



## INHERITED COLON CANCERS

Grobbelaar *et al.*<sup>1</sup> and Ramesar *et al.*<sup>2</sup> (in this issue) have identified germline mutations in certain families with two different types of inherited colorectal cancers. This means that blood tests are now available in South Africa for clinical use in these particular families. Within the families these DNA-based tests can separate individuals with the mutation that causes cancer from those who do not have it. Those with a mutation may pass the family-specific mutation to their children.

Hereditary non-polyposis colon cancer (HNPCC) accounts for between 1% and 6% of all colorectal cancers.<sup>3,4</sup> Familial adenomatous polyposis (FAP), although better known, accounts for approximately 1%. These two forms of familial colorectal cancer have a dominant inheritance pattern. The DNA tests do not apply to most patients with colorectal cancers (sporadic), or to patients with colorectal cancer who have close relatives with the disease but no clearly defined inheritance pattern.

The two types of inherited colorectal cancer have very different clinical features. Although the colorectal cancers associated with HNPCC follow the usual polyp-cancer sequence, very few polyps develop. The disease has two identifiable forms: a site-specific form (Lynch I) that is confined to the colon, and a site-nonspecific form (Lynch II) where family members may in addition develop cancers at other sites including the stomach, urinary tract, small intestine, biliary system, ovary, pancreas, breast, and endometrium.<sup>5</sup> Colonic cancers associated with HNPCC typically manifest in patients in their forties, are often multiple and are more commonly situated in the proximal colon.<sup>6</sup> FAP is characterised by the development of multiple colonic polyps during the late teens or early twenties, and with the development of colorectal cancer in the third decade.<sup>7</sup> Colorectal cancer will develop in more than 90% of individuals who have a mutation in the gene underlying either HNPCC or FAP.

The studies of Grobbelaar *et al.*<sup>1</sup> and Ramesar *et al.*<sup>2</sup> have shown that with the availability of new mutation detection techniques it is now simpler to detect new mutations within families. Testing will therefore become more readily available. It is important that these tests are used correctly as there are consequences that are not immediately obvious.

The implications that arise from mutation testing within a family should not be underestimated. The emotions resulting from test results can include anger in those who test positive, while those who test negative may be overwhelmed by guilt

for escaping a disease that affects a close relative. Testing positive may also have financial implications regarding life and medical insurance. Knowledge of mutation status is extremely useful for those who test negative, as they can be reassured and discharged from medical care. The advantage, however, for those who test positive is the potential prevention of cancer. Because of these factors, consent for genetic testing is an extremely important issue. It is essential that individuals at risk for these diseases are counselled by a qualified genetics counsellor before testing and that they undergo post-test counselling when the results are released. The Nuffield Council<sup>8</sup> and the British Medical Association<sup>9</sup> recommend that individuals who undergo testing should be of an age where they are legally responsible and have adequate understanding of the issues involved in both positive and negative test results. Dickenson<sup>10</sup> argues that testing of individuals younger than 18 years of age should be performed provided that the individual requests testing and has adequate understanding of the implications of the test results. Should an individual choose to have a genetic test, a genetics counsellor should release the result, in writing and verbally during the post-test counselling session. Results should not be released to anyone else (family members, doctors or insurance companies), unless the tested individual authorises this in writing.

How, then, should these diseases be managed now that genetic testing is available?

## HEREDITARY NON-POLYPOSIS COLORECTAL CANCER

An accurate family history is the best clinical method of detecting HNPCC. Surveillance of individuals at 50% risk by examination of the family tree (or pedigree analysis) should begin at age 25 or at least 5 years before the earliest cancer onset in that family.<sup>11</sup> Colonoscopy is the only effective surveillance tool for colonic lesions because the tumours tend to be proximal.<sup>12</sup> In addition to colonoscopy, regular mammography, abdominal ultrasound and endometrial sampling are needed for those individuals who belong to families with the site-nonspecific form of the disease.

In HNPCC more than five genes are known to underlie the more common forms of the disorder. For this reason it is advisable to submit families suspected of having HNPCC for research so that a 'designer' test for that specific family can be developed. Usually blood (or pathological specimens) from at least three affected individuals and an equal number of unaffected first-degree relatives (older than 50 years) is required to lead researchers to the gene that is involved in a particular family. The relevant gene is then investigated thoroughly for disease-causing mutations. Once the biological effect of the mutation has been confirmed through its tracking



with all affected individuals, pre-symptomatic mutation testing should only be offered to family members who have reached the age of legal consent. Pre- and post-test counselling by a qualified genetics counsellor is essential. Individuals who test negative can be reassured and discharged from follow-up. Those who choose not to be tested and those who test positive should be entered into a surveillance programme with colonoscopy performed every 2 - 3 years until the risk of dying from other causes exceeds the risk of dying from colorectal cancer.<sup>13</sup>

Prophylactic colectomy for mutation-positive individuals is not yet established management. This is because the risks associated with colonoscopy are much lower than those of surgery and polypectomy may prevent the development of cancer. Total colectomy with ileo-rectal anastomosis may become a candidate operation in this group of patients because rectal cancer is uncommon.<sup>14</sup>

## FAMILIAL ADENOMATOUS POLYPOSIS

At-risk family members should undergo an initial rigid or flexible sigmoidoscopy in their early teens. If sigmoidoscopy is negative, then it should be repeated every 2 years until 18 years of age. If biopsy-proven adenomatous polyps are identified, prophylactic surgery should be considered. This may be delayed until the individual finishes school because the risk of cancer is low in young asymptomatic individuals. Individuals should be offered genetic testing by a qualified genetics counsellor once they have attained the age of legal consent. If the individual tests negative for the family-specific mutation, he/she can be reassured and discharged from further medical care. Individuals who test positive should continue to undergo regular sigmoidoscopic examinations at 2-yearly intervals. Individuals who do not wish to undergo genetic testing should have sigmoidoscopy every 2 years until they are 45 years old, or longer if the family has late-onset disease. Families with a known mutation and a history of early onset of cancer should be treated according to the clinical trend of that specific mutation.

The role of prophylactic surgery, limitation of family size, use of donor gametes, pre-implantation diagnosis and selective termination of pregnancy based on prenatal diagnosis will become clearer with experience.

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