Early detection of colorectal cancer

Colorectal cancer is common and survival is strongly related to the stage of the disease at diagnosis.

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Colorectal cancer (CRC) is the third most common cancer and cause of cancer-related death worldwide.[1] Although the majority of individuals who develop CRC have sporadic disease, up to 20% may have a genetic predisposition.[2] Survival is strongly related to the stage of the disease at diagnosis. Where the cancer is locally confined, survival of over 90% has been reported.[3] Randomised controlled trials have shown that screening programmes using faecal occult blood and flexible sigmoidoscopy reduce mortality from CRC by early cancer detection as well as detecting advanced adenomas which are likely to develop into cancers.[4,5] Case-controlled trials have shown decreased mortality from CRC using colonoscopy as screening tool,[6] and there are on-going randomised trials to study this.[7]

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Screening of the average-risk person

Persons of average risk have a lifetime risk of developing colorectal cancer of about 5%. Average risk is defined as a person over the age of 50, with no other risk factors for CRC other than age. The average risk person is therefore an asymptomatic person with no family history of CRC or a first-degree or second-degree relative who developed CRC over the age of 60 years.

In practice there are two broad categories of CRC screening, namely faecal occult blood and endoscopic screening. Faecal occult blood tests (FOBTs) are based on the premise that CRCs bleed and therefore FOBTs will detect mainly asymptomatic cancers. Endoscopic tests will detect early cancers as well as pre-malignant polyps.

FOBTs are non-invasive, cheap and easy to use. The screened person does not require bowel preparation or sedation. Cancers bleed only intermittently and the sensitivity of a single FOBT is about 30%. If a programme of repeated testing is implemented, the sensitivity of FOBTs can be as high as 90%.[4] Studies have shown a cumulative reduction in CRC mortality of 21% at 18 years, using a biennial screening strategy with FOBTs.[8]

Endoscopic screening can be done using flexible sigmoidoscopy or colonoscopy. Flexible sigmoidoscopy is less invasive as it does not require full bowel preparation, it can be done after 2 phosphate enemas and sedation is not required. Flexible sigmoidoscopy is technically less demanding than colonoscopy. It allows for inspection of the mucosa of the left colon with tissue biopsy or removal of polyps. Detection of CRC using screening flexible sigmoidoscopy reduces cancer-related mortality by 31%.[9] However, adenomas and cancers proximal to the left colon may be missed when flexible sigmoidoscopy is used.

Colonoscopy visualises the mucosa of the entire colon and in experienced hands has a sensitivity for detecting advanced adenomas and cancers of up to 100%. It is the conclusive examination after any other positive screening test.[10] Colonoscopy is more invasive, as it requires full bowel preparation as well as sedation. A skilled endoscopist is required and there is morbidity associated with this procedure. Consequently, compliance with colonoscopy screening tends to be lower than in other screening methods. There are currently no randomised trial data to support a decrease in mortality when colonoscopy screening is used. Colonoscopy screening is based on the assumption that this method is superior to other screening tests and some indirect evidence.

There is no recognised screening programme for CRC in South Africa. In the USA, screening for CRC using colonoscopy, flexible sigmoidoscopy or FOBT is recommended. The only screening tool recommended by the European Union is FOBT. However, many European countries recommend screening using colonoscopy. Currently there is no evidence to show which screening modality is the most cost-effective for the average-risk individual. However, there is a general consensus that the average-risk individual should be offered a screening colonoscopy at the ages of 50, 60 and 70.

Increased risk for CRC as a result of family history

Up to 1 in 4 patients who develop CRC will have a family history of the disease.[11] The family physician can use 3 simple questions to screen for a family history of CRC:

- Have any relatives had colorectal cancer or a pre-cancerous polyp?
- If so, how many and were these first-degree relatives (parent, sibling or child) or second-degree relatives (grandparent, cousin, niece or nephew)?
- At what age were these cancers or polyps diagnosed?

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The magnitude of risk due to family history is influenced by the number of family members affected, whether they are first- or second-degree relatives, and the age at diagnosis.

The American College of Gastroenterology guidelines of 2008 suggest the following for screening persons at increased risk of CRC due to family history:[12]

- Definition of high-risk individual: single first-degree relative with CRC or advanced adenomas diagnosed at less than 60 years of age, or 2 first-degree relatives with CRC or advanced adenomas.
- Screen with colonoscopy.
- Start screening at age 40 or 10 years before the age of the youngest relative's diagnosis.
- Repeat screening every 5 years.

These recommendations are not evidence-based.

Familial colorectal cancer syndromes

Up to 5% of people who develop CRC have an inherited mutation. Of the familial CRC syndromes, familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), or Lynch syndrome, are the most common. Lynch syndrome is the commoner of the two, accounting for 1 - 3% of all persons developing CRC, while FAP accounts for fewer than 1%.

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Familial adenomatous polyposis syndrome

FAP is an autosomal dominant disorder caused by a mutation of the APC gene, which is located on chromosome 5. Because it has a 100% penetrance, all individuals with this mutation will develop CRC. Even though the majority of individuals with the disease have a known family history, some patients have sporadic mutations. Mutations in the APC gene are detected in approximately 80% of families with FAP and the rest are detected using colonoscopy which shows numerous colonic polyps at a young age.

Because of the high cancer risk, prophylactic colectomy is indicated in all with the disease. Colectomy is usually done at school-leaving age. These individuals are screened for extra-colonic manifestations of the disease. The most common extra-colonic cancer in patients with FAP is duodenal malignancy.

Hereditary non-polyposis colorectal cancer

HNPCC is an autosomal dominant disorder caused by germ line mutations in DNA mismatch repair (MMR) genes. It is characterised by the development of colorectal, endometrial and various other cancers at a young age.

Terminology in HNPCC can be confusing. The term Lynch syndrome should be reserved for individuals where a germ line mutation in an MMR gene has been identified. Familial colorectal cancer syndrome X should be the preferred term for a family meeting the Amsterdam Criteria, but without an identifiable mutation. HNPCC is often used as an umbrella term to include both these groups, although calls have been made to retire the term.

HNPCC is diagnosed using family history, clinical criteria, histopathological criteria and laboratory tests. The family physician plays an important role in identifying individuals at risk of HNPCC by obtaining a detailed family history. The Revised Amsterdam Criteria (Table 1) are designed to identify families who should be referred for further testing to diagnose or exclude Lynch syndrome. These criteria can be remembered as a simple 3, 2, 1 rule: 3 relatives, 2 generations, 1 of which was diagnosed before the age of 50.

All individuals and families that fulfil the Amsterdam Criteria should be referred for colonoscopic surveillance as well as further laboratory testing to diagnose or exclude Lynch syndrome.

Lynch syndrome

Families with mutations in MMR genes develop CRC with certain clinical and histopathological characteristics. The Revised Bethesda Criteria (Table 2) were proposed to identify individuals likely to have a mutation in one of the MMR genes, in addition to the family history proposed by the Amsterdam Criteria.

Tumours found in patients meeting the Revised Bethesda Criteria are tested with either immunohistochemistry or microsatellite instability (MSI) testing. If the immunohistochemistry or MSI testing identifies an individual who is likely to have a mutation in one of the MMR genes,

Table 1. Revised Amsterdam Criteria

- At least 3 relatives with HNPCC-related cancer (CRC, cancer of the endometrium, small bowel, ureter or renal pelvis)
- One should be a first-degree relative of the other two
- At least two successive generations should be affected
- At least one should be diagnosed before the age of 50 years
- Familial adenomatous polyposis should be excluded

Table 2. Revised Bethesda Criteria

Tumours from individuals should be tested for MSI in the following situations:

- Colorectal cancer diagnosed in a patient less than 50 years of age
- Presence of synchronous or metachronous colorectal or other HNPCC-associated tumours, regardless of age
- Colorectal cancer with MSI-H histology diagnosed in a patient less than 60 years of age
- Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under the age of 50 years
- Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumours, regardless of age

the patient is offered genetic counselling and testing. The aim of genetic testing is to identify the specific mutation of the MMR gene responsible for Lynch syndrome.

The importance of identifying individuals with germ line mutations lies in enrolling these individuals into screening programmes to allow for polyp and early cancer detection. Intensive screening for CRC by colonoscopy, as well as prophylactic gynaecological surgery, reduces the incidence of Lynch syndrome-related tumours and mortality.[13,14] If a germ line mutation has been identified in an individual, family members can be tested for that specific mutation. All members with the mutation should be enrolled in the screening programme, whereas those without the mutation can be screened as an average-risk individual.

Families meeting the Amsterdam Criteria but with no identifiable mutation should be labelled as 'familial colorectal cancer syndrome X' and be enrolled into appropriate screening programmes. These individuals are at a lower risk of developing CRC than those with Lynch syndrome, and are not at an increased risk of developing extra-colonic HNPCC-related malignancies.

Conclusion

CRC is a disease with high prevalence, which has a long pre-malignant, asymptomatic course. There are acceptable and effective screening tools as well as improved outcomes and decreased mortality when the disease is detected and treated early. This makes CRC a condition that is ideal for screening. To ensure cost-effectiveness of screening programmes, individuals should be classified into risk categories. Appropriate screening programmes aimed at the different risk categories reduce mortality from this disease.

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In a nutshell

- Colorectal cancer is the third most common cancer worldwide.
- It is an ideal disease to detect through screening.
- For cost-effective screening patients should be risk categorised.
- Screening tools include faecal occult blood testing, flexible sigmoidoscopy and colonoscopy.
- Randomised trials have shown a reduction in mortality from colorectal cancer using faecal occult blood testing and flexible sigmoidoscopy screening programmes.
- Even though there are no randomised trials to support its use, colonoscopy is perceived to be a superior screening tool and is recommended by the American Gastroenterology guidelines for colorectal cancer screening.
- A significant proportion of individuals developing colorectal cancer will have a family history of the disease.
- The most common familial colorectal cancer syndromes are hereditary non-polyposis colorectal cancer and familial adenomatous polyposis syndrome.
- The cornerstone for diagnosing a hereditary colorectal cancer syndrome is by obtaining a detailed family history.
- Appropriate screening and surveillance for colorectal cancer can save lives.