Genetics of Familial Gastrointestinal Malignancy

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INTRODUCTION

Gastrointestinal malignancies represent a significant proportion of the cancer burden in the United States. It is estimated that colon cancer will be the second most common cause of cancer death in the United States in 2007, with an estimated 52,180 deaths, while pancreatic cancer will be fourth, with an estimated 33,370 deaths (Table 1). Esophageal and stomach cancers will be responsible for 13,940 and 11,210 deaths, respectively, in 2007. Although most cases of gastrointestinal cancer are sporadic (nonhereditary), with hereditary syndromes accounting for only 5% to 10% of cancer cases, it is important for gastroenterologists to understand the many recent advances in our knowledge of the genetics of gastrointestinal malignancies. In the decades ahead, gastroenterologists will increasingly be able to recognize the underlying molecular events that lead to gastrointestinal malignancy, allowing for the development of improved approaches to prevention, diagnosis, and treatment. This manual reviews the genetic basis of hereditary syndromes that have been linked with colon cancer, pancreatic cancer, gastric cancer, and esophageal cancer and discusses approaches to recognizing these syndromes and performing surveillance testing for cancers associated with them.

FAMILY HISTORY

Obtaining a detailed family history of cancer is the most important initial step in the diagnosis of a hereditary cancer syndrome. Ideally, this history should consist of all cases of cancer at all anatomic sites and include age of onset. Questions should include: Did your mother/father die of cancer? If so, what type? Was there cancer history on your mother’s or father’s side of the family (ie, aunts or uncles, maternal and paternal grandparents, any other relatives)? Although individual patients may not be able to provide all this information, there is often a family member who knows the family history and may serve as a resource for obtaining an adequate history. Whenever possible, one should obtain a family history through 3 generations (first-degree and second-degree relatives).

Physicians must appreciate that a hereditary cancer syndrome diagnosis in a family can impact greatly upon their lifetime cancer destiny and influence the use of preventive and surveillance interventions that may contribute to their survival. When the family is sufficiently educated about this matter, in concert with genetic counseling, they often will appreciate the need to participate actively in the best available cancer screening and management strategies. Thus, it is essential to be aware of the different gastrointestinal syndromes and their management as this will allow for appropriate referral for genetic counseling and implementation of surveillance strategies. Important syndromes associated with these cancers are summarized in Table 2.

COLON CANCER

CASE PRESENTATION 1

A 60-year-old man is referred to a gastroenterologist by his primary care physician for a screening colonoscopy. The patient is completely asymptomatic and has a past medical history of hypertension, which is controlled by atenolol. The patient’s father died of colon cancer at age 65 years. Colonoscopy reveals a 2-cm sessile right-sided colon polyp, a 1-cm left-sided polyp, and 10 diminutive polyps ranging in size from 3 mm to 8 mm. All polyps are resected and are determined to be adenomatous. The patient is contacted with the results, and an attempt is made to obtain further family history. He knows other family members have had polyps and that some have had colon cancer as well as other types of cancer, but he does not recall exactly who had what or when they had it. The patient is referred for genetic counseling and is asked to gather information regarding his family history and attempt to obtain pathologic documentation of any reported cancers to verify histology.
• What familial gastrointestinal malignancies may be considered in this patient?

**FAMILIAL CANCER SYNDROMES**

This patient could have attenuated familial adenomatous polyposis (FAP), MYH-associated polyposis, or Lynch syndrome given the number of polyps and the vague family history. It is unlikely that he has full-blown FAP as he is older and has only 12 polyps. It is important to obtain further family history in order to determine if family members should be tested and what future course of action is in the patient’s best interest. If a specific mutation is found in this patient, then his family can undergo specific testing to determine who may have inherited the mutation.

**Familial Adenomatous Polyposis**

FAP accounts for less than 1% of colon cancer cases but has a high penetrance that approaches 100%. FAP has an autosomal dominant inheritance pattern and results from a mutation in the APC (adenomatous polyposis coli) gene, which helps to regulate cellular proliferation genes. Most patients with FAP develop polyps in their teens and are diagnosed with colon cancer in early middle age. These patients have hundreds to thousand of polyps, which usually carpet the bowel. This classic presentation is not seen in all patients, and patients with attenuated FAP can present at a later age with fewer polyps (approximately 30 on average). Attenuated FAP is one of the 3 known variants of FAP; the other 2 are Turcot’s syndrome and Gardner’s syndrome. Extraintestinal manifestations allow one to identify these syndromes. Gardner’s syndrome consists of colonic polyposis in association with epidermoid cysts, desmoid tumors, dental abnormalities and osteomas, and Turcot’s syndrome consists of adenomatous polyposis in association with central nervous system tumors. Patients with FAP should undergo upper gastrointestinal endoscopy to exclude ampullary malignancies. Colectomy is recommended for full-blown FAP and should be considered for attenuated FAP.

**MYH-Associated Polyposis**

Patients with MYH-associated polyposis present with a similar phenotype to FAP or attenuated FAP, but unlike these syndromes, MYH-associated polyposis is inherited in an autosomal recessive manner. Patients will present with multiple polyps, typically ranging from 10 to 100, although some patients may have more than 100 polyps. The majority of patients are diagnosed after age 45 years. Studies have suggested that biallelic MYH mutations occur in 10% to 20% of individuals who test negative for the APC-mutation despite fitting criteria for FAP or attenuated FAP.

**Lynch Syndrome**

Lynch syndrome accounts for 1% to 3% of cases of colon cancer. It should be suspected in patients who have a strong family history of colon cancer and other malignancies, particularly in individuals who have family members manifesting with the malignancy at a young age. Lynch syndrome is inherited in an autosomal dominant manner. In Lynch syndrome, polyps may occur anywhere, but most often cancers arise on the right side proximal to the splenic flexure. Histologic evaluation may distinguish Lynch syndrome tumors from FAP or attenuated FAP cancers because Lynch syndrome tumors usually demonstrate a lymphoid host response to the tumor as well as an abundance of extracellular mucin. Patients with Lynch syndrome may develop other types of cancer, with increased incidences of ovarian, gastric, urinary tract, renal, biliary, central nervous system, and small bowel cancer. Because ovarian cancer rates may be as high as 10% in affected woman, many clinicians recommend prophylactic oophorectomy. The polyp-cancer sequence shows much more rapid evolution in patients with Lynch syndrome than in the sporadic setting, and colonoscopy must be performed every 1 to 2 years.

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**Table 1. Estimated New Cancer Cases for Gastrointestinal Malignancies by Sex in the United States for Year 2007**

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Total (Male)</th>
<th>Total (Female)</th>
<th>Total Deaths (Male)</th>
<th>Total Deaths (Female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>15,560</td>
<td>12,130</td>
<td>13,940</td>
<td>10,900</td>
</tr>
<tr>
<td>Stomach</td>
<td>21,260</td>
<td>13,000</td>
<td>11,210</td>
<td>6,610</td>
</tr>
<tr>
<td>Colorectal</td>
<td>153,760</td>
<td>79,130</td>
<td>52,180</td>
<td>26,000</td>
</tr>
<tr>
<td>Pancreas</td>
<td>37,170</td>
<td>18,830</td>
<td>33,370</td>
<td>16,840</td>
</tr>
<tr>
<td>Small intestine</td>
<td>5640</td>
<td>2940</td>
<td>1090</td>
<td>570</td>
</tr>
<tr>
<td>Anus</td>
<td>4650</td>
<td>1900</td>
<td>690</td>
<td>260</td>
</tr>
</tbody>
</table>

cancer is found, subtotal colectomy is recommended.

Lynch syndrome results from a defect in mismatch repair genes, which are responsible for correcting single-base mismatch errors that occur during replication. Because replication errors are not fixed properly, cancer may result. The genetic defect in Lynch syndrome causes abnormalities consisting of mononucleotide, dinucleotide, or trinucleotide repeats in the short segments of DNA, which are known as microsatellites. Tumors resulting from these defects manifest microsatellite instability (MSI) positivity. Interestingly, patients who have sporadic cancer with MSI-positive tumors appear to have better survival compared with patients who have MSI-negative tumors. Several criteria have been developed for the diagnosis of Lynch syndrome. The most commonly used are the Amsterdam II criteria and the Bethesda criteria (Table 3 and Table 4).

**CASE 1 CONTINUED**

The patient returns for a follow-up visit with his sister and a family history is obtained. In addition to the patient’s father, a paternal uncle died of colon cancer at age 72 years. Several cousins younger than age 50 years have polyps.

- **What genetic testing and surveillance is appropriate for this patient?**

**TESTING AND SURVEILLANCE**

Although initially one may have considered testing this patient for attenuated FAP or MYH-associated polyposis based on his initial presentation with more than 10 adenomas, the added history is more suggestive of Lynch syndrome. The older age at which cancer onset occurred makes it more likely that this patient has Lynch syndrome. MYH-associated polyposis is unlikely since there appears to be an autosomal dominant pattern of inheritance. For Lynch syndrome, success rates of finding the mutation are 50% to 70%. If a disease-specific mutation is not found, more than likely one would recommend that this patient and his family members undergo annual or biannual colonoscopy and

### Table 2. Hereditary Syndromes Associated with Gastrointestinal Malignancy

<table>
<thead>
<tr>
<th>Hereditary Syndrome</th>
<th>Genes Involved</th>
<th>Cancer Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAP; AFAP</td>
<td>APC (adenomatous polyposis coli)</td>
<td>Essentially 100% (FAP) and 80% (AFAP) lifetime risk without therapeutic intervention9</td>
</tr>
<tr>
<td>MYH polyposis</td>
<td>MYH</td>
<td>50%–60% at time of diagnosis and almost 100% penetrance by age 65 yr4</td>
</tr>
<tr>
<td>Lynch syndrome (previously known as HNPCC)</td>
<td>Mismatch repair genes MLH1, MSH2, MSH6, PMS2</td>
<td>Lifetime risk ranges from 28%–75% for men and 24%–52% for women1</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11/LKB1</td>
<td>Risk increased 84-fold; 39% risk by age 65 yr4</td>
</tr>
<tr>
<td>Juvenile polyposis</td>
<td>MADH4, BMPR/A</td>
<td>Lifetime risk as high as 70%2</td>
</tr>
<tr>
<td>Esophagus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11/LKB1</td>
<td>Risk increased 57-fold6</td>
</tr>
<tr>
<td>Gastric</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>MLH1, MSH2, MSH6</td>
<td>Overall lifetime risk is low (&lt; 10%); 4.4-fold increase in cancer risk for patients with MLH1 mutation and 19-fold for patients with MSH2 mutation; risk associated with MSH6 is unknown, but it is increased6</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11/LKB1</td>
<td>Risk increased 213-fold in patients aged 15–64 yr4</td>
</tr>
<tr>
<td>Hereditary diffuse gastric carcinoma</td>
<td>CDH1</td>
<td>70% lifetime risk7</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hereditary breast-ovarian syndrome</td>
<td>BRCA1</td>
<td>Risk increased 2-fold16</td>
</tr>
<tr>
<td></td>
<td>BRCA2</td>
<td>Risk increased 3- to 9-fold11,12</td>
</tr>
</tbody>
</table>
| Peutz-Jeghers syndrome                  | STK11/LKB1                              | Risk increased 132-fold13-

**Table 3** and **Table 4**

AFAP = attenuated familial adenomatous polyposis; FAMMM = familial atypical multiple mole melanoma; FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colorectal cancer.
be observed carefully for other malignancies. If a specific mutation is found, affected individuals can be screened with colonoscopy. Patients who are negative on colonoscopy can undergo routine screening. FAP or MYH-associated polyposis may appear de novo.

CASE I CONTINUED

The gastroenterologist recommends that the case patient undergo genetic testing for Lynch syndrome as well as repeat colonoscopy in 1 year. The patient refuses to undergo further testing, and, after he has a disagreement with his sister, she refuses to be tested as well. Three years later, the patient’s primary care physician refers him for a colonoscopy after he is noted to be anemic. Colonoscopy reveals a right-sided colon tumor that is MSI positive. The patient undergoes a right hemicolectomy. A MLH1 germ-line mutation is identified by immunohistochemical analysis of the resection specimen and verified by blood test. After the patient’s surgery, testing reveals that his sister as well as several cousins also have a MLH1 mutation. She is seen by a gynecologist and is noted to have an abnormal ultrasound; she subsequently undergoes a hysterectomy and oophorectomy for endometrial cancer.

- How does family history influence risk for colon cancer?

FAMILY HISTORY AND CANCER RISK

Many patients (approximately 20%) with colon cancer have a family history of colon cancer; however, only a small percentage of colon cancers (5%–6%) are caused by inherited syndromes (germline genetic mutations) that confer a high lifetime risk for colorectal cancer development. Some of these cases represent attenuated FAP, which has a colon cancer risk of 50% to 80%, or the I1307 K mutation in Ashkenazi Jews as well as MYH gene mutations. The remaining patients have no identifiable genetic syndrome but likely have mutations in genes that have lower penetrance or modifying effects. For example, mutations that mildly affect the Wnt signaling pathway and polymorphisms that interact with aromatic hydrocarbons have been found to mildly increase an individual’s risk for developing colon cancer.

In general, the risk of colon cancer is 5% to 6% in the general population of the United States. Having a first-degree relative with colon cancer multiplies that risk 3 or 4 times. Having second- or third-degree relatives with colon cancer substantially increases the risk 2 or 3 times. Having 2 first-degree relatives or 1 relative under age 50 years with colon cancer increases the risk 3 or 4 times. Having second- or third-degree relatives with colon cancer development.

Table 3. Amsterdam II Criteria for the Diagnosis of Lynch Syndrome

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 3 relatives with colorectal cancer or with a Lynch syndrome–associated cancer (cancer of the endometrium, small bowel, ureter or renal pelvis)</td>
<td>One relative should be a first-degree relative of the other 2 at least 2 or more successive generations should be affected at least 1 tumor should be diagnosed before the age of 50 yr tumors should be verified by immunohistochemical examination</td>
</tr>
</tbody>
</table>


IHC = immunohistochemistry.

Table 4. Revised Bethesda Guidelines for Diagnosing Lynch Syndrome

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal cancer diagnosed at age &lt; 50 yr</td>
<td>Presence of synchronous or metachronous colon cancer or endometrial, stomach, ovarian, pancreas, ureter and renal, pelvis, brain, or biliary tumors</td>
</tr>
<tr>
<td>Colorectal cancer with MSI-H phenotype diagnosed in a patient aged &lt; 60 yr</td>
<td>Patient with colorectal cancer and a first-degree relative with Lynch syndrome–related tumor (one of the cancers being diagnosed at age &lt; 50 yr)</td>
</tr>
<tr>
<td>Patient with colorectal cancer with 2 or more first- or second-degree relatives with a Lynch syndrome–related tumor, regardless of age</td>
<td></td>
</tr>
</tbody>
</table>


IHC = immunohistochemistry; MSI = microsatellite instability.
CASE PRESENTATION 2

A 51-year-old man presents with a 2-month history of diffuse abdominal pain, fever, emesis, weight loss, and episodic melena accompanied by a 10- to 15-kg weight loss over the previous 6 months. The patient had a forced exile by the British 6 years earlier to the island of St. Helena during which he had a significant decline in his health. His family history was notable for a reported history of stomach cancer in his father at age 39 years and paternal grandfather at age 40 years. The patient failed treatment with antimony potassium tartrate, a 600-mg dose of mercuric chloride, and regular enemas, and subsequently died. Postmortem analysis suggested that the patient died of an advanced stage gastric carcinoma. Subsequently, the patient’s older brother and 3 younger sisters reportedly died of stomach cancer.

• Does the patient’s family fulfill criteria for hereditary gastric carcinoma?

DEFINITIONS OF HEREDITARY GASTRIC CARCINOMA

When one defines hereditary gastric cancer, it is essential to determine the histopathologic type of gastric cancer. A modification of the Lauren histologic classification system is useful when applied to the hereditary setting. This system organizes gastric cancer into 4 main types: isolated cell type, glandular, solid, and mixed carcinoma. In the familial setting, it is necessary to categorize gastric cancer cases into 2 main histopathologic types: a group with a diffuse component (isolated cell and mixed types) and a group without a diffuse component (intestinal/glandular and solid types) because somatic mutations in the E-cadherin (CDH1) gene are seen only in the diffuse group. Thus, review of the histopathology from the candidate family is the first part of any genetic evaluation.

Hereditary diffuse gastric cancer (HDGC) has an autosomal dominant inheritance pattern and is associated with the development of gastric cancer at a young age. A workshop of the International Gastric Cancer Linkage Consortium held in 1999 has provided the best definition of familial gastric cancer syndromes. The consortium defined HDGC as that which meets the following criteria: (1) 2 or more documented cases of diffuse gastric cancer in first- and/or second-degree relatives, with at least 1 diagnosed before the age of 50 years, or (2) 3 or more cases of documented diffuse gastric cancer in a first- and/or second-degree relative, independently of age of onset. Germline mutations in the E-cadherin (CDH1) gene are felt to be responsible for the cancer susceptibility in 30% to 50% of HDGC families; the genetic factor(s) responsible for the genetic predisposition of the other families is unknown.

The definition of familial intestinal gastric cancer (FIGC) depends on the cancer incidence of the family’s country. For countries with a high incidence of gastric cancer such as Japan and Portugal, FIGC is defined as: (1) at least 3 relatives with intestinal gastric cancer, 1 of them a first-degree relative of the other 2; (2) at least 2 successive generations should be affected; and (3) gastric cancer should be diagnosed before the age of 50 years in 1 of the relatives. In countries with a low incidence of gastric cancer such as the United States and United Kingdom, FIGC is defined as: (1) at least 2 first-/second-degree relatives affected by intestinal gastric cancer, 1 diagnosed before the age of 50 years; or (2) 3 or more relatives with intestinal gastric cancer at any age. The etiology of the gastric cancer susceptibility for these FIGC families is quite complex. It has been suggested that the familial aggregation of gastric cancer can be explained in some cases by a familial clustering of Helicobacter pylori infection. Additionally, in populations with a high incidence of gastric cancer, Lynch syndrome is responsible for a subset of these FIGC families.

In the case patient’s family, the number of gastric cancer cases over several generations suggests a hereditary component regardless of the histopathology; therefore, this family would meet any of these definitions for hereditary gastric cancer.

• What is the optimal management of families that meet the criteria for HDGC?

MANAGEMENT

Although the pathology is not available for this case, let us assume that it showed diffuse gastric cancer. In this situation, one should consider referral for genetic testing and counseling due to the known association between germline mutations of the E-cadherin (CDH1) gene and diffuse gastric cancer. Lynch et al have suggested that the following points be considered when counseling asymptomatic carriers of the germline mutation of E-cadherin on choosing between endoscopic surveillance and prophylactic gastrectomy: (1) The chance of developing a clinically detectable gastric cancer in persons who carry the E-cadherin mutation is greater than 70%. (2) A diffuse gastric cancer has a mortality rate of approximately 80% once it becomes symptomatic. (3) All 7 of 7 recently reported prophylactic gastrectomies...
Genetics of Familial Gastrointestinal Malignancy

performed on patients with apparent negative endoscopic screening had occult intramucosal gastric carcinomas. (4) Even if it does not detect all cancers, endoscopy, in particular chromoendoscopy, may have the potential to detect many cancers before they metastasize. (5) If the individual opts for surgery, it should be performed by a surgeon experienced in gastric surgeries after appropriate counseling on the associated and expected morbidity of the surgery as well as the expected low (< 1%) mortality rate. (6) Patients need to be counseled on associated cancers. Female carriers need to be referred to a high-risk breast cancer screening center due to the increased risk of lobular breast cancer. It is unknown what other cancers patients with the germline mutation of E-cadherin are at increased risk for, but it is recommended that colon cancer surveillance be offered to carriers who have family members with colon cancer.

- Who was the patient in this presentation?

As you likely surmised from the patient’s history, the proband was Napoleon Bonaparte. Napoleon along with his siblings were quite aware of their cancer risk. The Bonaparte family predisposition to cancer was first discussed in the medical journals by Sokoloff in 1938. Subsequently, there has been much debate over Napoleon Bonaparte’s death; however, most experts agree that he died of gastric cancer. Assuming that the reports on his other family members were accurate, his family meets the criteria for hereditary gastric cancer and thus is the earliest known familial gastric cancer kindred.

**PANCREATIC CANCER**

**CASE PRESENTATION 3**

A 43-year-old man presents to a gastroenterologist due to concerns that his 45-year-old sister has just been diagnosed with pancreatic cancer. His father also died of pancreatic cancer at age 58 years. The patient has a history of melanoma diagnosed at age 40 years. The physician obtains a complete family history as shown in Figure 1 with the patient shown in position III-9.

- What hereditary syndromes are associated with pancreatic cancer?

**HEREDITARY CANCER SYNDROMES**

It has been estimated that hereditary factors may play a significant role in the development of pancreatic adenocarcinoma in 5% to 10% of cases. Most of these familial aggregations have an autosomal dominant
pattern of inheritance. For the majority of these pancreatic cancer–prone families, the responsible germline mutation has not been identified; however, in a minority of cases, families develop pancreatic cancer associated with known cancer syndromes, including hereditary pancreatitis, familial atypical multiple mole melanoma (FAMMM), Peutz-Jeghers syndrome, hereditary breast-ovarian cancer, Lynch syndrome, and FAP.

Hereditary pancreatitis is a disease in which the affected individuals experience recurrent episodes of pancreatitis, often at an early age of onset. These individuals often progress to typical chronic pancreatitis and are at a significant risk for developing pancreatic carcinoma. Hereditary pancreatitis is caused by gain-of-function mutations in the PRSS1 gene (also known as the cationic trypsinogen gene).

FAMMM syndrome is characterized by the familial occurrence of skin melanoma in combination with multiple atypical precursor nevi. Affected individuals are at an increased risk for developing melanoma at an earlier age as well as pancreatic cancer. The subset of FAMMM families at increased risk for pancreatic cancer has a mutation in the CDKN2A gene, which encodes for the cyclin-dependent kinase inhibitor p16 and the p53 activator p14. To date, only germline mutations in p16 have been reported in the pancreatic cancer–melanoma families.

Peutz-Jeghers syndrome is characterized by the association of gastrointestinal hamartomatous polyps and mucocutaneous pigmentation. A mutation in the STK11 gene (also known as LKB1) is responsible in the majority of cases. Individuals are at an increased risk for a variety of cancers, including pancreatic, intestinal (esophagus, stomach, small intestine, and colon), and extraintestinal (lung, breast, ovary, endometrial, and testes) cancers.

Persons diagnosed with hereditary breast-ovarian cancer not only have a predisposition to these cancers at an early age, but also have an increased risk for other cancers, including pancreatic, prostate, and stomach cancers. Mutations in both BRCA1 and BRCA2 are responsible for hereditary breast-ovarian cancer. Lynch syndrome and FAP have been previously discussed in the colon cancer section. Family members of persons with these 2 syndromes have only a modestly increased risk (< 3-fold) for developing pancreatic cancer. It is important to be cognizant of these syndromes since these patients may desire to undergo more formal genetic counseling and testing, with a goal of intervening to prevent associated cancers (eg, breast, ovarian, colorectal) or clarifying cancer risks for other family members.

- Should this patient undergo genetic testing?
- What are the options for performing surveillance testing for pancreatic cancer on the patient (proband)?

GENETIC TESTING AND SURVEILLANCE

Review of this patient’s pedigree reveals that this family has a genetic predisposition for developing pancreatic cancer and melanoma, suggesting that the patient should be tested for FAMMM syndrome. After undergoing genetic counseling and subsequent testing, this family was found to have a p16 germline mutation, confirming this clinical suspicion. This case emphasizes the importance of obtaining an extended pedigree, which can be done by a qualified genetic counselor. In this family, if one only looked at the subset of the kindred (II-2 and her progeny), the occurrence of either pancreatic cancer (II-5, III-8) or earlier age melanoma (III-8) would not have been appreciated, and the clues that suggested testing for FAMMM syndrome could have been missed.

Presently there are no approaches that have been proven effective in detecting pancreatic cancer at an early, potentially curable stage. Many centers are currently working on strategies that can identify advanced precursor lesions, thereby allowing for the treatment of a patient prior to the development of invasive cancer. Examples of advanced precursor lesions include pancreatic intraepithelial neoplasia (PanIN) 3 lesions, mucinous cystadenomas, and intraductal papillary mucinous neoplasms (IPMN) before they progress to invasive carcinoma. The low incidence of pancreatic cancer in the general population does not make it practical to screen for pancreatic cancer, but many centers offer surveillance for some high-risk groups with a genetic predisposition for developing pancreatic cancer.

Several studies have suggested that endoscopic ultrasound (EUS)-based protocols can detect advanced precursor lesions of pancreatic cancer. The University of Washington first described their surveillance experience involving 3 large pancreatic cancer–prone kindreds with an autosomal dominant inheritance pattern utilizing both EUS and endoscopic retrograde cholangiopancreatography (ERCP). The goal of surveillance was to detect early pancreatic precursor lesions (PanINs), particularly PanIN 3 lesions (carcinoma in situ). The changes seen on EUS in this study were nonspecific and have been described in patients with pancreatitis and heavy alcohol use. Every patient with an abnormal ERCP in this study had an abnormal EUS. Decisions regarding surgical resection were based on the results of the ERCP. Patients who elected to undergo surgery had precancerous (PanIN 2 or 3) changes
in the pancreas. Recently, a prospective controlled study that utilized screening EUS and computed tomography followed by ERCP in 78 at-risk relatives from pancreatic cancer–prone kindreds revealed a high prevalence of these aforementioned pancreatitis-like changes (72% by EUS and 68% by ERCP). Notably, 10% of high-risk individuals treated by subtotal pancreatectomy had precursor lesions for adenocarcinoma consisting of IPMNs (1 with carcinoma in situ).

It is reasonable to offer surveillance to persons who are felt to be at a significant risk for developing pancreatic cancer, including the case patient who is a carrier of the \( p16 \) germline mutation. Persons for whom surveillance would be appropriate include those with a hereditary cancer syndrome that increases their risk for pancreatic cancer at least 10-fold (Table 2). Whenever possible, these surveillance procedures should be performed in the setting of peer-reviewed protocols following a discussion with the patient about the limitations of current studies and their yet to be proven survival benefits.

**CASE PRESENTATION 4**

A 65-year-old man presents to a gastroenterologist over concerns that he is going to die of pancreatic cancer. He reports that his father, paternal uncle, paternal aunt, and paternal grandmother have died of pancreatic cancer (Figure 2). He was diagnosed with a basal cell carcinoma but otherwise is in good health. The patient denies smoking or excessive alcohol use. He reports that no other family members have had any types of cancer other than those previously mentioned.

- **How should this patient be advised regarding genetic counseling and screening?**

**FAMILY HISTORY AND RISK FOR CANCER**

This patient is at significant risk for pancreatic cancer as review of his pedigree shows that he is a member of a pancreatic cancer–prone family. His family does not appear to fit any known cancer syndromes (as discussed above) that are associated with an increased risk of pancreatic cancer, but several studies have demonstrated the importance of germline mutations in \( BRCA2 \) in pancreatic cancer–prone families, often without a family history of breast and ovarian cancer. These studies suggest that the risk for cancer ranges from 12% to 19% for higher risk families defined as having at least 2 first-degree relatives with pancreatic cancer; identified only 5 \( BRCA2 \) germline mutations (3%). Thus, the patient should be counselled regarding the possibility of \( BRCA2 \) mutations accounting for his family's genetic predisposition and referred to a genetic counselor to discuss this in greater detail.

The patient’s estimated risk for developing pancreatic cancer can be determined by adapting results from a prospective study of the National Familial Pancreatic Tumor Registry at Johns Hopkins University. In hereditary pancreatic cancer–prone families, defined as having at least 2 first-degree relatives with pancreatic cancer, there was a 9-fold increase in risk for developing pancreatic cancer among first-degree relatives and a 32-fold increase in risk in the subset of individuals with 3 or more first-degree relatives; a 6.4-fold increase in risk was reported for individuals with 2 first-degree relatives. A recent large study from the Icelandic Cancer Registry estimated a 2.3-fold increase in risk for individuals with a single first-degree relative with pancreatic cancer.

- **Are there any recommendations for prevention?**

**Prevention**

There are no known chemopreventive agents for pancreatic cancer. We recommend vitamin D supplements to our patients based on the results of a recent epidemiologic study that demonstrated a lower risk of pancreatic cancer with a higher intake of vitamin D (> 600 IU).
appears reasonable to advise patients regarding dietary and lifestyle choices. Most importantly, patients should be advised to not smoke based on results of several studies demonstrating that cigarette smoking increased the risk for developing pancreatic cancer 2 to 3 times in members of pancreatic cancer–prone families. There are no strong data to suggest that the use of alcohol increases the risk for pancreatic cancer. However, chronic pancreatitis, which can occur as a consequence of excessive alcohol use, is a risk factor for pancreatic cancer. Thus, from a practical standpoint, patients should be advised to use alcohol in moderation. A diet high in fruits and vegetables has been reported to be associated with a lower risk for developing pancreatic cancer, while a high intake of total and saturated fat from red and processed meat increases the risk. Patients also should be advised to exercise regularly and watch their weight since the highest risks for developing pancreatic cancer appear to be in individuals with a higher body mass index (≥ 25 kg/m²) and low total physical activity.

**ESOPHAGEAL CANCER**

Esophageal adenocarcinoma is presently the most rapidly increasing cancer in the United States. There are limited data on the familial association of esophageal cancer. It is well known that individuals with Barrett’s esophagus, a metaplastic change in the normal squamous epithelium in the lower esophagus to a columnar-lined epithelium with intestinal-type differentiation, are at increased risk for developing either an adenocarcinoma of the esophagus or gastroesophageal junction. A review on the molecular basis of Barrett’s esophagus and esophageal adenocarcinoma has been published. A familial aspect of Barrett’s esophagus that is inherited in an autosomal dominant manner has been recognized for over 20 years and appears to be associated with an increased risk for esophageal cancer development. A recent study demonstrated that approximately 10% of esophageal and gastroesophageal junction adenocarcinomas were deemed hereditary in nature. Currently, the susceptibility gene(s) responsible for the predisposition for developing Barrett’s esophagus has not been identified.

**SUMMARY**

There is growing evidence to support the importance of genetic aspects in the development of gastrointestinal cancer. Although most cases of gastrointestinal cancers are sporadic, some are associated with known genetic syndromes. In many instances, an inherited susceptibility is recognized, but the underlying genetic factors responsible for the increased cancer risk remain unidentified. It is essential for practicing gastroenterologists to obtain an adequate family history and refer for genetic counseling when appropriate since individuals in these high-risk cancer-prone families will be candidates for surveillance and prevention strategies.

**REFERENCES**

35. Rulyak SJ, Lowenfels AB, Maisonneuve P, Brentnall TA.


