MANAGEMENT OF HIGH GENETIC RISK OF BOWEL CANCER

Barbara Leggett ■ Royal Brisbane and Women's Hospital, Herston, Queensland
Email: barbara_leggett@health.qld.gov.au

Abstract

The identification and appropriate genetic counselling of individuals at high genetic risk of bowel cancer is an excellent example of how improved understanding of the genetic basis of disease can lead to a reduction in morbidity and mortality. The key to good management is to make as accurate a diagnosis of the family syndrome as possible, since different syndromes require different surveillance regimens. Diagnosis requires not only verification of cancer diagnoses in the family, but also consideration of the number and types of polyps detected at colonoscopy and in colectomy specimens. In addition, assays to detect microsatellite instability in cancer specimens aid in the diagnosis of Lynch syndrome. Since so much can be done to prevent cancer developing in at-risk individuals, a major challenge in the future is how best to disseminate knowledge within a family and how to encourage compliance with appropriate surveillance.

Bowel cancer offers an opportunity for prevention available for virtually no other solid tumours. Not only can mortality be reduced by early detection of cancer, but in many cases the very occurrence of cancer can be greatly reduced without major surgery. This is because the disease develops in pre-malignant polyps which can be removed during surveillance colonoscopy, upper endoscopy and enteroscopy. Even in cases where the polyps are too numerous to safely control endoscopically, they can be identified in the pre-malignant phase and appropriate surgery planned electively.

However, endoscopic procedures are relatively invasive and carry some risk of morbidity and mortality. To use them appropriately in individuals at high genetic risk requires understanding of the natural history of the various genetic syndromes. Most polyps are adenomas and occur predominantly in the colon and rectum. They generally take between five and 15 years to evolve into invasive cancer. Thus for individuals with a moderately increased risk of bowel cancer, without the features of the specific genetic syndromes discussed below, colonoscopy every five years is appropriate to interrupt the natural history and greatly reduce the risk of cancer. If polyps are identified, increased frequency of colonoscopy may be appropriate according to published guidelines.[1]

For all the specific inherited susceptibility syndromes discussed below, the natural history of the polyps differs significantly from the above. Thus, the first and most important step in recommending appropriate surveillance is to make the most accurate diagnosis possible, based on the verified clinical history of as many family members as possible and including consideration not only of cancers but also the numbers, location and histological characteristics of polyps. As discussed by Kirk (in this issue of *Cancer Forum*), this may be confirmed by finding a causative germline mutation in an affected family member. But if the family has convincing clinical features of a genetic syndrome, a negative mutation search in a definitely affected family member should be regarded as "inconclusive" rather than negative; the family should be managed according to the clinical diagnosis, with periodic attempts to clarify the mutation status as technology and knowledge advances.

Familial Adenomatous Polyposis (FAP)

In classical FAP, individuals develop over 100 and often thousands of adenomatous polyps in the second and third decade of life.[2] Although each individual polyp is no more likely than any other adenoma to progress to cancer, the sheer numbers of adenomas and the early onset mean that colorectal cancer is virtually inevitable, with an average age of onset of 39 years. Adenomas also occur in the duodenum and periampullary adenocarcinoma is the most common threat to life in patients who have undergone colectomy.[3] Patients are also at risk of other extracolonic tumours, including intra-abdominal fibromatosis (desmoid tumours), papillary carcinoma of the thyroid and hepatoblastoma, however the lifetime risk of these is relatively low and there is no evidence to support screening.

FAP is due to mutation in the APC tumour suppressor gene and is inherited as an autosomal dominant trait with very high penetrance. About 30% of cases are due to de novo mutations.[4] Mutation searching is successful in over 85% of families. There is some genotype-phenotype correlation in classical FAP, however there is heterogeneity in clinical course, even between family members with the same mutation. Thus identification of the exact mutation is of limited value in planning management.

The recommended surveillance protocol for at-risk individuals is flexible sigmoidoscopy, annually or biennially, from age 12-15 years to at least age 30-35 years.[5] Once polyps are identified, prophylactic colectomy is planned. Appropriate surgical options are either total colectomy and ileorectal anastomosis, or restorative proctocolectomy with pouch formation. Lifetime surveillance of the rectum or pouch is needed because of the ongoing risk of cancer. If the causative mutation has been identified in the family, predictive

testing is usually offered at the age at which flexible sigmoidoscopy screening would commence. Mutation positive individuals should then undergo annual sigmoidoscopy. Surgery is not planned until there is pathological confirmation of the development of adenomas. Regular upper endoscopy to identify duodenal adenomas is advised after age 25.[5] Management of duodenal polyposis is very challenging as it is technically difficult to remove the polyps endoscopically and duodenectomy may be associated with high morbidity and mortality. Management of such patients should be in a tertiary centre.

It is now recognised that certain APC mutations result in an attenuated phenotype where individuals develop less than 100 adenomas, onset is at a later age and adenomas tend to be flat and may only be present in the proximal colon.[2] The lifetime risk of colorectal cancer is very high. Surveillance needs to be with colonoscopy, rather than flexible sigmoidoscopy, since significant adenomas may be present in the proximal colon when none have developed distally. Because of the later age of onset, surveillance does not usually need to commence until age 18. In some cases prophylactic surgery can be avoided, if polyp numbers remain low enough for the colonoscopist to be confident that all adenomas can be removed at each colonoscopy, but this decision needs to be individualised. Patients are also at risk of duodenal adenomas.

MYH-associated polyposis

The phenotype of this autosomal recessive condition mimics attenuated FAP. This is not surprising, since the molecular defect is biallelic, inactivating germline mutations in the base excision repair gene MYH, which normally produces a protein which repairs G to T (guanine to thymine) transversions in the APC gene.[2] Thus individuals with this genetic defect frequently inactivate APC in colonocytes and develop large numbers of adenomas at a young age. Affected or at-risk individuals need to be managed as described above for attenuated FAP. Generally, genetic testing is only offered for the common mutations, however more extensive mutation searching is worthwhile, especially in individuals with a typical clinical picture and who are heterozygous for a common mutation.

Hereditary Non-polyposis Colorectal Cancer/ Lynch Syndrome

The natural history of colorectal carcinogenesis is fundamentally different in hereditary non-polyposis colorectal cancer (HNPCC) as compared to that described above in moderate risk families, FAP and MYH-associated polyposis.[6] Despite its name, cancer does develop in polyps in this syndrome, but rather than there being a vast excess of adenomas, individual adenomas in individuals with HNPCC have a much greater risk of rapidly developing into invasive cancer. The estimated risk of colorectal cancer in affected individuals is approximately 70% by age 70 years. About two-thirds of cancers are in the proximal colon, unlike sporadic colorectal cancers which are more common distally.[7] Development of multiple primary cancers is common. The estimated lifetime risk for affected women developing endometrial cancer is 40-60%.[7] There is also an increased risk of cancers of the small intestine, ovary, hepatobiliary system, kidney and ureter.

HNPCC is an autosomal dominant condition due to germline mutation in one of the family of DNA mismatch repair genes. Most families have mutations in MLH1 or MSH2, but a significant minority have mutations in MSH6 or PMS2. Unlike FAP, de novo mutations are very rare and there is nearly always a family history of the disease, if the family history is truly known. Mutation of MSH6 is associated with a somewhat lower risk of colorectal cancer with a later age of onset, however the risks of endometrial cancer are at least as high as for the other genetic defects.[7] Dysfunction of the mismatch repair system leads to defective repair of mutations occurring during normal cell division. Thus in susceptible tissues, such as colonic polyps, somatic mutations occur in important cancer-related genes and cancer rapidly develops.

In cancers that develop due to defective DNA mismatch repair, repetitive DNA sequences, known as microsatellites, are especially prone to accumulate mutations and microsatellite instability (MSI) can be assayed in cancer tissue as a biomarker of HNPCC. Interpretation of MSI results needs to include an understanding that 10% of sporadic colorectal cancers exhibit MSI due to somatic inactivation of MLH1. Interestingly, both HNPCC and sporadic colorectal

Figure 1: *Guidelines for patients whose cancers should be tested for MSI to identify possible hereditary non-polyposis colorectal cancer (Lynch Syndrome)*

Bethesda Guidelines

1. Colorectal cancer under 50 years.
2. Synchronous or metachronous colorectal cancer or other HNPCC-associated cancer regardless of age.
3. Colorectal cancer with MSI-H histology under age 60.
4. Colorectal cancer with one first degree relative with colorectal cancer or other HNPCC-associated cancer with one of the cancers being diagnosed under 50 years.
5. Colorectal cancer with two or more first or second degree relatives with colorectal cancer or other HNPCC-associated cancers regardless of age.

cancers which display a high level of MSI, have distinctive histological features including mucinous histology, poor differentiation and tumour infiltrating lymphocytes.[8] Deficiency in mismatch repair in cancer tissue can also be assayed by performing immunohistochemistry for MLH1, MSH2, MSH6 and PMS2 proteins. Absence of one of these proteins indicates mismatch repair deficiency. Since these proteins act as heterodimers and loss of one partner destabilises the other protein, loss of MLH1 is accompanied by secondary loss of PMS2 and loss of MSH2 by secondary loss of MSH6. The results of MSI testing correlate very closely with immunohistochemistry, although occasionally a protein may be detectable on staining despite being dysfunctional.[9]

The ability to test cancer tissue for MSI is very useful in diagnosing HNPCC, since the phenotype of an individual patient is much less distinctive than in any of the polyposis syndromes. Before the genetic defect was understood the Amsterdam criteria, which specify a very strong family history of colorectal cancer with early age of onset and autosomal dominant inheritance, were used as a diagnostic tool.[7] However, many HNPCC families do not meet these criteria, especially if the family size is small and some families with other, as yet not understood genetic predispositions, do meet them. It is now recommended that MSI and/or immunohistochemistry be performed on the cancers of a much broader range of individuals who have some indication of possible HNPCC.[5,7,10,11] These criteria have been formalised into the Bethesda criteria as outlined in Figure 1.[11]

In 2006, the Royal College of Pathologists of Australasia issued a position statement recommending there be no requirement for additional consent or genetic counselling prior to performing MSI or immunohistochemistry for mismatch repair proteins. If this testing indicates HNPCC is likely in an individual meeting the Bethesda criteria, they should then be offered genetic counselling and further investigation to confirm the diagnosis, as outlined by Kirk in this issue of *Cancer Forum*, for other high risk families. If a family is referred directly to a genetic service with a history suggestive of HNPCC, archival cancer material on affected family members will be retrospectively tested to help confirm the diagnosis before a mutation search is undertaken. Immunohistochemistry is especially helpful in this regard since it indicates which gene is likely to be mutated.

Once a family has been diagnosed as transmitting HNPCC, all affected individuals and those at risk of the disease should be offered surveillance. If the germline mutation has been identified, those at risk can be offered predictive testing so that only those carrying the mutation need continue with surveillance. Surveillance should be by colonoscopy to the caecum annually or at least once every two years, beginning at age 25 or five years younger than the youngest affected family member (whichever is the earliest).[5,7] This frequent screening is essential to prevent interval cancers which would otherwise occur due to the different mechanism of carcinogenesis in HNPCC.

Individuals with HNPCC often develop cancer in very small, recently formed adenomas. There is no evidence that CT colography ("virtual colonoscopy") is a safe alternative and it is known to have poor sensitivity for small polyps. The efficacy of screening for extracolonic cancers has not been demonstrated, however it is generally recommended that patients be offered the following tests annually:

- transvaginal ultrasound from age 30 to 35 with endometrial sampling if there is endometrial thickening;
- CA-125 measurement (after the menopause);
- consideration of upper endoscopy in families where upper GI tract cancers have occurred.

If an individual with HNPCC presents with colorectal cancer, consideration should be given to total colectomy and ileorectal anastomosis because of the high risk of metachronous cancer. In addition, if the patient is female and past childbearing years, prophylactic hysterectomy and oophorectomy should be discussed. However, these decisions need to be individualised according to co-morbidities and patient preference.

Juvenile polyposis

This is a rare condition, characterised by the histologically distinctive juvenile polyp with cystically dilated tubules embedded in abundant lamina propria. The epithelium lining, the tubules and covering the surface of the polyp is normal, but when the polyps are numerous and longstanding there is a significant risk of malignancy. All the malignancies associated with the condition occur in the gastrointestinal tract, however are not confined to the colon.[12] It is inherited as an autosomal dominant condition with variable penetrance and is genetically heterogeneous. The two genetic causes defined so far are mutations in SMAD4 and BMPR1A and interestingly, both these genetic defects would be expected to disrupt the TGF (transforming growth factor) beta signalling pathway. A closely related but distinct disorder is Cowden Syndrome, due to mutations in PTEN. Although some of the polyps in Cowden Syndrome may have the histology of juvenile polyps, the majority of polyps do not. There is essentially no risk of gastrointestinal malignancy in Cowden Syndrome, which is instead associated with breast and thyroid cancer.

It is recommended that patients at risk of juvenile polyposis start having colonoscopy from age 15 or earlier if symptomatic.[12] Upper endoscopy and even capsule endoscopy should be considered, especially if there is a family history of gastric or small bowel cancer.[13] If possible, all polyps should be removed and if they are too numerous, surgery should be considered, especially if polyps start to show dysplasia.

Peutz-Jeghers syndrome

This rare syndrome is also characterised by a particular histological type of polyp, in which there is prominent hypertrophy of the smooth muscle layer which extends and branches up towards the epithelium, which does not usually show dysplasia. Polyps are most common in

the small intestine. In addition to conferring a risk of malignancy, they are associated with acute bowel obstruction. There are extra-intestinal manifestations, including mucocutaneous pigmentation on the lips and an increased risk of breast, pancreatic, ovarian and testicular cancers.[14] It is an autosomal dominant condition and in many families is due to mutation in STK11 (LKB1).

De novo mutations are common so there may be no family history. Surveillance with regular colonoscopy and endoscopy should commence in the late teens or earlier if there are symptoms. A most important aspect of management is surveillance for small intestinal polyps beyond the reach of the endoscope and capsule endoscopy, followed by push enteroscopy which has made a major contribution to better management of these patients.

Hyperplastic polyposis

This increasingly recognised syndrome is characterised by multiple (>20), large (>1cm) and proximal hyperplastic polyps.[15] It is now recognised that this syndrome confers a high risk of colorectal cancer. This has prompted a review of the pathological classification of hyperplastic polyps, which were previously thought to have no malignant potential. It is now recognised that the polyps occurring in this syndrome are in fact a particular form of serrated polyp named a sessile serrated adenoma.[16] This syndrome is associated with a marked tendency to hypermethylation of the CpG islands in the promoters of key cancer-associated genes. Many of the cancers have silenced MLH1 by hypermethylation of its promoter and thus show a high level of MSI. However, this condition is distinct from HNPCC (Lynch syndrome) and screening for a germline mutation in MLH1 is not productive.[5]

In many cases of hyperplastic polyposis there is no family history of polyposis or even colorectal cancer and the genetic aetiology of the condition is unclear. No predictive genetic testing can be offered at present. It seems likely that the polyps precede development of cancer by several years and it is recommended that first degree relatives be offered screening as for moderate risk families (five yearly colonoscopy from 10 years younger than the youngest affected subject in the family).[5] Management of affected individuals is complex and clear guidelines have only recently emerged. It is recommended that sessile serrated adenomas be completely removed endoscopically and that colonoscopy be repeated every one to two years if the subject meets the definition of hyperplastic polyposis (>20 polyps).[5,16] The risk of cancer increases if the polyps show dysplasia. In these subjects and those in whom polyps are too numerous to be safely removed during colonoscopy, colectomy and ileorectal anastomosis should be considered.

References

1 Winawer SJ, Zauber AG, Fletcher RH, Stillman JS, O'Brien MJ, Levin B, et al. Guidelines for Colonoscopy Sureveillance after Polypectomy: a consensus update by the US Multi-society Task Force on Colorectal Cancer and the American Cancer Society. Gastroenterology. 2006;130:1872-85.

2 Jass JR. What's new in hereditary colorectal cancer? Arch Pathol Lab Med. 2005;129:1380-4.

3 Aravantid ML, Jagelman DG, Romania A, Fazio VW, Lavery IC, McGannon E. Mortality in patients with familial adenomatous polyposis. Dis Colon Rectum. 1990;33:639-42.

4 Rozen P, Macrae F. Familial adenomatous polyposis: the practical applications of clinical and molecular screening. Familial Cancer. 2006;5:227-35.

5 Australian Cancer Network Colorectal Cancer Guidelines Revision Committee. Guidelines for the prevention, early detection and management of colorectal cancer. Sydney (Australia): The Cancer Council Australia and Australian Cancer Network; 2005.

6 Kinzler KW, Vogelstein B. Lessons form hereditary colorectal cancer. Cell. 1996;87:159-70.

7 Lindor NM, Petersen GM, Hadley DW, Kinney AY, Miesfeldt S, Lu KH, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch Syndrome. JAMA. 2006;296:1507-17.

8 Jass JR, Do K-A, Simms LA, Iino H, Wynter C, Pillay SP, et al. Morphology of sporadic colorectal cancer with DNA replication errors. Gut. 1998;42:673-9.

9 Lindor NM, Burgart LJ, Leontovich O, Goldberg RM, Cunningham JM, Sargent DJ, et al. Immunohistochemistry versus microsatellite instability testing in phenotyping colorectal tumours. J Clin Oncol. 2002;20:1043-8.

10 Southey MC, Jenkins MA, Mead L, Whitty J, Trivett M, Tesoriero AA, et al. Use of molecular tumour characteristics to prioritize mismatch repair gene testing in early-onset colorectal cancer. J Clin Oncol. 2005;23:1-9.

11 Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Ruschoff J, et al. Revised Bethesda guidelines for hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome) and microsatellite instability. J Natl Cancer Inst. 2004;96:261-8.

12 Chow E, Macrae F. Review of Juvenile Polyposis Syndrome. J Gastroenterol Hepatol. 2005;20:1634-40.

13 Leggett BA, Thomas LR, Knight N, Healey S, Chenevix-Trench G, Searle J. Hereditary Juvenile Polyposis is not due to a defect in the APC or MCC genes. Gastroenterology. 1993;105:1313-6.

14 Leggett BA, Young JP, Barker M. Peutz-Jeghers syndrome: genetic screening. Expert Rev Anticancer Ther. 2003;3:518-24.

15 Chow E, Lipton L, Lynch E, D'Souza R, Aragona C, Hodgkin L, et al. Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. Gastroenterology. 2006;131:30-9.

16 Snover DC, Jass JR, Fenoglio-Preiser C, Batts KP. Serrated polyps of the large intestine. Am J Clin Pathol. 2005;124:380-91.