National Screening Committee

Screening for Late Onset Genetic Disorders

Colorectal Cancer

October 2000

SCREENING FOR LATE ONSET GENETIC DISORDERS

COLORECTAL CANCER

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BACKGROUND

Colorectal cancer (CRC) is an important health problem in the UK. It is the third commonest cancer with a lifetime population risk of approximately 1 in 25 of developing the disease and approximately 30,000 cases and 15,000 deaths per year. Pre-symptomatic diagnosis can be achieved using screening procedures such as faecal occult blood testing or more invasive procedures such as colonoscopy, sigmoidoscopy and barium imaging. The National Screening Committee is currently running a pilot project to test the feasibility of population screening using faecal occult blood testing. Testing will target a population aged 50-69.

Approximately 20-25% of patients with CRC have a family history of the disease. Recent data from a Scandinavian twin study indicate that 35% of all colorectal cancer is attributable to a major genetic component. However, the majority of cases of colorectal cancer occur by chance or due to a shared environment, rather than due to inherited germ line mutations. Epidemiological and molecular evidence suggests that at least 7 major mutations are involved in the induction and progression of a colorectal malignancy. Two conditions can be identified in which the CRC is initiated by germline mutations in defined genes.

Two to five percent of all CRC is due to Hereditary Non-Polyposis Colon Cancer (HNPCC), a dominantly inherited disorder of cancer susceptibility with a high penetrance for CRC. The risk is

higher in men (approximately 80% by age 70) than females (approximately 40% by age 70) but females also have a 40-65% lifetime risk of developing endometrial cancer. Causative mutations have been identified in one of five different mismatch repair genes (MMR). MMR genes are responsible for recognising and correcting errors that arise during the replication of DNA. The proficiency of MMR genes can be determined by molecular analysis of simple repetitive DNA sequences, known as microsatellite repeat sequences. If MMR genes are deficient, these sequences become unstable in tumour DNA and this manifests as tumour microsatellite instability. The presence of a germline mutation in an MMR gene is associated with a very high risk of CRC. The disease tends to arise at an early age and the tumours tend to occur along the length of the colon and rectum. (The distal colon is the commoner site for sporadic CRC). Mutation of MMR genes also increases the risk of cancers in extra-colonic sites.

Familial Adenomatous Polyposis (FAP) accounts for a progressively smaller proportion of all cases of colorectal cancer, as a result of successful identification of families and prophylactic surgery. Currently 0.07% of all cases are due to FAP but these are mostly due to new (sporadic) mutations. When cancer does arise in FAP it tends to be in the 4^{th} decade of life. FAP cases are readily identifiable by the distinctive phenotype of multiple colonic polyps. FAP will not be considered further here.

In addition to these two conditions for which causative genes have already been identified, about 10% of patients with CRC have a family history consistent with genes of moderate to major effect, but for whom the causative genes have yet to be identified.

CRC caused by genetic predisposition tends to present at a younger age than its sporadic counterpart. Therefore, if screening is introduced, these people would need to undergo disease surveillance earlier in their life than is appropriate for people with a background population risk . Furthermore, in view of the higher cancer risk, there is considerable rationale in employing more

sensitive and specific surveillance techniques than methods such as the faecal occult blood test used for the population screening programme. These tests are however, more invasive. Known mutation carriers are at such high risk of developing CRC that disease surveillance is already part of accepted clinical practice for these people.

If a special programme were to be established to 'screen' for inherited CRC, this would require two elements. Firstly, a CASE FINDING approach would need to identify groups of people who are at high risk of the disease by nature of genotype, phenotype or family history. Inherent in this approach is a definition of high risk categories that would benefit from intervention. Secondly a programme of DISEASE SURVEILLANCE would be offered to these people to identify pre-symptomatic disease. The issue is further complicated by the fact that carriers of HNPCC mutations are also susceptible to other cancers including endometrium, stomach, small bowel and urinary tract. The risk of endometrial cancer in mutation carriers is 40% and may be sufficiently common to consider disease surveillance, but there is no good evidence that screening pre-symptomatic women provides benefit. Screening for ovarian cancer might be carried out at the same time as surveillance of the endometrium but the risk is only around 9%. The risk of gastric cancer is 20% but much of the data is historical and there is no evidence for benefit in gene carriers. Nonetheless, upper GI endoscopy could be carried out at the same time as colonoscopy and is well tolerated and associated with very low morbidity. All other cancers associated with HNPCC mutations are too rare to merit surveillance.

People who carry HNPCC mutations have a very high lifetime risk of developing CRC and it is therefore easier to justify the use of interventions (that carry their own risk of morbidity and mortality) in patients in this group. In people with a lower risk than this, careful consideration must be given to weighing the risk and benefit of disease surveillance. It is important to achieve national agreement on the level of risk for which an individual will be offered disease surveillance and the nature of this surveillance. This will ensure that people in different regions receive consistent care.

ASSESSMENT OF RISK

This is one of the most difficult areas to be considered. There is general but not complete agreement about the criteria used for risk stratification.

High risk individuals include all people that are known to carry a germline mutation in HNPCC, FAP and other monogenic syndromes predisposing to CRC. People who fulfil modified Amsterdam Criteria (AC) (see box) are also considered to be at high risk. There is also a need to allow clinical flexibility to enable Clinical Geneticists to classify people at high risk if they are likely to carry a mutation but do not fulfil AC (For example a pair of relatives with small bowel and endometrial cancer have an 80% chance of carrying an MMR without fulfilling modified AC)

Modified Amsterdam Criteria

- There should be at least 3 relatives with an HNPCC associated tumour (CRC, endometrium, small bowel, ureter or renal pelvis.
- One relative should be a first degree relative of the other two
- At least two successive generations should be affected
- The diagnosis of CRC should be made befor ethe age of 50 in at least one individual
- FAP should be excluded
- Tumours should be verified by histological examination

Moderate risk is determined by a person's family history- based on the number of affected relatives, their relationship to each other and the age of onset of the cancer. These people have at least a 10% lifetime risk of dying from CRC but not enough features to suggest a monogenic predisposition as defined above. This risk corresponds to a relative risk between 2 and 5 times the population risk. (See Appendix for fuller discussion and criteria for definitions)

Low risk people are all those who do not fit the moderate/high criteria

CASE FINDING

Several methods could be used to identify high risk individuals and gene mutation carriers:

1. **Using the family history as a screening tool.** This could be undertaken routinely in primary care, for example at registration checks. There is some evidence that this method does not cause any increase in anxiety. However, primary care workers do not generally have the skills or knowledge to take and interpret a family history. The accuracy of risk assessment using the family history has also been questioned, especially when the family is small. There are agreed criteria to identify high risk patients (Modified AC) who should then be referred for consideration of testing for a mutation. There are generally agreed criteria to identify moderate risk people (see appendix) but family history at this level is a weaker indicator of risk than age. A patient with a relative risk of 5 due to their family history has approximately the same absolute risk as the general population risk of a person 10-15 years older. In absolute terms a 40 year old with a relative risk of 5 still has less than 1% chance of developing CRC in the next 10 years. The family history as a screening tool also presents problems of verification of the family history where there are doubts about diagnosis and age of onset in other family members. Most health professionals with the exception of clinical geneticists are not skilled in this work.
2. **Genetic screening of the population.** The HNPCC mutations that have been identified are found in mismatch repair genes (MMR) which are situated at several loci and at each locus there are many different mutations. It is therefore necessary to undertake initial gene testing in a person who has developed CRC. Due to constraints of availability and technology, genetic testing currently will be restricted to cases with a high chance of carrying a mutation. Current research suggest that there may be rationale in offering mutation analysis for affected patients in certain subgroups stratified by age at onset, independent of the degree of family history. While Amsterdam Criteria reliably enrich for mutation carriers, it has been shown that people with lesser degrees of family history also may carry MMR gene mutations. One study in Edinburgh of 180 patients who developed colorectal cancer when aged under 45yrs (Dunlop et

al) 18% had a germ line MMR mutation. However, only 23% of these had a family history which fulfilled AC, thereby emphasising that an integrated approach to mutation detection is required.

3. **Cascade case finding** is one potential approach to identifying cases in the general population. Patients with CRC could be identified prospectively through hospital and GP databases. Those with early onset disease or a strong family history could identify a group that is enriched for mutation carriers. Such targeted genetic testing could identify a cohort of relatives at high and moderate risk and their relatives could then be offered testing and/or disease surveillance. This approach increases the number of mutations identified for a given number of people screened and has proved successful in Familial Hypercholesterolaemia (FH). However, the screening tool (blood test for serum cholesterol) and intervention (lipid lowering drug) are much more straightforward in FH than CRC

The yield (sensitivity and specificity), morbidity and cost of these methods are not known and further research is needed.

RISK STRATIFICATION

PATIENTS WITH A PROVEN HNPCC MUTATION (or those who fulfill modified AC) have a high lifetime risk of developing CRC and are therefore the group most likely to benefit from disease surveillance. Some families have a pedigree suggestive of a dominantly inherited gene mutation but none is identified. It is reasonable to include these people in this highest risk group on the advice of a clinical geneticist.

PATIENTS WITH A HIGHER RISK DUE TO FAMILY HISTORY ALONE are more problematic. Firstly there are the inaccuracies discussed above of using the family history for risk assessment. Secondly, because the absolute risk of these patients is less than patients with a proven

mutation, the benefit/risk ratio for any given intervention will be lower (and may not be in favour of intervention). Various guidelines have been produced to try to define this moderate risk group and the most appropriate programme to offer them. However, there is currently no national consensus.

DISEASE SURVEILLANCE

The main issues concerning disease surveillance are:

- Which method should be used?
- How often should this be offered (and what is the starting age)?
- In patients with HNPCC, what surveillance should be offered for the other cancers that these patients are susceptible to?

Which method?

There are advantages and disadvantages of both colonoscopy and barium enema. There is some evidence to suggest that the sensitivity of barium enema is lower than colonoscopy, although this is disputed in some literature. If a barium enema is positive for polyps then colonoscopy is indicated for snare polypectomy and histological assessment. Although colonoscopy has a higher morbidity and mortality than barium enema (which must be taken into account when considering risk/benefit analysis) it is currently the preferred method. There is also acknowledged variation in the effectiveness of colonoscopy with different operators. Visualisation of the whole of the colon and rectum is essential in HNPCC in view of the proximal location of many tumours arising in such cases. Multiple colorectal adenomas (>3 polyps) identified at one colonoscopy, adenoma greater than 1cm diameter and villous adenomas will also put a patient into a high risk group. However, an initial colonoscopy is required to identify these risk factors.

Patients with HNPCC

Although there have been no randomised controlled trials of colonoscopy in these patients, it is unlikely that a trial will ever be ethically acceptable. In a 15year comparative study of two groups

of HNPCC family members accepting or declining follow up by 3 yearly colonoscopy (133 subjects, 119 controls) with HNPCC (Jarvinen et al. Gastroenterology 2000), there were no deaths in the group complying with surveillance compared with 9 deaths in the non-compliers (p=0.003). The study showed a 62% reduction in cancer and 65% reduction in overall mortality. Although the composition of the "control" group is open to criticism, this is the best quality evidence available and it indicates a beneficial effect of regular colonoscopy.

Uterine cancer is the only other cancer in HNPCC patients with a high enough frequency to justify disease surveillance. Interventions include chemprophylaxis, disease surveillance using scans or prophylactic surgery. However, trials are needed to evaluate the effectiveness of these treatments.

Higher risk patients without proven mutation

Various regimes have been recommended but the risk/benefit ratio suggests that patients offered surveillance by colonoscopy should have a relative risk of six to benefit (Dunlop and Campbell BMJ 1997; 314:1779-80). Due to the low absolute risk of developing CRC in people aged less than 60yrs, triennial colonoscopy for 10 years would have to be performed on 1054 people aged 30yrs, or 210 people aged 40yrs, or 181 people aged 50yrs to prevent one cancer death in high moderate risk populations defined by family history criteria (See appendix). There have been no trials to compare surveillance regimes with different age at first colonoscopy and frequency of colonoscopy. Results of pilot population FOB screening schemes may indirectly provide valuable information to inform this debate.

DOES SCREENING OF HIGH RISK PATIENTS FOR CRC FULFIL THE WILSON/JUNGER SCREENING CRITERIA?

Subsections (a) and (b) refer to case finding and disease surveillance respectively

1) The condition screened must be important

CRC is a common cancer with an overall 60% mortality. A significant number of cases result from a predisposition due to germline mutation or have a significant family history. These cases tend to present at younger ages so curing these patients will mean more life years saved.

2) Acceptable treatments must be available

Surgical and other interventions are acceptable treatments for CRC

3) Facilities for diagnosis and treatment should be available

Colonoscopy, radiology and surgical and other treatments are all currently provided. However, the capacity to undertake the increased work that screening would produce is not known. If consensus is reached on which patients to screen and the frequency of this screening, some capacity could be made available by not offering screening to people who do not match consensus criteria. However, estimates suggest that there are 820 people aged 40-49 years and 660 people aged 50-59 years per million population with a high moderate risk (One first degree relative with CRC onset under 45 years and/or two first degree relatives). Screening would result in significant increased workload for each health economy.

4) There should be a recognised latent period

The adenoma/carcinoma sequence is accepted for CRC with a latent period between 5-10 years. This period may be shorter for HNPCC carriers. Germline mutation carriers have a latent period from birth to the appearance of the first adenoma.

5) There should be a suitable test or examination

a) High risk cases could be systematically identified by the use of a family history or screening for gene mutations. The family history has inherent inaccuracies and there is no consensus or research on how this tool could be used. Screening for genetic mutations is available in many parts of the UK from DNA diagnostic laboratories for people with a strong family history.

b) There are a number of suitable tests; colonoscopy is the currently preferred method. There is some evidence to support regular colonsocopy surveillance in HNPCC patients but little evidence to support its use in other higher risk categories.

6) The natural history of the disease should be understood

The penetrance of gene mutations and the adenoma/carcinoma sequence for CRC are well established.

7) There is an agreed policy on whom to treat

a) There is agreement (those who fulfil modified AC) on which patients should be considered at highest risk, and therefore should be offered gene testing. Once tested, those with an MMR mutation are indisputably at high risk. There is general but not total agreement on what patients fall into the moderate risk group.

b) There is agreement on the benefits of regular colonoscopy for HNPCC patients (but debate on the regime to use). There is some agreement on the intervention regime to offer those at moderate risk, based on expert opinion only.

8) The cost of case finding should be economically balanced

Some economic evidence on cost effectiveness is found in the Appendix

CONCLUSIONS

1) There is currently no case to offer population screening to identify people at high risk of inherited CRC on the basis of family history.
2) The benefit from intervention is greatest for patients with established mutations of HNPCC. If resources are limited, priority should be given to identifying the estimated 319 people per million population who carry an MMR mutation. This should be done firstly by ensuring that genetic registers for CRC are established in each region and families of people with known mutations are properly followed up and advised. Secondly, by testing cancer patients with high risk characteristics and cascade case finding. It is strongly recommended that these people are offered disease surveillance.
3) It is ethically easier to discuss these issues if patients present themselves to health professionals, either with CRC itself or a concern about their family history of CRC (as opposed to being

called for screening). In the absence of a screening programme these patients should be accurately assessed. Many primary care professionals will need assistance with these tasks through the use of guidelines or the computerised risk assessment tools that have been developed. Those at higher risk should continue to be referred to an appropriate specialist department (Clinical Genetics or Colorectal surgeon) for full assessment of risk. There should be a national consensus on which patients fall into the low and moderate risk category and what intervention should be offered to those at moderate risk.

4) Further research is required to establish the best methods to identify higher risk patients and also the most effective and cost effective interventions to offer them.

Acknowledgements

This report is based on papers delivered at a workshop organised by the National Screening Committee in Edinburgh on 10th October 2000 in Edinburgh. Thanks are due to the speakers on that day: Dr Harry Burns, Professor John Burn, Professor Malcolm Dunlop, Dr Harry Campbell, Dr Hilary Burton, Professor Sandy McCall-Smith, Professor Neva Haites, Professor John Scholefield, Dr Sheila Lawson, Dr Alan Stevenson, Dr Wendy Atkin and Dr Mary Porteous.

APPENDIX

This is a report of the Eastern Region Cancer Genetics Working Group giving a more detailed account of the background to this paper