Molecular genetic alterations in gastrointestinal polyposis syndromes: with emphasis on the Peutz-Jeghers syndrome

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Chapter 2

Upper Gastrointestinal Polyps in Familial Adenomatous Polyposis

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ABBREVIATIONS: Familial adenomatous polyposis (FAP); Adenomatous Polyposis Coli (APC)

SUMMARY
Familial adenomatous polyposis (FAP) is an autosomal dominant disease in which affected family members develop numerous colorectal adenomas with a virtually 100% chance of malignant degeneration unless the colon is prophylactically removed. After colectomy the main cause of death is upper gastrointestinal malignancy. The majority of FAP patients also develop upper gastrointestinal polyps, and especially those in the antrum and duodenum are usually neoplastic. Therefore, surveillance of FAP patients through endoscopy plus biopsy is recommended. The Spigelman classification in which the number of adenomas, the size, architecture and degree of dysplasia account for the scoring system, provides a guide for follow-up in these patients. Molecular genetic markers to assess the risk of upper gastrointestinal cancer in FAP patients are as yet not available.

INTRODUCTION
Familial adenomatous polyposis (FAP) is an autosomal dominant disease caused by a germline mutation of the adenomatous polyposis coli (APC) gene located on chromosomal arm 5q (1,2). Both genders are affected equally and the colorectum of these patients harbors hundreds of premalignant adenomatous polyps. All FAP patients develop polyps, usually during the first decades of life, and the risk of developing colorectal cancer is virtually 100% unless the colorectum is prophylactically removed (3). However, an increased risk of extra colonic tumors remains even after prophylactic surgery (Table 1).

Patients with FAP are at risk for hepatoblastoma, a malignant embryonal liver tumor that develops during infancy and early childhood (4). Brain tumors may also develop at a higher frequency than expected and are primarily medulloblastomas occurring during the second decade of life (5). Nasopharyngeal angiofibroma is a highly vascular locally invasive tumor that is reported at a high frequency in male adolescents (6). Desmoid tumors, which develop in 10% of FAP patients, are benign fibromatous neoplasms which exhibit aggressive local growth, causing multiple sequelae (7). Furthermore, an increased relative risk for pancreatic and thyroid cancer exists in FAP patients (8). The most threatening malignancies occurring in FAP patients after prophylactic colectomy, however, are carcinomas of the upper gastrointestinal tract which are the most common cause of death after colorectal cancer (9). These malignancies arise from the adenomatous polyps in the stomach and duodenum.

UPPER GASTROINTESTINAL POLYPOSIS
Commonly, multiple polyps are seen in the stomach of FAP patients, but these are usually non-neoplastic fundic gland polyps. This type of polyp is found in approximately half of the patients and consists macroscopically of sessile polyps occurring in the gastric fundus (10). Microscopy shows cystic dilated glands lined by specialized glandular cells and columnar...
**TABLE 1 Extracolonic Cancer**

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Relative risk</th>
<th>Absolute lifetime risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>7.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Thyroid</td>
<td>7.6</td>
<td>2.1</td>
</tr>
<tr>
<td>Duodenum</td>
<td>330.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Ampullary</td>
<td>123.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Pancreas</td>
<td>4.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Hepatoblastoma</td>
<td>847.0</td>
<td>1.6</td>
</tr>
</tbody>
</table>

epithelial cells, generally without epithelial dysplasia; very rarely, dysplasia is observed in fundic gland polyps (11). Since fundic gland polyps may appear before the development of colorectal polyposis, they can act as a marker for the disease. Gastric adenomas are less frequent and usually located in the antrum (10). They are by definition dysplastic and premalignant but, interestingly, the rate of gastric adenocarcinoma in the antrum is not increased in Western FAP patients (9). This contrasts with Korean and Japanese FAP families where an increased risk for gastric cancer exists (12). This may point to an environmental factor given the already high risk of stomach cancer in these general populations.

The majority of FAP patients develop duodenal adenomas (13). The incidence increases with age and the anatomical distribution shows a predilection for the periampullary area (10). This has led to incriminate compounds in the bile as the culprit for tumor formation (14). Most adenomas are relatively small tubular adenomas with mild or moderate dysplasia, but larger tubulovillous or villous adenomas with higher grades of dysplasia are also encountered and obviously carry a higher risk for malignancy (10,14). Single crypt adenomas, "microadenomas", may be seen at microscopy of biopsies obtained from macroscopically normal-looking mucosa, a phenomenon virtually non-existent in biopsies other than FAP patients. The adenomas can be seen on top of the mucosal folds. They contain a hyperplastic Paneth cell population, and a large number of endocrine cells can be seen scattered throughout the dysplastic epithelium. The meaning of these findings is unclear (15,16). Epidermal growth factor is expressed at high levels in duodenal adenomas of FAP patients (17).

Adenomas are premalignant lesions and indeed periampullary and duodenal carcinoma occurs more often in FAP patients than in the age-matched general population. The Johns Hopkins Polyposis Registry demonstrated a relative risk of 331 for duodenal carcinoma and of 124 for ampullary cancer (9). The absolute risk of the two combined was one case per 1698 person-years. To put these data into perspective, the risk of adenocarcinoma in Barrett mucosa is estimated at one case per 500 person-years. Other series of FAP patients have also established an increased risk, but the precise frequency of malignancy in duodenal adenomatosis remains unknown. Nevertheless, agreement exists that regular surveillance of the upper gastrointestinal tract in FAP patients is indicated.

**UPPER GASTROINTESTINAL SURVEILLANCE IN FAP PATIENTS**

Although the precise cancer risk and natural history of duodenal adenomas is unknown, regular surveillance through upper gastrointestinal endoscopy appears indicated and justified. At St. Mark's Hospital, the initial screening of the upper gastrointestinal tract is typically started when the patient enters the hospital for prophylactic colectomy, usually around the age of 20. There is no way to determine which patients are at risk for developing cancer. There appears to be no correlation between the position of the mutation in the coding region and the occurrence of upper gastrointestinal adenomas (18). Also, patients with attenuated forms of polyposis coli with fewer colorectal polyps carry a risk for upper gastrointestinal cancer. The stage of duodenal polyposis that predicts cancer risk can be calculated utilizing the classification derived by Spigelman at St. Mark's Hospital (10,14). This classification assigns scores at numbers, size, degree of dysplasia, and villous component of the polyps (Table 2). The majority of patients will fall into the lower Spigelman stages 0, I or II and regular follow-up at 2-3 years appears adequate; the more advanced stages III and IV need closer follow-up at intervals of 6-12 months (10). At present, the options for treatment are limited. In contrast to the colon, the response to chemoprevention seems disappointing (19,20). Therefore, excision or destruction of neoplasms through electrocaugulation or laser destruction remains, but the latter two have high risks of complications like perforation. Thus, radical
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surgical treatment with pancreaticoduodenectomy (Whipple’s procedure) is recommended for cases where invasive growth develops.

Obviously, a pressing need exists for developing biomarkers which would yield a better risk profile predictive of upper gastrointestinal cancer in FAP patients. In the future, application of molecular techniques may provide new ways of more precisely assessing risk. Presently, optimal management depends on conventional tools in which a close collaboration between the endoscopist, the pathologist and the surgeon is the best guarantee for optimal patient care.

CONCLUSIONS

FAP patients carry an increased risk for upper gastrointestinal cancer and regular endoscopic biopsy surveillance is recommended. Adenomas, most often found in the periampourary region are the precursor lesions of malignancy. Size, degree of dysplasia, and villous architecture are markers for malignant potential and these three parameters together with polyp number form the base of the Spigelman classification to stage the disease. Spigelman 0-II stage patients should be followed-up at intervals of 2-3 years, stages III-IV need closer follow-up every 6-12 months. Once invasive growth is likely and carcinoma is present, surgical resection is the treatment of choice.

ACKNOWLEDGEMENTS

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REFERENCES


<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>The Spigelman Classification Based on Risk Factors for Cancer can be used to Clinically Stage Patients with Duodenal FAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duodenal disease grading: points</strong></td>
<td>1</td>
</tr>
<tr>
<td>Polyp number</td>
<td>1-4</td>
</tr>
<tr>
<td>Polyp size (mm)</td>
<td>1-4</td>
</tr>
<tr>
<td>Histology</td>
<td>Tubular*</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Mild</td>
</tr>
</tbody>
</table>

*or hyperplasia, inflammation; stage O: 0 points, I: 1-4 points, II: 5-6 points, III: 7-8 points, IV: 9-12 points.