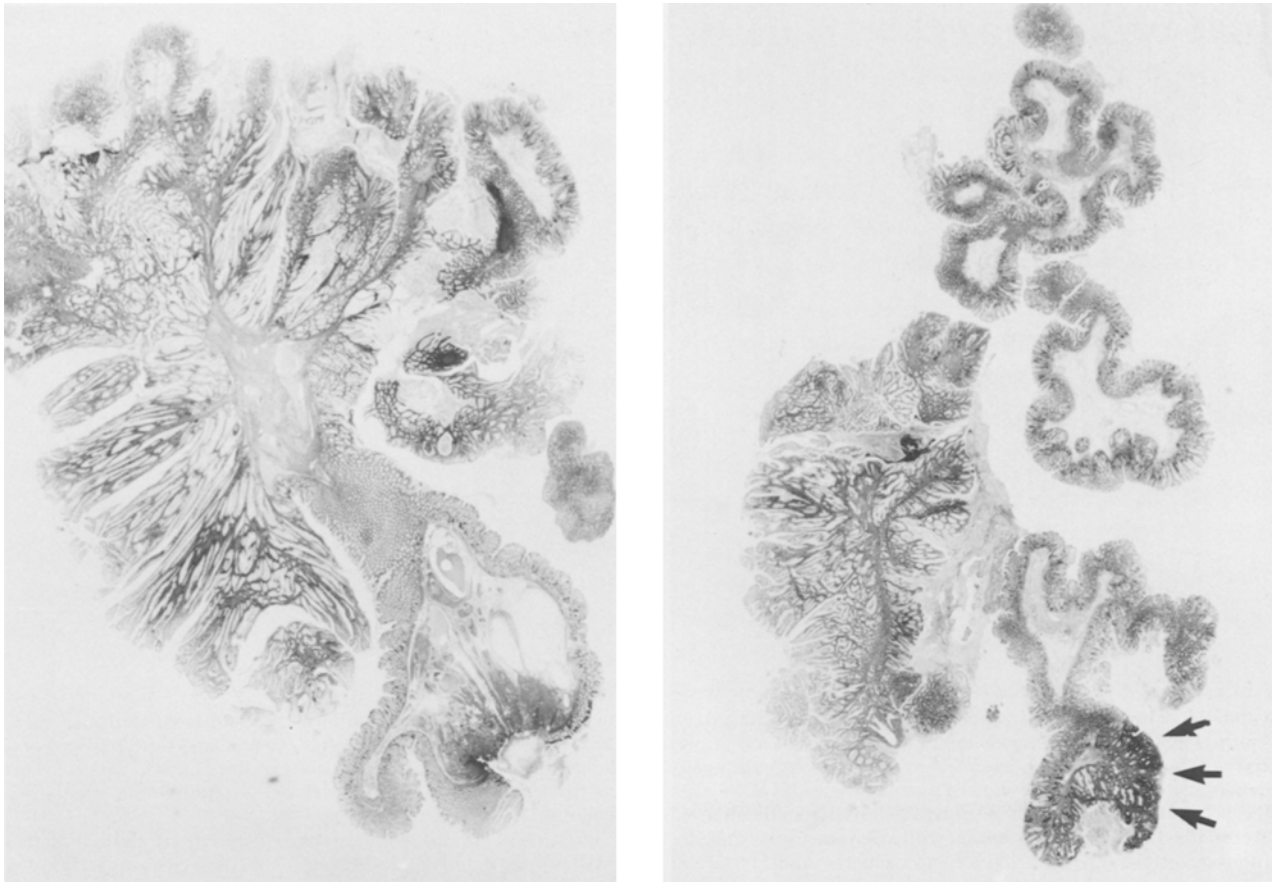

FIG. 1. (Patient 1). Low-power view of two sections from a colonic Peutz-Jeghers polyp. A focus of adenocarcinoma is present (arrow) (hematoxylin and eosin; × 3.6).

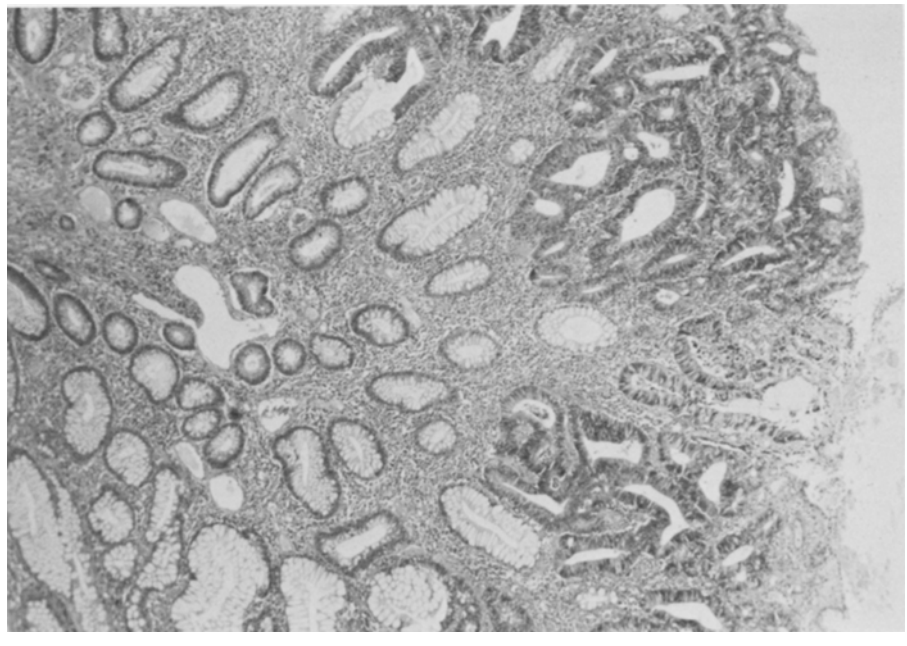

FIG. 2. High-power view of adenocarcinoma in Fig. 1 (hematoxylin and eosin; × 31).

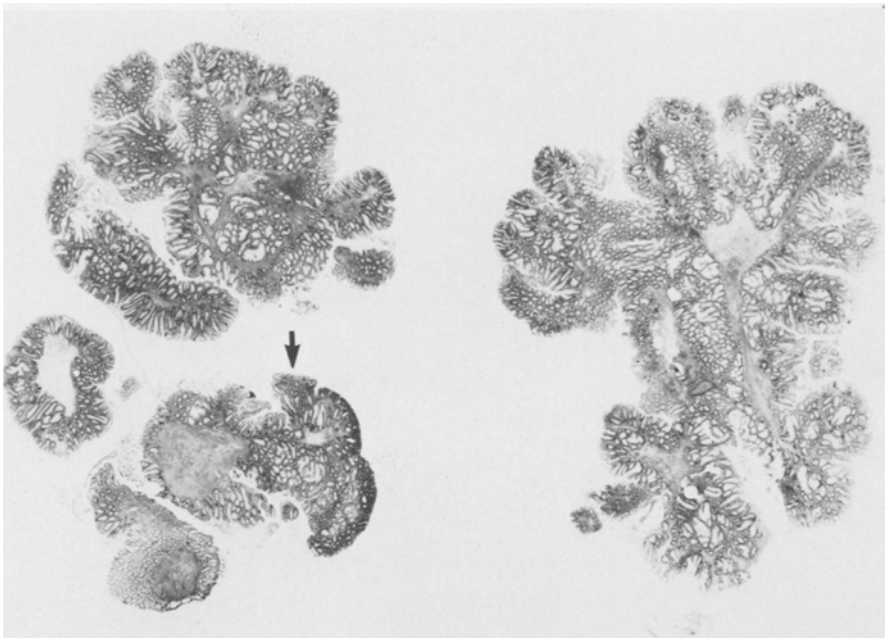

FIG. 3. (Patient 1). Low-power view of two sections from rectal polyp. A focus of adenocarcinoma is present (arrow) (hematoxylin and eosin;× 2.7).

tous changes with a focus of adenocarcinoma (Figs. 3 and 4). In November 1985, barium-enema examination revealed several polyps throughout the large bowel. Fourteen colonic polyps were removed by colonoscopic polypectomy. All showed histologic features of a Peutz-Jeghers polyp (Fig. 5) and one of the polyps removed from the sigmoid colon contained adenomatous changes with a definite focus of adenocarcinoma (Figs. 6 and 7). The carcinomatous changes in the rectal and sigmoid colon polyps showed no invasion into the submucosa.

**Patient 3:** In January 1984, a 60-year-old man vomited about 100 ml of blood after drinking alcohol. A barium-meal study at a local hospital showed multiple polyps in the duodenum and the patient was referred to the surgery department for further investigation.

Neither his mouth nor his digits had pigmentation, and none of his family members had a history of gastrointestinal disease or skin pigmentation. A repeat barium-meal study showed multiple polyps, measuring 0.5 to 1.5 cm in the first, second, and third portions of the duodenum, but no polypoid lesions in the stomach. Biopsies of the polyps revealed non-neoplastic duodenal epithelium, suggesting a diagnosis of Peutz-Jeghers polyp.

Barium-enema and colonoscopic examinations showed scattered small polyps, mainly in the left side of the colon. Stenosis at the splenic flexure was seen, also, and was considered to be caused by an extramural mass. Histology of colonic polyps removed by colonoscopic polypectomy showed features compatible with Peutz-Jeghers polyps.

In March 1984, the patient was admitted to the department of surgery with symptoms of bowel obstruction. On admission, the abdomen was distended and a hard, fixed tumor was palpable at the left hypochondrium. Abdominal scout films showed a distended colon, and abdomi-

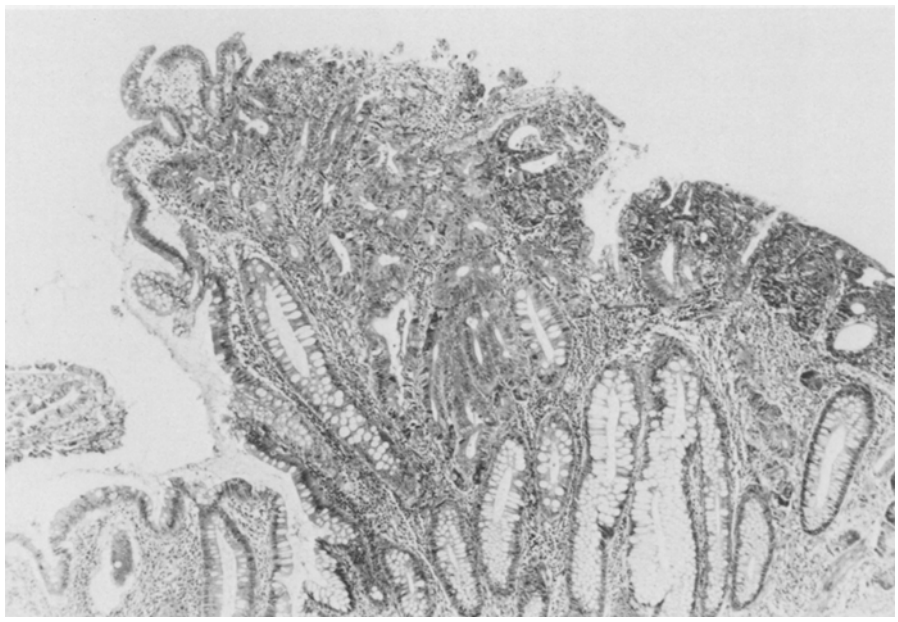

FIG. 4. High-power view of adenocarcinoma in Fig. 2 (hematoxylin and eosin; × 31).

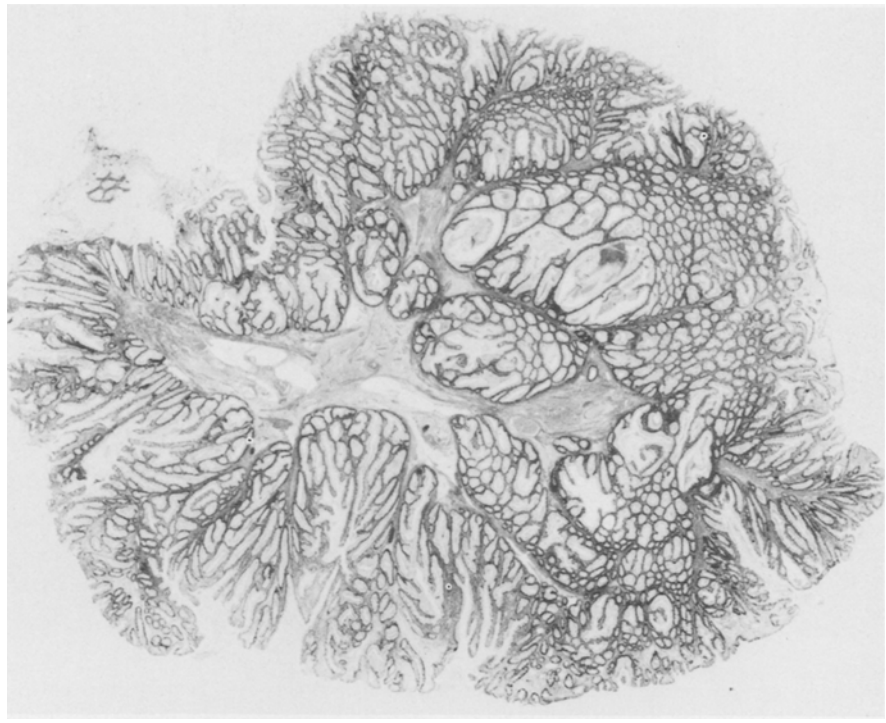

FIG. 5. (Patient 2). Colonic polyp showing typical features of Peutz-Jeghers polyp (hematoxylin and eosin; × 5.1).

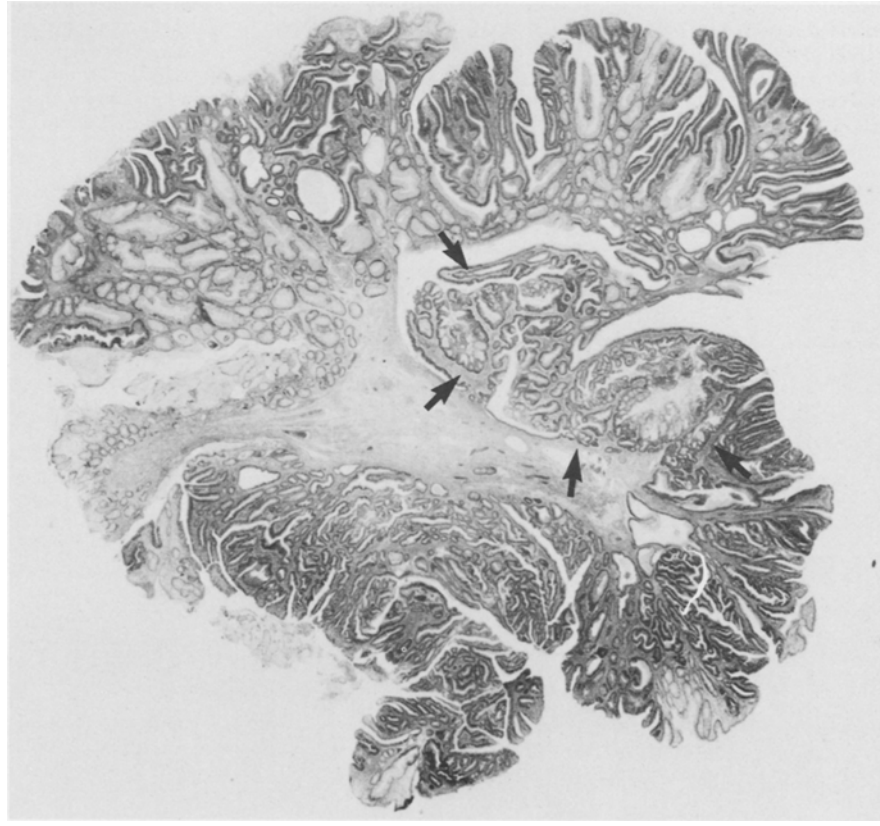

FIG. 6. (Patient 2). Low-power view of colonic polyp. A focus of carcinoma (arrow) surrounded by adenomatous change is present. Non-neoplastic glands in this polyp are considered to be the remnant of Peutz-Jeghers polyp (hematoxylin and eosin; × 10.0).

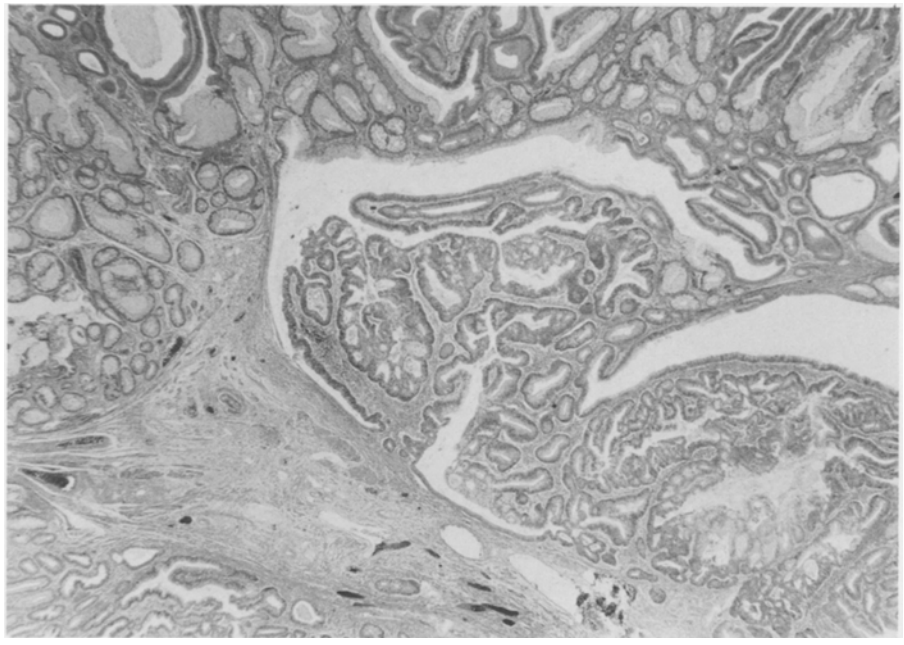

FIG. 7. High-power view of carcinoma in same polyp as in Fig. 6 (hematoxylin and eosin; × 23).

nal ultrasonography revealed moderate ascites. Serum carcinoembryonic antigen was slightly increased with a value of 4 ng/ml. Computed tomography and ultrasonography suggested the presence of a carcinoma in the body of the pancreas.

In April 1984, laparotomy revealed a large, hard tumor, measuring about 10 cm, in the left upper quadrant of the peritoneal cavity. The tumor was obstructing the splenic flexure of the colon. Pancreatic carcinoma was not confirmed because the approach into the bursa omentalis was prevented by extensive cancer invasion. There were numerous nodules of peritoneal seedings involving almost the entire peritoneal cavity. On palpation of the small intestine, there were several polypoid lesions in the proximal jejunum and one in the distal ileum. Two jejunal polyps and one ileal polyp were removed through small enterotomies in order to obtain histologic confirmation of Peutz-Jeghers polyposis. Histology of these polyps showed features typical of Peutz-Jeghers polyps. Ileosigmoid side-to-side anastomosis was performed for palliation of the colonic obstruction. The patient gradually deteriorated postoperatively and died in September 1984.

At autopsy, a poorly demarcated tumor, measuring 4 cm, was present in the body of the pancreas. Histology showed well-differentiated adenocarcinoma with massive mucous production (Fig. 8). Widespread peritoneal seedings were seen and the colon around the splenic flexure was involved by one of the larger peritoneal seedings. Metastases were found in the regional lymph nodes and bilaterally in the lungs, but not in the liver. The entire gastrointestinal tract was examined. There were 32 fairly evenly distributed polyps in the duodenum. Most of the polyps were pedunculated and some were lobulated. In the proximal jejunum, there were seven pedunculated polyps. The distal jejunum and ileum were mostly free of polyps except for one polyp in the terminal ileum. There were no polyps in the right colon and the

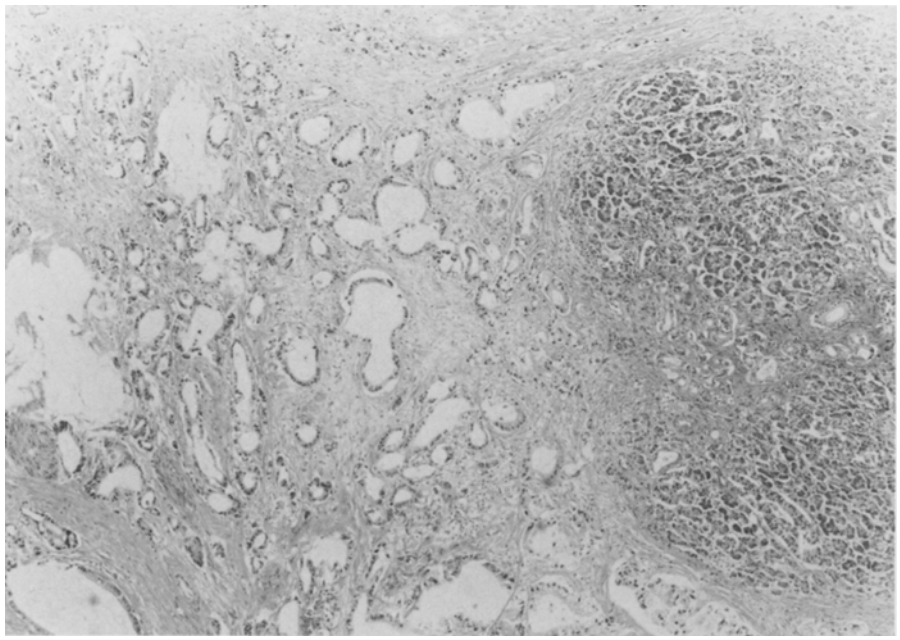

FIG. 8. (Patient 3). Pancreatic carcinoma (hematoxylin and eosin; × 31).

FIG. 9. (Patient 3). Duodenal polyp showing typical features of Peutz-Jeghers polyp (hematoxylin and eosin; × 6.8).

transverse colon. The sigmoid colon and rectum contained about ten small polyps. Histology of these polyps showed features typical of Peutz-Jeghers polyps (Fig. 9) and one of the jejunal polyps removed at surgery had a focus of adenomatous change (Fig. 10).

### Review of the Reported Cases

Previous reports of malignancies in Peutz-Jeghers syndrome in the world literature were collected and reviewed. Some benign tumors are also included in them. Altogether, 117 lesions in 103 reported cases were analyzed. The number of reported tumors in the various organs are shown in Table 1.

There were 50 carcinomas of the gastrointestinal tract. Among the specific sites of these gastrointestinal carcinomas, the large bowel[2,5-14] had the highest number reported (20 lesions). The duodenum[10,15-23] ranked second

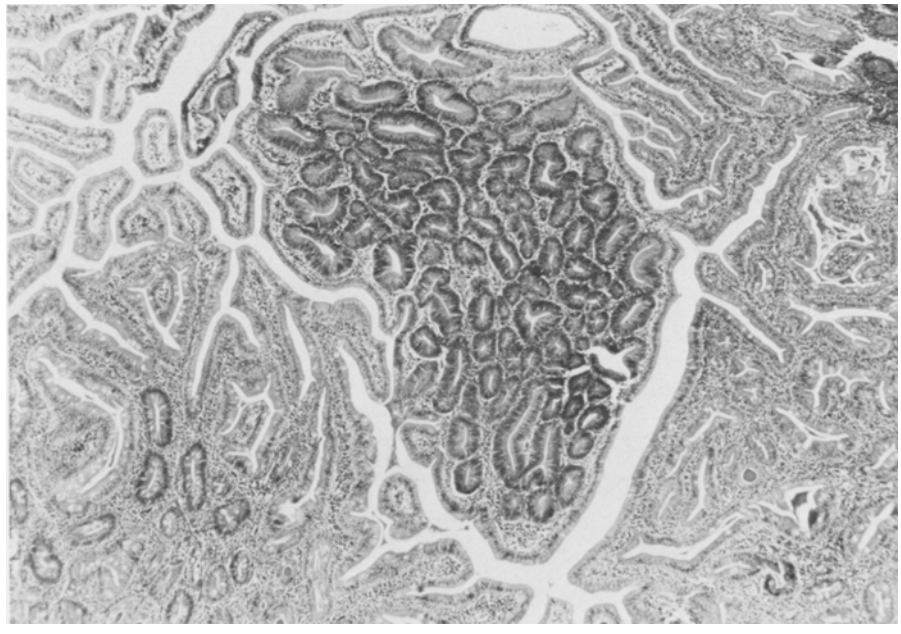

FIG. 10. (Patient 3). Adenomatous change in a Peutz-Jeghers polyp (hematoxylin and eosin; × 30).

TABLE 1. *Site and Number of Reported Tumors in Peutz-Jeghers Syndrome (117 Lesions in 103 Patients)*

| Site | Number |
|---|---|
| Stomach | 8 |
| Duodenum | 10 |
| Jejunum | 9 |
| Ileum | 3 |
| Colon and rectum | 20 |
| Pancreas | 2 |
| Bile duct | 1 |
| Gallbladder | 1 |
| Liver | 1 |
| Sex cord tumor with annular tubule (SCTAT) of the ovary | 28 |
| Uterus | 7 |
| Ovary (non-SCTAT) | 12 |
| Testis | 2 |
| Breast | 8 |
| Lung | 2 |
| Tonsil | 1 |
| Bone | 1 |
| Leukemia | 1 |

with ten, and the jejunum[7,17,22,24-28] and stomach[10,18,29-34] followed, with nine and eight, respectively. There were three ileal carcinomas.[35-37] Including the two cases reported here, 13 of the 20 colorectal cancers were in Japanese patients, seven of which were reported by Utsunomiya *et al.*[10] In the Japanese patients there were only a few carcinomas in other sites within the gastrointestinal tract. Table 2 shows the difference in distribution of gastrointestinal carcinomas between Western and Japanese patients. In the reported cases, including the present ones, there were 23 lesions in 19 patients where carcinoma was found within the Peutz-Jeghers polyp. Table 3 shows the subsite distribution of these lesions. The highest numbers were found in the jejunum and duodenum. Age distribution and mean age of the patients with carcinomas of the colon, duodenum, and stomach are shown in Table 4. The mean age at cancer diagnosis in these patients appears to be younger than the average age at cancer diagnosis in the general population.

The number of carcinomas in the pancreas,[10,33] bile duct,[38] and liver[10] totaled five. There were only two reported cases of pancreatic cancer in Peutz-Jeghers syndrome.

TABLE 2. *Distribution of Gastrointestinal Carcinomas in Western and Japanese Patients*

| | Western Cases | Japanese Cases |
|---|---|---|
| Stomach | 7 | 1 |
| Duodenum | 9 | 1 |
| Jejunum | 8 | 1 |
| Ileum | 2 | 1 |
| Colon and rectum | 8 | 12 |

TABLE 3. *Reported Cases of Carcinoma Arising in Peutz-Jeghers Polyp (Including This Study's Cases)*

| Site | Number of Lesions |
|---|---|
| Stomach | 3 |
| Duodenum | 6 |
| Jejunum | 7 |
| Ileum | 1 |
| Small bowel (unspecified) | 1 |
| Colon and rectum | 5 |

Besides these aforementioned tumors, there is a conspicuously high incidence of tumors of the female reproductive organs. There were 28 cases of "sex cord tumors with annular tubules,"[24,39-43] mostly benign, reported mainly by Scully[40] and Young *et al.* and 19 other various tumors of the ovaries and uterus.[6,10,24,43-54] Other miscellaneous tumors are listed in Table 1.[3,15,24,42,55-57]

## Discussion

In the present report, two cases of colorectal cancer found in Peutz-Jeghers polyps and one case of pancreatic cancer are reported. In two of the three cases there was no mucocutaneous pigmentation. Despite this, these two cases were included because the pathologic features of gastrointestinal polyposis in both patients were consistent with Peutz-Jeghers syndrome. Lin *et al.*[19] also reported a case of a duodenal carcinoma in Peutz-Jeghers polyposis without mucocutaneous pigmentation. Morson and Dorson[1] stated that not all characteristic features of the syndrome appeared in each patient, and that the pigmentation was sometimes lacking, while intestinal polyposis showed the features of the Peutz-Jeghers syndrome. They suggested that the pigmentation may disappear as a patient ages.

Carcinomas of the gastrointestinal tract in Peutz-Jeghers syndrome have been reported since the original report by Jeghers *et al.* in 1949.[58] Since then, there seems to be substantial evidence accumulating that suggests an increased risk of developing gastrointestinal carcinoma in this syndrome. Although it is well known that this cancer risk certainly does not approach that of familial adenomatosis coli, it is impossible to know exactly how

TABLE 4. *Mean Age of Patients with Carcinoma in Peutz-Jeghers Syndrome**

| Site | Mean Age (Years) |
|---|---|
| Gastric carcinoma (8 cases) | 31.2 |
| Duodenal carcinoma (9 cases) | 39.7 |
| Colorectal carcinoma (13 cases) | 48.0 |

*Cases in which age of patient was not specified are excluded.

much the risk of developing carcinoma is increased in this syndrome. In 1957, Baily[2] found carcinoma of the gastrointestinal tract recorded in 16 of 67 cases reported up to that time, which yields a cancer risk estimate of 24 percent. In the same year, Bartholomew *et al.*[3] reported six more cases and concluded that 20 percent of the 75 cases of Peutz-Jeghers syndrome they collected from the world literature showed low-grade malignant changes in the polyps. They commented that the evidence for truly malignant transformation in the polyps was not completely convincing, however, as metastasis was not observed in any of the 75 cases. The high malignancy rate in these two reports may well be due to histologic misinterpretation of the presence of non-neoplastic glands within smooth-muscle fibers as invasion, before these polyps were widely recognized as hamartomas. In 1969, using a stricter definition of malignancy, Dozois *et al.*[4] reviewed the 326 cases of Peutz-Jeghers syndrome reported up to that time and found only 11 cases with gastrointestinal carcinoma, eight of which had metastasized, yielding a malignancy rate of 2 to 3 percent. It is conceivable that the percentage cited in their report is the most dependable one available because, in recent years, there is probably an increasing trend for uncomplicated cases of Peutz-Jeghers syndrome to go unreported and carcinoma-associated cases to be selectively reported. In 1974, Reid[59] agreed with the 2 to 3 percent figure, accepting only the 14 cases with metastasizing lesions reported up to then, and suggested that the stomach and duodenum were the locations at highest risk. It is worth mentioning, however, that Linos *et al.*[60] followed 48 patients with Peutz-Jeghers syndrome for a median of 33 years and found no intestinal carcinoma or decreased survival. Reviewing these previous reports, it can be concluded that there is an increased risk of developing carcinoma of the gastrointestinal tract in this syndrome, but that the risk is not very high—probably a few percent at the greatest. Recent evidence suggests that the risk of neoplasm at other sites may be elevated as well, particularly in the female reproductive tract. Miyaki *et al.*[61] report an experimental study in which they found skin fibroblasts from Peutz-Jeghers patients to be five times more sensitive to transformation by murine sarcoma virus than fibroblasts from controls.

According to analysis of the reported cases, there is a striking difference in the distribution of gastrointestinal carcinomas between Japanese and Western patients. In the former category, the large bowel is the site where the greatest number of cancers were found. It is interesting to note that the site of malignancy in two of this study's three patients was also the large bowel. In Western patients, carcinomas occur at a similar frequency in the stomach, duodenum, jejunum, and large bowel. It is hard to identify any possible reasons for this difference. In Japanese, Western, or Japanese and Western patients combined, distribution of the carcinomas found in the gastrointestinal tract in Peutz-Jeghers syndrome obviously differs from that seen in the general population. An unusual location in the gastrointestinal tract, together with occurrence at an early age, characterizes the carcinomas in Peutz-Jeghers syndrome.

It has not yet been determined whether the gastrointestinal carcinomas in Peutz-Jeghers syndrome arise from the Peutz-Jeghers polyp or from the normal mucosa. In the literature reviewed, there were 21 lesions where carcinoma is reported to have risen within a Peutz-Jeghers polyp, including the colorectal cancer cases reported here. Although not all reported cases have adequate histologic photographs showing the area surrounding the carcinoma within the polyp, the available evidence suggests that a substantial number of carcinomas in this syndrome may arise in Peutz-Jeghers polyps. In two of this study's colonic cancer patients there was evidence of carcinoma arising in the Peutz-Jeghers polyp. Furthermore, in one patient with colonic carcinoma, adenomatous tissue was seen around the focus of carcinoma (Figs. 3 and 4) and, in the patient with pancreatic carcinoma, there was an adenomatous change in one of the jejunal Peutz-Jeghers polyps (Fig. 10). These findings, particularly the former, lead to the speculation that the adenoma-carcinoma sequence may aptly describe the carcinogenesis in Peutz-Jeghers syndrome.

An appropriate surveillance protocol for early detection of gastrointestinal carcinoma in patients with Peutz-Jeghers syndrome is difficult to determine. As already discussed, the incidence of carcinoma in this syndrome is not very high, *i.e.*, probably 2 to 3 percent. Therefore, frequent investigations of the gastrointestinal tract may not be necessary. If one considers the very limited number of patients with this syndrome and the definitely increased, although not high, incidence of cancer in such patients, however, periodic investigation of the upper and lower gastrointestinal tract, preferably by endoscopy, may be warranted for early detection of carcinoma. Furthermore, if laparotomy is ever indicated, usually for small bowel intussusception, as many small-bowel polyps as possible should be removed, not by bowel resection, but by enterotomy with invagination.[10]

### Acknowledgment

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