

Inherited colorectal cancer: A plea for a national registry

Colorectal cancer (CRC) is the third most common cancer and cause of cancer-related death worldwide.^[1] The majority of individuals who develop CRC have sporadic disease, but up to 20% may have an inherited predisposition.^[2] The two most common forms of autosomal dominant inherited colorectal cancer disorders are hereditary non-polyposis colorectal cancer (HNPCC), or Lynch syndrome, and familial adenomatous polyposis (FAP).^[3-8] The interesting publication by Vergouwe *et al.*^[9] in the February issue of *SAJS* highlights the high incidence of inherited CRC in a low-incidence area in South Africa. The authors postulate that inherited CRCs may constitute a significant portion of the total disease burden of CRC in South Africa. To put the implications of this article in context, it is important to understand the advances in understanding of the genetics and their implication for early detection and treatment of patients and their families with these hereditary conditions. Lynch syndrome is the commoner of the two, accounting for 2 - 7% of inherited colorectal cancers, with FAP accounting for less than 1%.^[6,10]

FAP is an autosomal dominant disorder with 100% penetrance, caused by mutations in the adenomatous polyposis coli gene located on chromosome 5q21-q22.^[11] Mutations are detected in over 80% of individuals with FAP and most others are detected phenotypically. Prophylactic colectomy is indicated for individuals with the disease, and they should be enrolled for surveillance for extracolonic manifestations, especially duodenal polyps.^[12,13] Family members with mutations should be screened after proband testing, using family trees and genetic testing. Prophylactic surgery and surveillance for these individuals result in decreased mortality from FAP.^[14]

Terminology in HNPCC can be confusing. The term Lynch syndrome should be reserved for individuals in whom a germline mutation in a mismatch repair (MMR) gene has been identified. Familial colorectal cancer syndrome X should be the preferred term when referring to a family meeting the Amsterdam criteria, but without an identifiable mutation.^[15] HNPCC is often used as an umbrella term including both these groups, although calls have been made to retire the term.^[10]

The importance of identifying individuals with germline mutations lies in enrolling them in screening programmes to allow for detection of polyps and early cancer. Intensive screening for colorectal cancer by colonoscopy as well as prophylactic gynaecological surgery reduces the incidence of Lynch syndrome-related tumours and mortality.^[16,17]

The diagnosis of Lynch syndrome has evolved over the last two decades to include family history, tumour histopathological characteristics, immunohistochemistry and testing for microsatellite instability (MSI), as well as germline genetic testing, as modalities for making the diagnosis. The Amsterdam criteria were proposed in 1990^[18] and revised in 1997 to identify families at risk of HNPCC.^[19] These criteria were proposed before

laboratory methods were in clinical use. The Amsterdam II criteria have a sensitivity of 78% in detecting individuals with Lynch syndrome.^[20] Improved understanding of the clinical and histological manifestations of Lynch syndrome led the National Cancer Institute to create the Bethesda guidelines in 1996, to identify colorectal cancers that should undergo testing for MSI. These guidelines were revised in 2004.^[21,22] Individuals meeting the Amsterdam or Bethesda criteria, but without any other laboratory features of Lynch syndrome, should be labelled as familial colorectal cancer syndrome X and be enrolled in the appropriate screening programme. The risk of developing colorectal cancer in these individuals is lower than in families diagnosed with Lynch syndrome, and they are not at increased risk of extra-colonic malignancies.^[23]

MSI testing is currently used as the 'gold standard' in many centres to exclude individuals lacking MSI, who are highly unlikely to have Lynch syndrome. Tumours testing MSI high (MSH-H) are then further tested with immunohistochemistry, and patients with tumours that display loss of one of the MMR proteins should then be offered genetic testing. In Lynch syndrome, there is an inherited mutation in the gene coding for one of the MMR genes *MLH1*, *MSH2*, *MSH6* and *PMS2*. Tumours of patients with these mutations have a functional loss of one of these MMR proteins or gene products, and more than 90% of these tumours will lack expression of the involved protein.^[24-26] MSI testing, however, is labour intensive and time consuming and requires a skilled molecular geneticist.

Immunohistochemistry is a cost-effective substitute for MSI testing as the first screening tool for Lynch syndrome^[27] and is currently used in our unit to detect tumours with possible MMR deficiency. When immunohistochemistry shows absence of an MMR gene product, the patient is offered germline genetic testing for that specific gene. If immunohistochemistry shows presence of all gene products but there is a strong clinical suspicion, MSI testing should be offered.

The Vergouwe study showed that in a low-prevalence area for CRC, inherited cancers form a bigger proportion of the total burden of disease and hence represent a target for focused screening and surveillance.^[9] In developed countries and locally, this strategy has been shown to be cost-effective and reduces mortality.^[16,28] There are very few, if any, other hereditary cancer registries in southern Africa and the African continent like the Lynch syndrome registry from the Western and Northern Cape, which provided the impetus for the Vergouwe study.^[9] One way to start such a registry is to identify patients at risk by using the inexpensive immunohistochemistry technique used by Vergouwe *et al.*, which detects absence of the hMLH1 gene product on all resected colorectal cancers.^[9] Those identified in such a manner should undergo genetic counselling,^[5,6] and targeted screening of the appropriate family members should be offered. Genetic nurse

counsellors are a cost-effective alternative to clinical geneticists and are invaluable in the formulation and maintenance of family trees, which is an important part of a cancer registry.^[29]

There is a need for colorectal surgeons and their association to establish such a registry and to implement focused surveillance programmes, which ultimately will save lives.

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