Alternatives to colonoscopy for population-wide colorectal cancer screening

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ABSTRACT

Colorectal cancer is one of the top three cancers in the world in terms of incidence. Colonoscopy, which many regard as the gold standard in diagnosis of colonic polyps and neoplasm, is costly, invasive and labour-intensive, and deemed an unsuitable population-wide index screening tool. Alternative modalities, including guaiac and immunohistochemical faecal occult blood tests, computed tomographic colonography, colon capsule endoscopy, flexible sigmoidoscopy, and double-contrast barium enema are available. The procedures, test characteristics, and their implications are reviewed. Immunohistochemical faecal occult blood testing appears to be the most suitable population-wide screening test for an average-risk population, with flexible sigmoidoscopy as an alternative. More evidence is needed to determine the role of computed tomographic colonography and colon capsule endoscopy in colorectal cancer screening.

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Introduction

Colorectal cancer (CRC) became the second and third most common cancer in women and men in 2012.[1] Most cases of CRC arise from adenoma, the process known as the adenoma-carcinoma sequence, and are therefore amenable to screening and early treatment.[2-4] Ecological studies have shown that 2.6% to 5.6% of advanced adenoma progress to CRC annually.[5]

Colonoscopy remains the gold standard for diagnosis,[6] and has even been used as a primary screening method in some countries (eg the US). Nonetheless its use in most countries as an index tool for mass screening of an average-risk population is impractical due to its cost, invasiveness, and need for expertise (ie endoscopists).

In this study, we reviewed the literature about the procedures, test characteristics, and implications of the following alternative screening modalities: guaiac faecal occult blood testing (gFOBT), immunohistochemical faecal occult blood testing (iFOBT), computed tomographic colonoscopy (CTC), colon capsule endoscopy (CCE), flexible sigmoidoscopy (FS), and double-contrast barium enema (DCBE).

Guaiac faecal occult blood testing

The gFOBT offers the strongest evidence as a suitable screening tool for CRC. Its mechanism involves detection of haemoglobin in the stool. The test is not specific for human haemoglobin however, and false-positive results can arise due to plant peroxidases and heme in red meat. False negatives can occur when stool contains certain chemicals, eg vitamin C. It also detects bleeding from the gastro-intestinal (GI) tract other than the colon and rectum. Two or more samples are usually required.

Four large-scale randomised controlled trials (RCTs) of gFOBT with long-term follow-up have been conducted; they include Minnesota study in the US,[7] Nottingham trial in the UK,[8] Göteborg study in Sweden,[9] and Funen study in Denmark.[10] A total of 328 767 individuals, aged 45 to 80 years, were involved. The results consistently showed reduction in CRC mortality by 12% to 33%, after up to 30 years of follow-up.[7-10] The results are summarised in Table 1.

In screening for significant or advanced adenoma, test sensitivity was 23.8%,[11] and specificity was 97.7% to 99.0% with positive predictive values (PPVs) of 39.0% to 55.3%. The detection rate in intention-to-screen (ITS) analysis was 0.6% and that in per protocol (PP) analysis was 1.2%. The NNScreen, or the number of average-risk individuals needed to recruit in a screening programme to detect one advanced adenoma, was 84 to 181.[12,13] The NNScope, or the number of colonoscopies needed to diagnose an advanced adenoma after

screening revealed a likely significant lesion, was 2.2.[12] Although NNScreen is useful in assessing each modality individually, NNScope of a test provides additional information about the role of gFOBT in a screening programme to select patients for further diagnostic colonoscopy. For CRC, the sensitivity was 54.2%, and specificity ranged from 96.9% to 98.1% with a PPV of 5.2% to 13.6%. Detection rate in ITS analysis was 0.1%, while that in PP analysis was 0.2%. The NNScreen was 392 to 936 and the NNScope was 10.3.[11-14]

The Funen study[10] showed the CRC mortality dropped from 18% to 11% after five screening rounds, as a result of decreased compliance. Similar findings were echoed in the Tenerife study in Spain.[11]

全民大腸癌篩查：大腸鏡檢查的替代方案

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大腸癌是全球發病率最高的三大癌症之一。大腸鏡檢查被認為是診斷大腸息肉和腫瘤的金標準，可惜這種方法成本高，屬侵入性檢查和勞動密集型，所以被認為不適合作全民篩查的工具。其他替代大腸鏡檢查的方案包括愈創木脂和免疫化學大便隱血測試、電腦斷層結腸成像、結腸膠囊內視鏡檢查、乙狀結腸內視鏡檢查和雙對比鋇劑灌腸。本文綜述了這些替代方案的程序、試驗特點及可能的影響。要開展無症狀全民大腸癌篩查，似乎免疫化學大便隱血測試最為適合，其次為乙狀結腸內視鏡檢查。至於電腦斷層結腸成像和結腸膠囊內鏡檢查方面，則須搜集更多有關其作為篩檢工具的證據。

Immunochemical faecal occult blood testing

The iFOBT employs an antibody-based assay, detecting globin or early degradation products of human haemoglobin.[15] The antibodies used are human-specific, thus the number of false positives due to non-human blood is minimised. As globin is more rapidly degraded than heme throughout the GI tract, less upper GI tract bleeding is detected. It requires no dietary restrictions[16] and has a participation rate of 38.9% to 71.9%.[17-19] The results can be qualitative or quantitative.[20] Sampling technique, distribution of blood in faeces, and sample instability make true quantification difficult, however.[15] Adjustment of performance parameters is possible by altering the cut-off values. It is generally agreed that a cut-off of 75 ng/mL provides a balance between higher detection rate and lower NNScope.[12,15,18,21,22] It should also be noted though that different brands of iFOBT kits may yield different results even when the same cut-off is used.

The iFOBT on one or two consecutive faecal samples is recommended. A study showed that 1-day sampling had a higher miss rate for CRC compared with 2-day sampling.[23] Another study showed that performing iFOBT at 1-, 2-, or 3-year intervals did not yield significantly different results in terms of advanced adenoma detection, but compliance decreased with frequent screening.[24]

The stability of the iFOBT kit is temperature-dependent, making results vulnerable to changes in environmental temperature and the sample return time.[20] In moderate climates, the sample return time should not exceed 7 days.[25] Manufacturers are developing buffer solutions to overcome this problem.[15]

A potential disadvantage of iFOBT is its decreased sensitivity to proximal colonic lesions. A German study showed a sensitivity of 33% and 20% for left- and right-sided lesions, respectively. Nonetheless the results were statistically insignificant,[26] and were contradictory to another Dutch trial.[27]

The positivity rate of iFOBT ranges from 5.5% to 11.0%.[12,13,17,19,28,29] The sensitivity and specificity for CRC ranges from 53.3% to 94.1% and 87.5% to 96.9%, respectively.[18,28,30,31] The PPV ranges from 5.2% to 12.8% at a cut-off value of 75 ng/mL.[12,13,17-19,28-32] The NNScreen and NNScope ranges from 213 to 936 and

TABLE 1. Summary of four randomised controlled trials comparing screening with guaiac faecal occult blood testing with no screening* [7-10]

Study	Year	Screening	Control	Follow-up duration (years)	Age at recruitment (years)	Reduction in CRC mortality (%)	Relative reduction in CRC mortality (95% CI)
Shaukat et al[7]	2013	15 570 (annual); 15 587 (biennial)	15 394	30	50-80	33 20	0.68 (0.56-0.82) 0.78 (0.65-0.93)
Scholefield et al[8]	2012	76 056	75 919	0.0-28.4	45-74	12†	0.88 (0.79-0.98)†
Lindholm et al[9]	2008	34 144	34 164	11.3-19.5	60-64	16	0.84 (0.71-0.99)‡
Kronborg et al[10]	2004	30 967	30 966	17	45-75	17	0.84 (0.73-0.96)

Abbreviations: CI = confidence interval; CRC = colorectal cancer

* Intention-to-treat analysis

† Calculation based on the first 12 years of study

‡ Odds ratio used in original article, relative risk calculated for representation here

TABLE 2. Studies showing performance of iFOBT, with or without comparison with gFOBT[12,13,17-19,28-32]

Study	Country	Year	Screening tests*	Total No.	Age (years)	Sensitivity (%) (95% CI)	PPV for CRC (%) [95%CI]	NNScope (95%CI)	NNScreen (95%CI)
Allison et al[28]†	United States	2007	gFOBT2 iFOBT7	N/A	≥50	64.3 (35.6-86.0) 81.8 (47.8-96.8)	1.5 (0.8-3.0) 5.2 (2.6-10.0)	N/A	528.1 672.2
Levi et al[18]	Israel	2007	iFOBT2	1859	N/A	88.2 (72.9-100)‡ 94.1 (82.9-100)§	12.9‡ 11.9§	N/A	N/A
van Rossum et al[13]	The Netherlands	2008	gFOBT1 iFOBT2	10 322 10 301	50-75	N/A	10.7 (4.7-16.6) 8.6 (5.3-11.9)	9.4 11.7	430.1 936.5
Hol et al[12]	The Netherlands	2009	gFOBT1 iFOBT2	4843 4796	50-74	N/A	10.0 (4.0-20.0) 10.0 (6.0-17.0)	10.3 9.8	392.0 213.0
Fu et al[19]	Singapore	2009	iFOBT2	751	40-85	78.8	5.3	17.3	250.3
Park et al[31]	Korea	2010	gFOBT1 iFOBT2	N/A	50-75	30.8 (9.1-61.4) 92.3 (64.0-99.8)	6.7 (1.8-15.9) 12.8 (6.6-21.7)	N/A	N/A
Faivre et al[32]	France	2012	gFOBT1 iFOBT2 iFOBT5 iFOBT6	85 149 32 215 19 244 33 690	50-74	 2.1 (1.6-2.8)‖ 1.7 (1.3-2.1) 1.8 (1.3-2.3)	5.2-6.4 5.6 (4.3-6.9) 3.9 (2.9-4.9) 5.7 (3.9-7.1)	 12.8 (10.8-15.9) 16.6 (13.9-20.7) 12.7 (10.3-16.6)	366 (303-455) 354 (286-435) 296 (238-385)
Tan et al[17]	Singapore	2013	iFOBT1	20 989	≥50	N/A	6.7	15.0	636.0
Brenner and Tao[30]	Germany	2013	gFOBT1 iFOBT2 iFOBT3 iFOBT4	N/A	50-79	33.3 73.3 60.0 53.3	4.5 10.0 8.1 7.3	N/A	N/A
Raginel et al[29]	France	2013	gFOBT1 iFOBT2 iFOBT6	N/A	50-74	N/A	6.9 6.2 6.5	14.6 16.2 15.1	1041.9 549.9 449.9

Abbreviations: CI = confidence interval; CRC = colorectal cancer; gFOBT = guaiac faecal occult blood testing; iFOBT = immunohistochemical faecal occult blood testing; N/A = not available; NNScope = the number of colonoscopies needed to diagnose an advanced adenoma after screening revealed a likely significant lesion; NNScreen = the number of average-risk individuals needed to recruit in a screening programme to detect one advanced adenoma; PPV = positive predictive value

* gFOBT1 = Hemoccult II; gFOBT2 = Hemoccult Sensa; iFOBT1 = OC-Light; iFOBT2 = OC-SENSOR; iFOBT3 = RIDASCREEN Haemoglobin; iFOBT4 = RIDASCREEN Haemo-/Haptoglobin Complex; iFOBT5 = FOB-Gold; iFOBT6 = Magstream; iFOBT7 = FlexSure OBT

† Studied distal colorectal cancer only

‡ Cut-off value at 100 ng/mL

§ Cut-off value at 75 ng/mL

‖ Sensitivity ratio (ratio of true positives with iFOBT to that with gFOBT) was estimated as sensitivities could not be directly calculated

9.8 to 17.3, respectively.[12,13,17,19,28-30,32] These results are summarised in Table 2. For advanced adenoma, the sensitivity and specificity ranges from 33.9% to 41.3% and 91.4% to 97.3%, respectively.[18,28,31] The PPV ranges from 49.0% to 51.8%.[12,13] The NNScope and NNScreen ranges from 2.2 to 2.4 and 88.0 to 135.6, respectively (single sample).[29]

Compared with gFOBT, studies in the literature showed superior results for iFOBT that generally had a higher positivity rate, often 2 times higher than that of gFOBT.[13,28] The detection rate for CRC in a study by Faivre et al[32] was 1.6 to 2.1 times higher than in gFOBT. This was echoed by another large-scale RCT which showed a significantly higher detection rate using iFOBT.[13] Studies showed the detection rate for advanced adenoma using iFOBT to be at least double that of gFOBT.[12,29] In the study by Faivre et al,[32] iFOBT was 1.7 to 2.1 times more sensitive than gFOBT for CRC.[32] A study by Brenner and Tao[30] showed significantly higher PPV for iFOBTs than gFOBTs (7.3%-10.0% vs 4.5%). In two comparative studies, the NNScreen of iFOBT was about half that of gFOBT[29,32]; iFOBT also had a 13.0% to 15.0% higher participation rate than gFOBT.[13,15,16,20,33]

The iFOBT is more costly than its guaiac-based counterpart,[20] but modelling studies showed that it is more cost-effective.[34-37] This is largely explained by the higher participation rate, detection rate, sensitivity and PPV, and with lower NNScope and NNScreen. There is a general consensus that it should replace gFOBT.[16,20,38]

Computed tomographic colonography

The CTC was first described in 1994.[39] It provides a non-invasive structural assessment of the colon. Compared with conventional colonoscopy, CTC is sedation-free and has an extremely low risk of bowel perforation (0.005%-0.059%).[40,41] Furthermore,

assessment of the extra-colonic organs can be performed at the same time.[42] A lower volume bowel preparation may be used[43] and the radiation risk is negligible.[41] Its main disadvantage is that biopsy is not possible, and the patient may require a second procedure with another bowel preparation, thus imposing additional costs and discomfort to the patient. Its role in CRC screening remains debatable. The American Cancer Society supports screening with CTC every 5 years.[44] Other guidelines including the National Institutes of Health Asia Pacific Consensus Recommendations do not support its use, however, stating its lack of evidence as a screening technique in an average-risk population.[45,46]

Studies of CTC in the literature use detection of polyps in general as the end-point. Data for detection of invasive carcinoma as well as reduction in CRC mortality were not available. Different studies use either 'per patient' or 'per polyp' for analysis. Two large US trials supported CTC as a screening tool in asymptomatic average-risk populations.[47,48] Per-patient analyses demonstrated a sensitivity of 78.0% to 93.8%, and specificity of 79.6% to 96.0%, respectively.[47,48] Meta-analyses in 2011 and 2014 reviewed 15 trials,[49,50] including the two aforementioned studies. All trials focused on a population aged over 50 years with average risk. Martín-López et al[49] showed an overall per-patient sensitivity and specificity for CTC of 66.8% and 80.3%, which was lower than that of colonoscopy of 92.5% and 73.2%, respectively. The sensitivity and specificity were higher for larger polyps. For polyps larger than 1 cm, the sensitivity was 91.2% and specificity 87.3%. Another meta-analysis reported sensitivities for ≥6-mm and ≥10-mm polyps as 75.9% and 83.3% and specificities as 94.6% and 98.7%, respectively.[50]

Estimation of the cost-effectiveness remains complicated. Based on a systematic review of 16 studies,[51] the cost-effectiveness of CTC remains controversial. There is generally a stronger preference for CTC over colonoscopy in asymptomatic individuals,[52] although some may hold an opposite opinion due to more pain and discomfort in CTC.[53] The use of 'low-prep' or laxative-free CTC is being further investigated.[43]

The CTC can detect asymptomatic polyps and has the potential to prevent them from progressing to advanced adenoma and CRC. These polyps may not be detected by gFOBT or iFOBT until they result in microscopic haemorrhage in the lower GI tract. This is an advantage of CTC compared with gFOBT and iFOBT. The role of CTC in reducing CRC mortality remains uncertain, however.

Colon capsule endoscopy

The CCE makes use of a double-headed capsule with a wide viewing angle, visualising the colon beyond the haustral folds.[54] Its sensitivity and specificity for significant polyps has been reported to be 83% and 89%, respectively.[55-57] The European Society of Gastrointestinal Endoscopy recommends CCE as an alternative screening method for average-risk individuals.[58] In February 2014, it also received the US Food and Drug Administration clearance for use in patients following incomplete colonoscopy. It is also proven to be beneficial when the patient is unwilling or is unable to undergo colonoscopy.[59,60] With its presumed increased uptake, it is a promising new CRC screening modality.[61] The newest generation of CCE has improved resolution by adapting its frame rate to the speed of capsule movement. Some newer capsules also have four cameras to provide a 360-degree view.[62]

Despite its promising role in screening, some disadvantages of CCE have limited its use thus far. Strict bowel preparation, diet restrictions, and use of suppositories and prokinetics may be needed to ensure a smooth and quick journey of the capsule through the bowel, while minimising the interference of debris when identifying lesions.[63] Potential complications include capsule impaction and retention (1.4%[64]) that may require endoscopic or surgical removal. It is also not recommended in pregnancy or with implanted electromedical devices such as pacemakers.[62] The cost of CCE is much higher than that of colonoscopy,[65] and includes the reading of the captured video footage. There is also no current evidence to prove the mortality benefit of CCE use in CRC.

Flexible sigmoidoscopy

The FS examines the distal 40 to 60 cm of the lower GI tract. Full colonoscopy can be performed when there are positive findings. Compared with colonoscopy, it requires a simpler bowel preparation and dietary restriction is not necessary.[66]

In two large-scale RCTs that involved 170 432 and 55 736 individuals, in PP analysis, there was a 43.0% reduction in CRC mortality and improved hazard ratio of 0.41.[67,68] This was echoed by another RCT that involved 77 445 patients and showed a 21% reduction in the incidence of both proximal and distal cancer and a 50% reduction in mortality from distal cancer.[69] The PPV was 91.9% for any adenoma.[70] The positivity rate for adenoma was 17.3%.[71] Most studies were in individuals aged ≥50[70-72] or ≥55 years.[68,69,73]

The sensitivity of FS depends on the adequacy of mucosal inspection and is operator-dependent.[73] Studies have shown inadequate screening in up to 91.7% of cases, ie <50 cm depth of insertion.[73] The technique had relatively low and fluctuating participation rates (20.9%-63.0%).[70,71] A 35.3% decrease in adherence from baseline to subsequent study was observed.[69]

The impact of FS as a screening tool is well established in the literature and accepted in various

screening protocols.[44,46] This technique should be included as an alternative choice for a population-wide screening programme, and the shortage of endoscopists could be partially addressed by training specialised nurses in the procedure.[74]

Combining flexible sigmoidoscopy with guaiac and immunohistochemical faecal occult blood testing

Flexible sigmoidoscopy cannot replace the role of colonoscopy in individuals with a positive faecal occult blood test.[72] In a non-randomised trial, the detection rate of combined gFOBT and FS for cancer was higher than that of gFOBT alone (1.5 vs 0.7 per 1000), but was not superior to FS alone (1.5 vs 5.2 per 1000).[70] Results were similar for advanced neoplasia.

Double-contrast barium enema

The DCBE involves an X-ray study of the colon and rectum following injection of air and barium transrectally. Once regarded as a routine screening tool, its role has diminished since the introduction of other screening modalities. While it was the safest screening method next to FOBT with a perforation rate of 1 in 25 000,[75] the sensitivity for polyps of ≥10 mm was only 48%, rendering it suboptimal for screening.[76,77]

Combining double-contrast barium enema with flexible sigmoidoscopy

When DCBE was combined with FS, they had the same sensitivity for cancer as colonoscopy (96.7%).[78] Two RCTs in the 1990s reported a lower detection rate for small polyps for FS plus DCBE when compared with colonoscopy.[79,80] Nonetheless the detection rate for cancers and large polyps was comparable.[79] Sensitivity analyses in both studies revealed that in screening, FS plus DCBE was less cost-effective than colonoscopy.

Current guidelines

The Asia Pacific Consensus Recommendations in 2015 suggested the use of iFOBT over gFOBT, and FS and colonoscopy were deemed effective.[46] On the contrary, CTC and CCE were not recommended for screening. In the US, surveillance programme guidelines from the American Cancer Society provided two sets of test options for asymptomatic adults aged ≥50 years.[44] For adenomatous polyps and cancer, FS, DCBE, or CTC every 5 years, or colonoscopy every 10 years was recommended. For cancer alone, annual gFOBT or iFOBT testing was recommended. The American College of Gastroenterology supported replacement of gFOBT by iFOBT as a first-line screening test.[81] The National Health Service in the UK recommends screening for average-risk men and women aged 60 to 74 years with FOBT every 2 years.[82] The European Union did not offer a comprehensive system, with a recommendation of FOBT for men and women aged 50 to 74 years.[83] The Australian government encouraged biennial iFOBT for an asymptomatic population aged >50 years.[84]

There is no formal consensus on a CRC screening programme in Hong Kong. The Hong Kong Cancer Fund, a cancer support organisation, recommends screening of the average-risk population aged ≥50 years, with either FOBT every year, FS or DCBE every 5 years, or colonoscopy every 10 years.[85]

Discussion

Colonoscopy remains the gold standard diagnostic tool for CRC, but its costs, discomfort, inconvenience, and potential complications render it impractical as the first-line investigation in a population-wide CRC screening programme for average-risk individuals. Multiple alternative tools have since been developed, aimed at minimising discomfort and inconvenience and thus achieving better compliance, while at the same time not jeopardising the screening effectiveness. While it is not possible for these tools to replace colonoscopy for diagnosis, they may assume an essential role in a screening programme as an index investigation for risk stratification, thus selecting patients to undergo further diagnostic colonoscopy.

These screening modalities differ in their development. Both gFOBT and FS are time-honoured, heavily researched, and proven to reduce CRC mortality. Large amounts of research data are emerging in support of newer options such as iFOBT and CTC. While comparison of gFOBT and iFOBT is easily achievable, direct comparison of CTC and iFOBT is more difficult as there are different 'performance' parameters.

The technique iFOBT is evolved from gFOBT and shares a similar mechanism. While gFOBT has been well proven by long-duration RCTs to reduce CRC mortality, it has been postulated that iFOBT may achieve the same effect. For a population-wide screening programme to be successful, the test has to be acceptable to asymptomatic individuals. This eventually determines the penetration and compliance with the programme. Compared with gFOBT, iFOBT undeniably has a higher participation rate,[13,20,33] and even more so compared with FS.[70,71] In a population-wide screening programme with iFOBT, implementation could be achieved in a relatively short period of time as it could be performed by primary care physicians and nurses. Installation of sophisticated hardware is not required. Given a positivity rate of 5.5% to 11.0%,[12,13,17,19,28,29] however, it would have a significant impact on health care

services. A major increase in the number of referrals for colonoscopy would be anticipated and thus require a corresponding increase in the availability of endoscopy centres and endoscopists.

Test characteristics are not the only factor that dictates the success of a screening programme; compliance plays a crucial role. Studies have shown that those who communicate well with their health care providers are more likely to adhere to a screening programme.[86] When implementing a population-wide programme, recruiting primary care physicians to promote CRC screening and perform office-based iFOBT would be logical and is feasible.

Conclusion

Each CRC screening modality has its own niche, providing unique prognostic benefits but with their own shortcomings. Based on the available evidence to date, feasibility, and participant acceptance, iFOBT appears to be the most suitable CRC index screening tool for the average-risk population, with FS as an alternative.

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