by a Dukes C2 colon cancer involving the ascending colon. Three years later the patient died of recurrent colon cancer.

Discussion

Only a minority of patients with colon cancer who present with a positive family history of colon cancer will be neatly categorized into a well described cancer family syndrome such as HNPCC, familial adenomatous polyposis, or Turcot's syndrome. In identifying inherited predispositions to malignancy, several indicators are of value. These include an early age of tumor onset, multiple affected family members in successive generations, the presence of multiple primary tumors in a single individual, rare forms of cancer, and an identifiable pattern of inheritance. Both of the cases presented above fulfill the Amsterdam criteria for HNPCC [8], and demonstrate the 1-2-3 rule for this disease: 1) or more colorectal cancer cases diagnosed before age 50 years, affecting at least 2 generations, and the presence of histologically verified colorectal cancer in; 3) or more relatives. While the long interval between the development of transitional cell and colon cancers from the initial diagnosis and treatment of uterine cancer in the second patient raise the possibility that these tumors may have been radiation induced, the extent of the patient's family history and the development of multiple polyps during her illness argue otherwise.

Genetic counseling

HNPCC is a genetic condition, and therefore, not just a disease of the individual, but a disease of the family. Consequently, when a diagnosis of HNPCC is suspected, the patient and their relatives should be referred for genetic counseling. Family members need to receive accurate information concerning the natural history of the disease, lifetime cancer risks associated with the condition, issues of clinical management, and screening recommendations for at-risk individuals. This often requires extensive exploration of the family history. A 1985 study by Love et al. demonstrated that the accuracy of a patient's report concerning the cancer history in the family is dependent on their degree of relation to the family member with cancer. The primary cancer site was correctly identified 83% of the time for first degree relatives with accuracy decreasing to 67% and 60% for second and third degree relatives respectively [14]. Therefore, when possible, each reported cancer diagnosis should be confirmed by medical records.

Genetic counseling aims to provide technical information regarding the condition but also to explore with the patient and family their emotional responses to the information. Occasionally, as in case II, family members
may not have considered themselves to be at risk for an inherited cancer. While the proband in case I was aware of the extent of his family history, he waited for six months before seeking medical attention when symptoms suggestive of malignancy developed. The personal experiences of patients with cancer, whether it be their own diagnosis or close contact with an affected family member, may shape their perception of risk and level of fear. These factors impact on their daily activities and healthcare choices.

**Genetic testing**

The initial genetic counseling session with the patient and family in the cases presented above included a discussion of currently available genetic testing options, and the risks and benefits of testing. The cloning of four genes associated with HNPCC has led to the development of genetic testing for germline mutations. Of these genes, alterations in the MLH1 and MSH2 genes account for over 90% of the mutations that have been identified [15]. Currently, commercial testing is available only for these two genes.

The most informative genetic testing strategy requires that an individual with cancer be the first family member tested, as the likelihood of detecting a mutation (if one is present) is greatest in them. If a mutation is identified, predictive testing can be offered to at-risk relatives. On the other hand, if no mutation is identified, testing should not be offered. Failure to identify a mutation would represent an inconclusive result, as the sensitivity of the test depends on the method used and varies from 65%-99%. An at risk person can only be given a true negative result when a mutation has previously been documented in a family, and the at-risk individual is found not to carry that mutation.

As a result of the complexities of genetic testing, oncologists and other physicians must take care in the interpretation of test results so as not to provide false reassurance to individuals who remain truly at-risk for an inherited cancer syndrome. Erroneously indicating that an individual is 'negative' for HNPCC may lead patients to withdraw from screening programs. This potential pitfall has recently been observed among patients at risk for familial adenomatous polyposis in which misinterpretation of genetic test results by requesting physicians occurred in over 30% of cases [16].

**Risks and benefits of genetic testing**

Benefits from genetic testing occur to both individuals who test positive as well as negative for a cancer susceptibility gene. An individual who tests positive can begin a screening regimen and may be more compliant with it. Persons who receive a true negative test result can forgo the rigorous cancer screening required of at-risk and gene positive patients. Other benefits of genetic testing include the alleviation of fear and uncertainty in both gene-positive and gene-negative individuals.

In addition to the potential benefits of genetic testing there are several associated risks. Survivor guilt, as result of being 'spared' from the disease when other family
Clinical case

Hereditary nonpolyposis colorectal cancer

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Key words: colon cancer, hereditary nonpolyposis colorectal cancer, Lynch syndrome

Background

Colorectal cancer is a leading cause of cancer related death in both Europe and the United States. Approximately 20% of cases occur in familial aggregations making this disorder the most frequent form of hereditary neoplasia [1]. Consequently, patients with colorectal cancer often present with a positive family history which may have significant implications for their care. Recent advances in the genetic basis for some forms of hereditary colon cancer has led to the clinical availability of genetic testing for these patients.

Hereditary non polyposis colorectal cancer (HNPCC) is an autosomal dominant condition characterized by an early age of colorectal cancer onset (median age 44 years), an excess of proximal colon tumors (70% proximal to the splenic flexure) and of metachronous disease, and an increased risk of extracolonic malignancies within the pedigree [2]. Between 1% and 5% of all colorectal cancers may be attributable to this disorder [2, 3]. The syndrome was initially described in 1913 by Warthin, a professor of pathology at the University of Michigan [4], and subsequently in 1966 by Lynch et al. at Creighton University in Nebraska [5, 6]. Colorectal cancer was found to be the most predominant cancer in this syndrome but its recognition was not aided by distinguishing clinical or pathologic signs such as the multiple adenomas of familial adenomatous polyposis. Therefore, the syndrome was labeled HNPCC. In 1984, the terms Lynch syndrome I and II were proposed on the basis of the absence (Lynch I) or presence (Lynch II) of extracolonic malignancies such as ovarian, endometrial or gastric cancers [7]. In 1991, formal research criteria (the Amsterdam Criteria) were developed to characterize this disorder (Table 1) [8]. The discovery of microsatellite instability in almost all cancers from patients with HNPCC, and in 12%–15% of sporadic cancers [9–11], led to the association of this genetic abnormality with defects in the mismatch repair system [12]. Four HNPCC genes have been identified [13], commercial genetic testing is currently available for two of them. These four genes account for 70% of cases of HNPCC [2]. This article discusses recent discoveries in the understanding of HNPCC and the implications of these advances in the management of affected patients and families.

Case histories

Case I

A 33-year-old stockbroker with a significant family history of malignancy (Figure 1), presented for a second opinion concerning newly diagnosed colon cancer. The patient had noticed bleeding per rectum 10 months previously, and presented six months later to a local emergency room with hematochezia, syncope, and iron deficiency anemia. At colonoscopy an annular carcinoma at the splenic flexure was diagnosed, and a right hemicolectomy and transverse colectomy was performed for a Dukes B2 colon cancer with zero of 57 nodes involved. Postoperatively adjuvant therapy was recommended with five fluorouracil, leucovorin, and levamisole. Treatment was discontinued due to severe hematologic and gastrointestinal toxicity.

Case II

A 39-year-old homemaker was referred by her mother's medical oncologist for genetic counseling. During counseling it became apparent that neither she, nor her sister, were aware of the extent of their family history of cancer which extended through three generations (Figure 2). The patient's mother was initially diagnosed with uterine cancer at age 32 which was treated with surgery and radiation therapy. At age 61 transitional cell cancer of the right ureter was diagnosed, followed one year later...
members have tested positive, may occur in those with true negative results. Patients who test positive may develop anger or depression. They may experience increased anxiety about the health of their children or a period of denial which may influence their decision making. One of the largest concerns of patients is 'genetic discrimination' occurring to gene-positive individuals. Employers may be hesitant to hire or promote persons with a positive gene test result fearing that the employee may be disabled at a young age, leaving the company to face the high cost of cancer treatments. Indeed, prior to the development of cancer, carriers may be labeled as having a 'pre-existing' condition, leading to the denial of insurance coverage. A recent study polled 332 members of genetic support groups for 101 different genetic conditions; 22% of the respondents reported that they or a family member had been refused health insurance, 25% had been refused life insurance, and 13% had been denied or were let go from a job as a result of their family history [17]. Legislation has been introduced in several regions of the United States to make it illegal for insurance companies to decline health insurance on genetic grounds [18, 19]. However disability and life insurance may not come under the same legislative umbrella. In a recently conducted postal survey of insurance companies 1000 anonymous questionnaires were mailed to insurance company presidents [20, 21]. Only 79 of these surveys were returned; however, it was evident from these replies that HNPCC carriers or their children would be denied life insurance or required to pay increased premiums by 14 of 46 companies. Similar results were obtained for disability insurance.

Replication error repeat (RER) testing

Recently, there have been concerns that the Amsterdam Criteria may lead to an underestimation of the incidence of HNPCC as they do not acknowledge the contribution of extracolonic malignancies to HNPCC. In addition, incomplete and age dependent genetic penetrance, small family size, and inadequate acquisition of information about family history may limit recognition of HNPCC pedigrees. In such circumstances, RER testing may be used to help identify families which may benefit from genetic testing. RER testing involves an assessment for somatic mutations, such as nucleotide insertions or deletions, in the microsatellites or simple repeated sequences of tumor DNA. Accumulation of somatic mutations due to defects in DNA replication is termed microsatellite instability and arises in patients with HNPCC due to faulty DNA mismatch repair. RER+ve tumors are more likely to be mucinous, right-sided and poorly differentiated. Up to 92% of colorectal tumors occurring in HNPCC are RER+ve, as are 75% of the endometrial tumors in HNPCC [22, 23]. An RER-ve tumor is unlikely to have been caused by an inherited germline mutation in one of the mismatch repair genes. However, a negative RER test result does not completely rule out a hereditary form of colon cancer as the individual or family may carry a mutation in an unknown colon cancer gene that does not result in the RER phenotype. Recently the 'Bethesda Criteria' have been developed to address the shortcomings of the Amsterdam Criteria and to provide guidelines as to which patients are appropriate to refer for RER testing [24].

Screening and prevention

The presence of metachronous and synchronous colorectal cancers is a hallmark of HNPCC and is rarely observed in the setting of sporadic colorectal cancer. In a study of 10 kindreds of HNPCC, 21 of 116 patients (18%) presented with multiple cancers in the colon and rectum. In addition, the 10-year cumulative incidence of metachronous cancer was 40% if the first cancer was treated with less than a subtotal colectomy [25]. Several groups have observed a high rate of advanced colorectal cancers diagnosed within two to five years of a negative screening colonoscopy [26, 27]. Such rapid progression from adenoma to carcinoma contrasts with the findings of the National Polyp study in which the adenoma carcinoma sequence in the general population may take eight to 10 years [28, 29]. The molecular basis for this clinically significant, accelerated rate of progression to cancer is unknown.

As illustrated by both cases presented in this report, patients with HNPCC are also at higher risk of extracolonic neoplasms. In one study of 315 affected HNPCC family members, 63% of the tumors were in the colon or rectum, 8% were in the endometrium, 6% were in the stomach, 4% were in the biliary or pancreatic tree and smaller numbers were in other organs [30]. Watson and Lynch determined that a significant excess of extracolonic lesions was present in 1300 high-risk members of 23 kindreds with HNPCC (Table 2) [31]. Subsequently, it was estimated that the cumulative incidence of endometrial cancer in these families is 20% by age 70 years as compared with 3% for the general population [32]. Moreover, endometrial cancer in HNPCC appears to occur at a younger age compared to sporadic cases [31, 32]. As awareness of HNPCC increases and genetic

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Observed</th>
<th>Expected</th>
<th>O/E ratio (Poisson test result)</th>
<th>Median age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectum</td>
<td>287</td>
<td>46</td>
<td>22 (P &lt; 0.001)</td>
<td>46</td>
</tr>
<tr>
<td>Endometrium</td>
<td>53</td>
<td>46</td>
<td>21 (P &lt; 0.001)</td>
<td>46</td>
</tr>
<tr>
<td>Stomach</td>
<td>17</td>
<td>41</td>
<td>4.1 (P &lt; 0.001)</td>
<td>54</td>
</tr>
<tr>
<td>Small intestine</td>
<td>10</td>
<td>0.4</td>
<td>25 (P &lt; 0.001)</td>
<td>53</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>7</td>
<td>1.4</td>
<td>4.9 (P &lt; 0.05)</td>
<td>66</td>
</tr>
<tr>
<td>Kidney</td>
<td>10</td>
<td>3.1</td>
<td>3.2 (P &lt; 0.01)</td>
<td>66</td>
</tr>
<tr>
<td>Ureter</td>
<td>5</td>
<td>0.2</td>
<td>22 (P &lt; 0.001)</td>
<td>56</td>
</tr>
<tr>
<td>Ovary</td>
<td>13</td>
<td>3.6</td>
<td>3.5 (P &lt; 0.001)</td>
<td>40</td>
</tr>
<tr>
<td>Breast</td>
<td>19</td>
<td>22</td>
<td>0.9 (NS)</td>
<td>51</td>
</tr>
</tbody>
</table>

Abbreviations: O/E – observed/expected; NS – not significant.
Adapted from Watson and Lynch [31].
testing becomes more prevalent, these estimates may change.

Prevention of HNPCC relies primarily on screening of at-risk members. Those at risk are unaffected individuals known to carry a mutation in one of the mismatch repair genes, those in pedigrees with known mismatch mutations, and members in families with an autosomal dominant colorectal cancer by pedigree analysis. At present, the optimal screening strategies for HNPCC families are unknown. Nevertheless, the risk of colorectal cancer in HNPCC is estimated to be 68% to 75% by age 65 [2,33]. The average age of diagnosis of colorectal cancer is 44 years, but not infrequently individuals in the third decade of life are affected. Consequently, full colonoscopy to the cecum is recommended every one to three years beginning at age 20 to 25 [34,35].

As mentioned above, endometrial cancer is the second most common cancer seen in HNPCC. Also, women with HNPCC are also at 3.5-fold higher risk of ovarian cancer than the general population. Therefore, annual gynecologic screening beginning at age 25 to 35 is recommended by the latest consensus panel [34]. The optimal method of screening has not been determined; choices include endometrial aspirate or transvaginal ultrasound at each visit.

 Authorities recommend subtotal colectomy with ileorectal anastomosis in HNPCC-associated mutation carriers with either colorectal cancer or adenomas. Lifetime estimates of cancer risk are not yet available for these patients; however it is important to note that for the first 12 years after abdominal colectomy patients have a 3% risk of developing a metachronous tumor in the remaining rectum every three years [36], therefore, more consideration should be given to total proctocolectomy. More controversial is the role of prophylactic subtotal colectomy in patients that are unaffected carriers of mismatch gene mutations. In women with mismatch repair gene mutations, insufficient evidence exists to recommend for or against the use of prophylactic hysterectomy and oophorectomy to reduce cancer risk [34].

There is no data on the effectiveness of other interventions to prevent cancer development in HNPCC. The use of nonsteroidal anti-inflammatory agents is considered to reduce the risk of sporadic colorectal cancer [37], but has not been studied in HNPCC. Although a life style incorporating high physical activity and a diet high in fiber, fruits and vegetables, and low in fat and red meat appears protective against sporadic cancer and is advocated by many authors [e.g., 38], there is no direct evidence supporting a protective effect in HNPCC.

Outcomes

Case I

Genetic testing of the mismatch repair genes was offered to the 33-year-old affected proband. He chose not to pursue commercial genetic testing at this time, because of concerns that insurance discrimination would affect his children. RER testing was also discussed emphasizing that this test is a screening test that does not provide definitive information regarding specific familial genetic mutations. Because RER testing is less costly, many families prefer to begin with this rather than testing for a germline mutation.

The patient was particularly concerned about his siblings' increased risk for colorectal cancer, as they were approaching his age of cancer diagnosis. He believed that his siblings would benefit from genetic testing and was encouraged to discuss the possibility of testing with them. If they were interested, they would receive genetic counseling individually to facilitate independent decision-making about testing. Individual genetic counseling sessions also reduce family pressure about genetic testing. We consider that such referrals are also appropriate for at-risk family members who are reluctant to undergo predictive testing as it may improve their knowledge about HNPCC and their compliance with screening guidelines. The patient was retreated with 5-fluorouracil and leucovorin administered weekly for six months as adjuvant therapy. As he had received a subtotal colectomy, screening sigmoidoscopy was recommended at least yearly for the rest of his life.

Case II

In discussing the implications of her family history with the 39-year-old proband in case II, the consultation focused on her personal risk of developing cancer. To help define her risk germline testing was offered. This testing would begin with a family member with a personal history of cancer. If the affected family member had a mutation identified in one of the mismatch repair genes, she could then in turn elect predictive testing. This testing would, with virtually 100% accuracy, determine whether she carried the same cancer susceptibility gene.

When presented with this option she declined testing as she felt strongly that she did not wish to know if she was a gene carrier. She believed that this knowledge would evoke ongoing fears which would negatively affect her quality of life, causing her to constantly wonder each morning whether this was the day that she would become ill. Instead, she chose to use the information presented about HNPCC and her cancer risk to make choices about her healthcare. At the time of consultation, she had not yet had a colonoscopy examination. Following the visit she expressed her intention to schedule one and to adhere to the screening recommendations. In addition, she has chosen to focus on dietary and lifestyle changes that may help to reduce her cancer risks.

References

2. Marra G, Boland CR. Hereditary nonpolyposis colorectal can-