Screening for colorectal cancer

With access to one of the few population-based colorectal cancer screening programs in the world, Australian patients have the opportunity to have bowel cancer prevention incorporated into their health maintenance plans. Screening asymptomatic people can detect cancers at an earlier, and therefore more curable, stage, resulting in a reduction in mortality.

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Colorectal cancer (CRC) is the second leading cause of cancer-related death in Australia. In 2006, there were more than 13,500 new diagnoses of CRC, and more than 3800 deaths associated with the disease.[1] The risk of CRC in Australia up to the age of 85 years is one in 12.[1]

It is well established that screening asymptomatic people who are at average risk of CRC can detect cancers at an earlier, and therefore more curable, stage, theoretically resulting in a reduction in mortality.[2,3] In Australia, since its launch in May 2006, the National Bowel Cancer Screening Program (NBCSP) has had a measurable impact on the stage of CRC found at diagnosis, with 40% of asymptomatic cancers detected in the NBCSP being stage I compared with 14% of symptomatic cancers.[4] Reports of an improvement in survival are anticipated. The suggested bowel cancer

IN SUMMARY

- **Screening asymptomatic people who are at average risk of colorectal cancer (CRC) can detect cancers at an earlier, and therefore more curable, stage, theoretically resulting in a reduction in mortality.**
- **Three risk categories have been identified to stratify patients into appropriate screening programs – high, increased and average risk.**
- **Patients with features of an inherited CRC syndrome are at high risk of CRC and should be advised to pursue genetic counselling and, if appropriate thereafter, genetic testing for significant gene mutations.**
- **Individuals may be at increased risk of CRC based on family or personal history of previous adenomatous polyps or CRC, or a personal history of inflammatory bowel disease.**
- **Patients with one first-degree relative before the age of 55 years or two first-degree relatives at any age with CRC should be screened regularly starting at the age of 50 years or 10 years before the age at which the earliest case of CRC occurred in the family.**
- **Stool examinations are noninvasive tests that include faecal occult blood tests (FOBTs) such as faecal immunohistochemical testing (FIT) and also faecal DNA tests.**
- **Direct detection of adenomatous polyps and CRC is possible with use of a barium enema, CT colonography, flexible sigmoidoscopy or colonoscopy.**
- **Colonoscopy is the common end-point for all screening studies, and is considered the gold standard for the diagnosis of both colon and rectal polyps and malignancy.**

Bowel cancer screening pathway

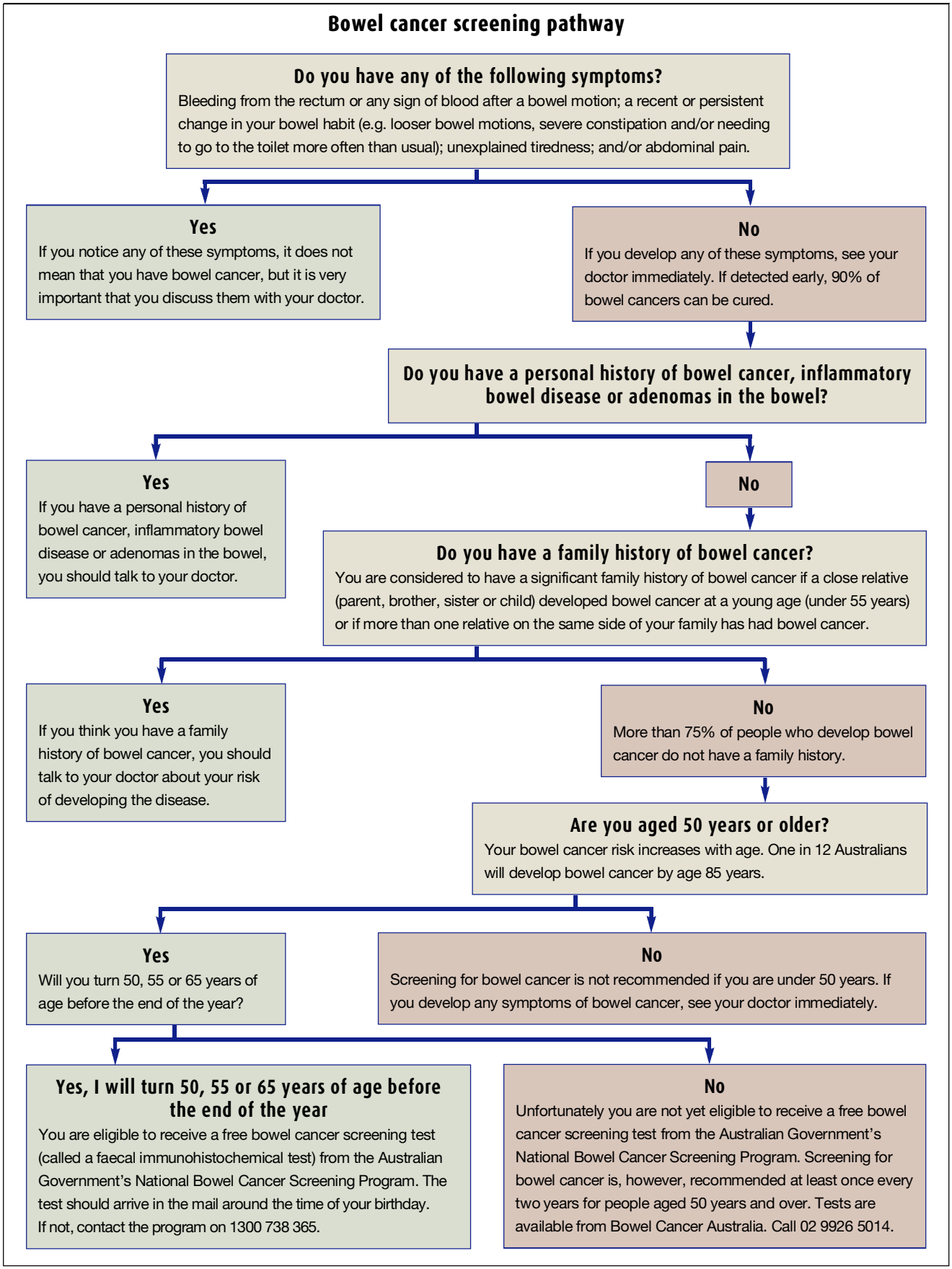

Table 1. Summary of screening recommendations for individuals at high risk of colorectal cancer[5]

Condition	Age to begin	Interval	Test	Comment
FAP	12 to 15 years	Every one to two years	Flexible sigmoidoscopy	Genetic testing Consider early colectomy
HNPCC	25 years*	Every one to two years	Colonoscopy	Genetic testing Vigilance for non-colonic HNPCC-related cancers

ABBREVIATIONS: FAP = familial adenomatous polyposis, HNPCC = hereditary nonpolyposis colorectal cancer.
* Or five years before youngest family member developed colorectal cancer.

screening pathway as advocated by Bowel Cancer Australia is shown in the flowchart on page 26.

Individual risk of colorectal cancer

Three risk categories have been identified to stratify patients into appropriate screening programs – high, increased and average risk. Only 25% of new cases of CRC occur in those with easily identifiable risk factors. The remaining 75% occur in patients considered at average risk. Individuals with a high risk of CRC can have up to a 100% chance of developing CRC in their lifetime, and this group includes those with hereditary risk factors for CRC, such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis CRC (HNPCC).

Individuals with an increased risk of CRC include those with a personal or family history of colon adenomatous polyps or cancer, and those with a personal history of long-standing idiopathic inflammatory bowel disease (IBD; either Crohn's disease or ulcerative colitis). Individuals with an average risk of CRC are those older than 50 years with no personal or family history of CRC or colonic adenomatous polyps or no personal history of long-standing IBD.

High-risk group

Patients with features of an inherited CRC syndrome, such as FAP and HNPCC, should be advised to pursue genetic counselling and, if appropriate thereafter, genetic testing for significant gene mutations. This is important for the purposes of defining familial risk, and sometimes assists in treatment planning of the affected individual. The NHMRC screening recommendations for individuals at high risk of CRC are given in Table 1.[5]

Familial adenomatous polyposis

FAP is an autosomal dominant condition resulting from a germline mutation of the *APC* gene. Although most patients with FAP have a family history of the disease, 20% of affected cases are due to spontaneous mutations and, therefore, could be the first affected member of the family. FAP accounts for only 1% of all CRC; however, its penetrance is almost always complete and patients with FAP have a risk of developing CRC of almost 100%.

Patients with classic FAP start to express their phenotype in the early teenage years with the development of adenomas; however, cases of attenuated FAP are also being increasingly recognised. In patients with attenuated FAP, there are less than 100 adenomas present, often only in the proximal colon, and they tend to develop at a later age. The progression to CRC is also slower than in patients with classic FAP.

When an *APC* gene mutation has been identified in a family, individuals within the family can be evaluated by genetic testing for the *APC* gene mutation. Alternatively, they can be enrolled into a colonic screening program from their second decade of life until such time when colectomy is deemed by both physician and patient to be the best treatment option. The colonic screening program involves annual flexible sigmoidoscopy until colonic adenomas are detected and annual colonoscopy thereafter.[6]

It is important to note that patients with FAP are also at increased risk of duodenal (and ampullary) cancers and adenomas, and gastric adenomas. Therefore, upper endoscopic surveillance is also recommended for patients with FAP, including use of a side-viewing scope to evaluate the ampulla.[7] This surveillance should continue after a colectomy.[7] Additionally, *Helicobacter pylori* infection should be tested for and eradicated in patients with FAP because of the increased risk of chronic active gastritis and subsequent gastric adenomas in the presence of infection.[7]

Hereditary non-polyposis colorectal cancer

HNPCC is the most common hereditary syndrome associated with CRC. It comprises 3 to 5% of all cases of CRC, and tends to cause more right-sided cancers than occurs in the population with sporadic non-HNPCC CRC. HNPCC is associated with several other cancers, including endometrial, ovarian, pelviureteric, gastric, small bowel, pancreatic and hepatobiliary cancers. Although disease penetrance is less than with FAP, almost 70% of individuals with HNPCC will eventually develop a malignancy.[8,9]

continued

Table 2. Revised Bethesda criteria for clinical evaluation of risk for HNPCC[8]

- CRC before age 50 years
- Synchronous or metachronous CRC or other HNPCC-related tumours,* regardless of age
- CRC with MSI-high morphology before age 60 years
- CRC with one or more first-degree relative with CRC or other HNPCC-related tumours,* one cancer diagnosed before age 50 years or an adenoma before age 40 years
- CRC with two or more relatives with CRC or other HNPCC-related tumours,* regardless of age

ABBREVIATIONS: CRC = colorectal cancer, HNPCC = hereditary nonpolyposis colorectal cancer, MSI = microsatellite instability.

* Colorectal, endometrial, ovarian, pelvi-ureteric, gastric, small bowel, pancreatic or hepatobiliary.

Patients may be clinically screened for HNPCC using the revised Bethesda criteria (Table 2).[8] Individuals who fulfil the criteria should have any tumour stained and examined immunohistochemically for the presence of mismatch repair gene products (proteins hMLH1, hMSH2, hMSH6 and hPMS2). Those patients with tumours that have a negative stain suggestive of a deficient protein should be offered genetic testing. Those patients with tumours that stain positively on genetic testing, or patients at risk of CRC when genetic testing is unsuccessful in an affected proband, should undergo colonoscopy every two years starting at age 20 to 25 years or five years younger than the youngest case of CRC in the family, until age 40 years, then annually thereafter.[5] Separate screening guidelines exist for the many other cancers affecting patients with HNPCC.

Increased-risk group

Individuals may be at increased risk of CRC because of a family or personal history of adenomatous polyps or CRC, or a personal history of IBD (particularly long-standing pancolitis). These patients have a two to sixfold increased risk of developing CRC, and should ideally be screened by colonoscopy. The NHMRC screening recommendations for individuals at increased risk of CRC are given in Table 3.[5]

Family history

Patients with one first-degree relative with CRC before the age of 55 years or two first-degree relatives with CRC at any age should be regularly screened starting at the age of 50 years or 10 years before the age at which the earliest case of CRC occurred in the family. These patients should be screened with a colonoscopy every five years assuming a normal preceding colonoscopy.[5]

Individuals with one first-degree relative with CRC at the age of 55 years or older or two or more second-degree relatives with CRC at any age should be screened as for an individual with an average risk of CRC, because their lifetime risk is only increased 1.5-fold compared with the general population.[5]

Suspicions of a hereditary CRC syndrome are raised in patients who have a first-degree relative with CRC before the age of 50 years, or two first-degree relatives with CRC at any age. Clustering of HNPCC-related tumours may also be seen, and these patients should be referred to a familial cancer clinic for evaluation of the possibility of the presence of a CRC syndrome, such as FAP or HNPCC.

Personal history

Individuals with a history of CRC who have undergone surgical resection with curative intent should ideally have had a full colonoscopy before resection, because 5% of patients will harbour a synchronous cancer and 15% of patients will have a synchronous adenomatous polyp. If complete colonoscopy was not performed before resection, it may be performed intraoperatively or three to six months after resection. Thereafter, patients should undergo colonoscopy within three to five years of resection.[5] If adenomatous polyps are identified, these patients are surveyed for future disease based on the number, size and histopathology of the polyps.

Patients with adenomatous polyps that were incompletely excised or excised on a piecemeal basis have a high rate of recurrence. These patients should be re-evaluated with another colonoscopy in two to six months.[5,10] Patients with polyps that cannot be completely excised or who have multiple recurrences of polyps should be considered for surgical resection.

Individuals with more than 10 adenomas on a single examination should have a repeat colonoscopy in three years and be considered for the presence of a possible hereditary syndrome. Further family history should be sought, especially with regard to possible clustering of HNPCC-related tumours, and referral to a genetic counsellor considered.

Patients with three to 10 adenomas, one adenoma of 1 cm or more in diameter or an adenoma with villous features or high-grade dysplasia should have a repeat colonoscopy in three years.[5] If the follow-up colonoscopy is normal or shows only one or two small tubular adenomas with low-grade dysplasia then the interval for the subsequent examination should be four to six years.[5]

Patients with one or two small tubular adenomas with low-grade dysplasia should have repeat colonoscopy in four to six years. The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, the preferences of the patient and the judgement of the physician).[5]

Individuals with hyperplastic polyps should be subsequently screened as for average-risk individuals except in the case of a hyperplastic polyposis syndrome.

Inflammatory bowel disease

Patients with idiopathic IBD (either ulcerative colitis or Crohn's disease) are at an increased risk of developing CRC after eight to 10 years of chronic colitis. This risk is estimated at 0.25% per year of disease duration, and is four times higher in the presence of primary sclerosing

Table 3. Summary of screening recommendations for individuals at increased risk of colorectal cancer[5]

Condition	Age to begin	Interval	Test	Comment
Family history of colorectal cancer				
First-degree relative younger than 55 years or two or more first-degree relatives any age	Age 50 years or 10 years younger than youngest case in family	Every five years	Colonoscopy	–
First-degree relative 55 years or older or two or more second-degree relatives any age	Age 50 years	Every two years	Faecal immuno-histochemical testing	–
Personal history				
Colorectal cancer		Three to five years after surgery	Colonoscopy	Assuming clearance colonoscopy performed
Sessile polyp removed piecemeal		Two to six months	Colonoscopy	If complete removal confirmed surveillance individualised If not amenable to complete resection or multiple recurrences then surgical resection
More than three adenomas or one adenoma more than 1 cm in diameter or high-grade dysplasia or villous histology		Three years	Colonoscopy	Adenomas must be completely removed Consider familial syndrome if more than 10 adenomas detected If follow-up colonoscopy normal or shows up to two small tubular adenomas then subsequent examination in five years
Up to two small tubular adenomas with low-grade dysplasia		Four to six years	Colonoscopy	–
Hyperplastic polyps		Every two years	Faecal immuno-histochemical testing	–
Inflammatory bowel disease				
Ulcerative colitis or Crohn's disease	Eight years after the onset of pancolitis or 12 to 15 years after the onset of left-sided colitis	Every one to two years	Colonoscopy	If primary sclerosing cholangitis present, begin screening at the time of this diagnosis

Table 4. Absolute risk of colorectal cancer in people with no risk factors[1]

Age (years)	Risk of colorectal cancer within a time period (years)			
	5	10	15	20
30	1 in 7000	1 in 2000	1 in 700	1 in 350
40	1 in 1200	1 in 400	1 in 200	1 in 90
50	1 in 300	1 in 100	1 in 50	1 in 30
60	1 in 100	1 in 50	1 in 30	1 in 20
70	1 in 65	1 in 30	1 in 20	1 in 15
80	1 in 50	1 in 25		

Table 5. Summary of screening recommendations for individuals at average risk of colorectal cancer[5,18]

Screening option	Age to begin	Interval	Test
Option 1*	50 years	Every two years	Faecal immunohistochemical testing
Option 2†	50 years	Every 10 years	Colonoscopy
Option 3†	50 years	Every five years	Flexible sigmoidoscopy or CT colonography with yearly faecal immunohistochemical testing

* Recommended by the National Health and Medical Research Council (NHMRC).[5]
† Alternate screening options not yet endorsed by the NHMRC, but in concordance with American guidelines.[18]

cholangitis.[11] Colonoscopy should be performed every one to two years starting eight years after the onset of pancolitis or 12 to 15 years after the onset of left-sided colitis. If primary sclerosing cholangitis is present, surveillance should be started at the time of diagnosis.

Average-risk group

Individuals with no personal or family history of CRC or polyps and no IBD have an increasing risk of CRC with increasing age (Table 4). Population screening with an FIT every two years is recommended by the NHMRC from the age of 50 years in asymptomatic individuals (Table 5).[5,18] Symptomatic patients (e.g. with rectal bleeding, severe constipation, abdominal pain, weight loss and/or lethargy) need to be evaluated by their primary care physician and individually assessed for further investigation. The available options for CRC screening and their advantages and disadvantages are summarised in Table 6.

Surrogate markers for colonic neoplasia – stool examinations

Stool examinations are noninvasive tests that include faecal occult blood tests (FOBT) such as faecal immunohistochemical testing (FIT) and also faecal DNA tests. The basis for these tests is that advanced neoplasia and CRC will bleed intermittently or shed malignant cells into the bowel.

All the tests are relatively easy to perform, have almost no risk of complications, can be performed in the privacy of the patient's home and therefore have the highest compliance rates in population screening.[17] However, patients should be aware that the screening tests are less likely to detect early CRC as compared with invasive tests, because screening tests must be repeated at regular intervals to be effective. If a positive result is returned, a colonoscopy is required.

Faecal occult blood tests

Guaiac-based faecal occult blood testing

Guaiac-based FOBTs (gFOBTs) detect blood in the stool based on a reaction with the pseudoperoxidase activity of haem. The test is not specific for human haemoglobin and can cross react with peroxidases in fruits, vegetables and non-human blood. Therefore, a strict three-day elimination diet excluding all meat and some raw vegetables is required before testing. NSAIDs and vitamin C should also be avoided before testing to minimise the possibility of false-positive and false-negative results, respectively.[12]

gFOBTs require collection of a sample of stool for three consecutive days and do not distinguish between upper and lower gastrointestinal bleeding. Despite these limitations, in a systematic review of four randomised controlled trials involving more than 320,000 individuals, a 16% reduction in the overall relative risk of death from CRC was noted, and a 25% reduction was seen when adjusted for screening attendance – that is, of those who participated in an FOBT and followed through with a colonoscopy, a 25% reduction in risk was seen.[13] The Hemoccult II SENSA test has been shown to be the most sensitive of these tests. Its sensitivity for detecting carcinomas and

continued

Table 6. Summary of screening tests for colorectal cancer

Test	Advantages	Disadvantages
FIT*	Noninvasive No need to take time off work Inexpensive	Nonbleeding polyps and cancers will not be detected Requires continued yearly testing
gFOBT	Noninvasive No need to take time off work Inexpensive	Requires multiple samples Requires dietary restrictions Lower sensitivity and specificity than FIT
Flexible sigmoidoscopy	Minimal bowel preparation No fasting required	No sedation, so therefore is uncomfortable Quality depends on skill of operator
Colonoscopy	Complete bowel examination Diagnostic and therapeutic	Complete bowel preparation required General anaesthesia used; day off work and chaperone required Risks include perforation and bleeding of the colon Expensive
CT colonography	Minimal risks	Complete bowel preparation required Radiation exposure
Faecal DNA	Higher specificity for CRC	Expensive Larger sample of stool required, with problematic packaging and shipping to laboratory

ABBREVIATIONS: CRC = colorectal cancer, CT = computed tomography, FIT = faecal immunohistochemical testing, gFOBT = guaiac-based faecal occult blood test (Haemoccult Sensa).
* Only screening test endorsed by the National Health and Medical Research Council guidelines.

neoplasms is 79.4% and 71.2%, respectively, with a specificity of 86.7 and 87.5%, respectively.[14]

Faecal immunohistochemical testing

FIT specifically detects nondegraded human haemoglobin and identifies bleeding in the colon and rectum only (blood from the upper gastrointestinal tract is degraded to haem products before its transit to the colon). It does not require dietary or medicinal exclusion diets before testing, and only requires one stool sample to be collected. This has translated to increased participation rates in population screening studies.[15]

Sensitivity of FIT for detecting cancer has been reported at 94.1% and specificity at 87.5%.[16] Two large randomised controlled trials have recently shown the superiority of FIT over gFOBT, detecting advanced neoplasms and cancer at a rate of two to 2.5 times more when used as a screening tool in asymptomatic individuals .[16,17]

Faecal DNA testing

Current generation faecal DNA testing analyses stool samples for 21 known genetic defects in the DNA of the cells shed by polyps and/or CRCs. It requires a larger stool sample (30 g) than other tests and this sample must be mailed to a processing facility. Test sensitivity for detecting CRC in studies in the USA involving stool DNA testing ranged from 52 to 91%, with specificity ranging from 93 to 97%.[18] The lower sensitivity in some of these studies has been attributed to a suboptimal sensitivity performance of DNA resulting from DNA degradation during the transit of specimens to the laboratory.

The evidence to support the efficacy of faecal DNA testing as CRC screening in the average-risk population is scarce. With similar test characteristics to high-sensitivity FIT yet a much higher cost, the cost-effectiveness of faecal DNA testing is likely to be limited. Before faecal DNA testing as CRC screening is broadly implemented, large studies should be conducted in screening populations to prove the accuracy of the faecal DNA marker or panel and the cost of testing ideally should be reduced.

Direct detection of colonic neoplasia

Direct detection of adenomatous polyps and CRC is possible with use of a barium enema, CT colonography, flexible sigmoidoscopy and colonoscopy. Barium enema and CT colonography are relatively noninvasive, but flexible sigmoidoscopy and colonoscopy are valued for their ability to offer a therapeutic solution at the time of examination, and they have a theoretical role in decreasing

CRC incidence and mortality by removing precursor lesions.

All these tests, however, are more invasive, require more patient participation than stool examinations, and carry a low but not negligible risk of complications, including bleeding, missed lesions and perforation.

Double-contrast barium enema

The double-contrast barium enema technique evaluates the colon by coating the mucosa with high-density barium and air introduced through a flexible catheter. Multiple radiographs are then taken to identify lesions within the colon. A full bowel preparation is required, although sedation is typically not needed, and positive studies must be evaluated with a colonoscopy. The entire procedure usually requires 20 to 40 minutes.

Reported sensitivity of double-contrast barium enema for the detection of CRC is between 85 and 97%, and the sensitivity for detecting adenomas larger than 7 mm is only 73%.[18] This technique does not allow good imaging of the sigmoid colon, and should ideally be used in conjunction with sigmoidoscopy. Additionally, due to waning radiologist enthusiasm for its labour-intensive nature and the availability of newer and more effective technology (such as CT colonography), there has been a steady decline in the use of double-contrast barium enema.

CT colonography

CT colonography, also referred to as virtual colonoscopy, is a minimally invasive imaging examination of the entire colon and rectum. CT colonography uses CT to acquire images and advanced two-dimensional and three-dimensional image display techniques for interpretation. Although more attractive to patients than other more invasive techniques, a bowel preparation and air insufflation via a rectal tube are required. Suspicious findings must be evaluated with a colonoscopy, preferably on the same day.

The sensitivity of CT colonography for the detection of adenomatous polyps is dependent on size. CT colonography sensitivities are 93.8%, 93.9% and 88.7%, and specificities are 96.0%, 92.2% and 79.6% for polyps 10 mm or more, polyps 8 mm or more or polyps 6 mm or more, respectively.[19] It is recommended that patients with polyps larger than 6 mm be referred for colonoscopy.[19]

The management of smaller polyps found on CT colonography remains controversial. Additionally, the detection of significant extracolonic findings, which in some studies approaches 66% of investigations, warrants further evaluation.[20] It should be stressed that the use of CT colonography must be considered experimental at this stage, because population-based evaluation of CT colonographic screening is only just

beginning and the risk of repeated radiation exposure needs to be assessed.

Flexible sigmoidoscopy

Flexible sigmoidoscopy is an endoscopic procedure that examines the distal part of the colon lumen, which is where most cancers are found. It is typically performed without sedation, so no prior fasting is required, and with a more limited bowel preparation than colonoscopy (usually just an enema prior to investigation). As sedation is not required, flexible sigmoidoscopy can be performed in office-based settings, and patients do not require the whole day off work or an escort home. Any adenoma identified on flexible sigmoidoscopy requires a subsequent colonoscopy for further evaluation.[21]

When performed by adequately trained personnel, flexible sigmoidoscopy can be a valuable tool in screening individuals with an average risk of CRC. In combination with yearly gFOBT or FIT, many institutions have used this method to provide effective screening for CRC. Sigmoidoscopy is associated with a 60 to 80% reduction in CRC mortality.[20] Emerging evidence has also shown that as a one-off screening tool, despite lower participation rates, flexible sigmoidoscopy detects three times more advanced neoplasia or CRC than FIT and six times more than gFOBT.[18]

Colonoscopy

Colonoscopy is the common end-point for all screening studies, and is considered to be the gold standard for the diagnosis of both colon and rectal polyps and malignancy. Although effective at both diagnosis and treatment, colonoscopy requires a large amount of patient participation. A liquid diet is generally recommended the day before, with the ingestion of a large volume of lavage or laxative solutions. During the procedure, patients typically receive sedation to decrease the discomfort, and this means the patient cannot work on the same day and must be escorted home after the procedure.

Many large population studies have demonstrated the decreased incidence of CRC after a clearance colonoscopy, although to date there have been no randomised controlled trials of colonoscopy screening to assess benefit over risks. The reduction in incidence of CRC has been estimated to be between 70 and 90%.[22,23]

Despite it being the best investigation for diagnosis and treatment, colonoscopy is not infallible. Controlled studies have demonstrated a miss rate of about 6 to 12% for polyps 10 mm in diameter,[24] and this is where optimal bowel preparation and adequate training of proceduralists is paramount. Additionally, complications are more frequent and severe than for the previously mentioned investigations, with a significant bleeding rate of one in 500, bowel perforation rate of one in 1000 and death rate of one in 10,000 colonoscopies.[25]

Conclusion

There is compelling evidence to support screening to decrease the morbidity and mortality from CRC, the second leading cause of cancer-related death in Australia. Although those at high or intermediate risk of CRC are more likely to develop the condition, and thus warrant more intensive and invasive screening, the burden of disease is in the group at average risk of CRC who are completely asymptomatic.

Screening programs are only effective if individuals participate in them and are compliant to the screening pathway. Primary care physicians have a pivotal role in this regard in educating their patients in the importance of such programs, facilitating entry into and ensuring maintenance in screening programs. Incorporating bowel cancer prevention into the health maintenance plans of all patients aged 50 years and over is therefore necessary. Australia has one of the few population-based CRC screening programs in the world, and our patients should be educated and supported during CRC screening. MT

References

A list of references is available on request to the editorial office.

COMPETING INTERESTS: None.

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