# Colorectal cancer mass screening event utilising quantitative faecal occult blood test

Chew M H, Suzanah N, Ho K S, Lim J F, Ooi B S, Tang C L, Eu K W


## ABSTRACT

**Introduction: Colorectal cancer (CRC) is a leading cause of morbidity and mortality with human and financial costs. Screening by faecal occult blood test (FOBT) has proven to be effective in decreasing mortality from CRC in both randomised trials and case-control studies. We report on the results of a CRC screening event using quantitative FOBT (QFOBT) held in Singapore.**

**Methods: The mass screening event was held over two days, and participants 40 years or older without prior screening performed in the preceding year were eligible. Those with significant symptoms or medical comorbidities were excluded. Stool sampling was done with two issued immunochemical QFOBT kits, and participants with positive stool samples with equal or greater than 100 ng haemoglobin/ml sample solution in any two samples were advised to have a colonoscopy screening conducted.**

**Results: A total of 1,048 participants took part in the screening event. 222 (21 percent) of the participants claimed to have some abdominal symptoms prior to screening. 49 participants (26 males, 23 females) tested positive for QFOBT and 47 were evaluated. 10 (21 percent) had polyps and one case of colorectal cancer was detected. Seven of these cases had significant neoplasia (lesions 1 cm or larger) and were treated. Two patients required surgery.**

**Conclusion: Our study demonstrates wide variation in the attitudes of participants who turned up for screening. In addition, the number of significant colorectal neoplasia patients (14 percent) in those with positive QFOBT provides further evidence of the importance of screening with a potential reduction in CRC mortality. Continuous education of the public in events such as this, is essential to improving attitudes towards screening.**


**Keywords: cancer screening, colorectal cancer, faecal occult blood test, quantitative faecal occult blood test**

*Singapore Med J 2009; 50(4): 348-353*

## INTRODUCTION

The faecal occult blood test (FOBT) is the least expensive and simplest of tests recommended in national guidelines for colorectal cancer (CRC) screening.[1-4] Screening by FOBT has proven to be effective in decreasing mortality by 14%–18% from CRC in both randomised trials[5-8] and case-control studies.[9,10] In Singapore, the Ministry of Health has released screening guidelines on CRC since 2003.[11] Individuals are divided into three categories: average risk, high risk and very high risk groups, for the purpose of CRC screening. Colonoscopy is the recommended screening tool for the high risk and very high risk groups, but for an average-risk individual, FOBT is the recommended screening test with barium enema and flexible sigmoidoscopy as suggested alternatives. The overall mortality rate in Singapore from CRC remains high at approximately 50%.[12] One of the main reasons for this is the high proportion of the advanced stage of the disease in our cohort at presentation. These patients are usually symptomatic on presentation. The challenge remains of how to encourage the asymptomatic individual to come forward for voluntary screening, so as to increase the detection of CRC at an earlier stage of the disease, or to detect polyps which are CRC precursors.

The traditional FOBT utilises guaiac to detect peroxidase activity of haeme in the faeces. There are, however, problems associated with guaiac FOBT due to its low specificity and sensitivity.[13] Newer faecal immunochemical tests (FIT) use antibodies that specifically detect human haemoglobin (Hb) in stools. As globin is rapidly digested in the stomach and small intestine, FITs are more selective than guaiac FOBTs for occult bleeding of colorectal origin. The development of this technology has allowed improved accuracy in the detection of CRC and significant adenomas with higher sensitivity and specificity.[14-16] A further evolution has been the development of QFOBT (quantitative FOBT).

**Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 169608**

Chew MH, MBBS, MMed, MRCSE
Registrar

Suzanah N, BHSc, MSc
Programme Manager

Ho KS, MBBS, FRCSE, FAMS
Senior Consultant

Lim JF, MBBS, FRCSE, FAMS
Consultant

Ooi BS, MBBS, FRCSE, FAMS
Senior Consultant

Tang CL, MBBS, FRCSE, FAMS
Senior Consultant

Eu KW, MBBS, FRCSE, FAMS
Senior Consultant and Head

**Correspondence to:**
Prof Kong Weng Eu
Tel: (65) 6321 4677
Fax: (65) 6226 2009
Email: eu.kong.weng@sgh.com.sg

**Fig. 1** Photograph shows a quantitative faecal occult blood test kit used for stool collection.

**Fig. 2** Photograph shows an automated desktop machine which allows for multiple samples of faecal occult blood test kits to be analysed at the same time.

This test uses the principle of latex agglutination immuno-turbidimetry and allows the quantification of the amount of occult blood in the stool. The introduction of quantification allows the physician to choose the optimal faecal Hb threshold level that triggers a follow-up colonoscopy. Various reviews have indicated the positivity threshold at 100 ng Hb/ml sample solution.[17-20] Vilkin et al correlated faecal Hb (threshold level of 100 ng/ml) with colonoscopic findings in high-risk symptomatic patients and revealed a high sensitivity of 76.5% of all significant colorectal neoplasia (adenomas ≥ 10 mm and CRC) and a specificity of 95.3%.[18] These values are encouraging and serve to decrease the need for unnecessary colonoscopy while maintaining cancer detection rates. We report on the results of a CRC mass screening event using QFOBT held in Singapore. Concurrently, the efficacy of QFOBT was also evaluated in screening for colorectal neoplasia in an asymptomatic cohort of patients.

## METHODS

The mass screening event was held over a period of two days in a shopping mall located in a prime shopping district in Singapore. This event was held in conjunction with an exhibition cum carnival. Prizes and goodie bag redemptions were given out to participants of the carnival activities including the mass screening event. The entire event was publicised in the mass media. All participants were screened for eligibility by doctors via a questionnaire. The inclusion criteria for screening followed the National Clinical Practice Guidelines drawn out by the Ministry of Health, Singapore.[11] As it was one of the objectives of the event to educate the younger population, the criteria designed included all participants who were ≥ 40 years of age, rather than the minimum age limit of 50 years as stipulated for an "average risk" population. Exclusion criteria included participants who have had a previous screening, either with FOBT, barium enema or colonoscopy, performed within the last year. In addition, participants who had sinister symptoms of visible bleeding per rectum, loss of weight and appetite, a change in bowel habits or abdominal pain were advised by the on-site doctors to undergo a proper and thorough medical evaluation, and were excluded from the screening event. Participants with a history of colonic disease, previous abdominal surgery, significant medical comorbidities or who required counselling on anticoagulation or antibiotic prophylaxis were advised to undergo a proper medical evaluation and were excluded from participation. We did not, however, exclude participants who were on long-term use of non-steroidal anti-inflammatory drugs or anti-platelets from the screening event.

Participants were counselled on-site on the proper method of stool sample collection by nurse educators. Written instructions were issued individually to the participants as well. Participants were instructed to perform bowel movement only after voiding urine and flushing the toilet. This was done on disposable paper lining of the toilet bowl to prevent the contact of stool with water. Stool sampling was done with two issued immunochemical quantitative FOBT kits (OC-Sensor μ, Eiken Chemical, Japan) (Fig. 1). The sampling probe was inserted into different areas of the stool and placed in the tube container. The probe tip with the faecal sample was suspended in a standard volume of a Hb-stabilising buffer. Instructions were provided for two consecutive stool samples to be collected on two different days. No dietary restriction or

medication restriction was observed. Participants were required to write their name and identification number as well as date of stool collection on the tube, placed in resealable bags (ziplock bags) and stored in their home refrigerator. Participants were encouraged to return samples to the Singapore General Hospital within five days; the samples were subsequently analysed by using the semi-automated OC-Sensor μ instrument (Eiken Chemical, Japan) (Fig. 2). The machine itself had been calibrated using control standards provided by the manufacturer, and the level of occult blood for a positive reaction was preset to be 100 ng/ml by the manufacturer. Participants with positive stool samples ≥ 100 ng Hb/ml sample solution in any of the two samples were contacted via both phone and mail with advice to return for medical evaluation and colonoscopy screening.

Colonoscopy was performed up to the caecum or an obstructing lesion. Incomplete colonoscopy examination because of inadequate bowel preparation, technical problems or patient discomfort either resulted in a repeat colonoscopy, double-contrast barium enema or computed tomography (CT) colonography. Reported lesions on luminal studies were re-evaluated with repeat colonoscopy. All lesions found were biopsied or removed. Polyps were classified by number, size (≤ 5mm, 6–9 mm or ≥ 10 mm), location (proximal lesions were from the caecum to the splenic flexure, distal lesions from the descending colon to the rectum) and histology (hyperplastic, tubular, serrated, tubulovillous or villous). Dysplasia was classified as mild, moderate or severe. Patients were grouped according to the more advanced lesion if there was more than one lesion. Clinically significant neoplasia includes colorectal cancer, adenomas ≥ 10 mm in diameter, adenomas with ≥ 20% villous histological characteristics, or any severe dysplasia regardless of size.

## RESULTS

A total of 1,048 participants took part in the screening event. The median age of the participants was 54 (range 40–85) years, and the majority (52%, 547) were females. All but ten participants were Chinese. 15% (163) had first degree relatives with a history of colorectal cancer. 21% (222) of the participants claimed to have some abdominal symptoms of either abdominal discomfort, change in bowel habits, per rectal bleeding or loss of weight. 34 participants had previous screening by colonoscopy or FOBT within the previous year.

768 participants returned the stool kits for evaluation, giving a response rate of 73%. Of these, 49 participants (26 males, 23 females) tested positive for QFOBT (Table I). The median age of this group was 56 (range 40–81) years, and all the participants were Chinese. 39% (19) of this cohort had abdominal symptoms and two of these participants had previously undergone FOBT testing the year before, with one undergoing a colonoscopy which was reportedly normal. 43 of these participants underwent complete colonoscopy, three had barium enemas, one underwent CT colonography, and two of the participants declined further investigations (including the participant who had had a normal colonoscopy evaluation).

**Table I. Demographics and clinicopathological characteristics of participants with a quantitative faecal occult blood test positive test.**

| Factor/Category | No. (%) of patients |
|---|---|
| Gender | |
| Male | 26 (53) |
| Female | 23 (47) |
| Family history of colorectal cancer | |
| Yes | 5 (10) |
| No | 44 (90) |
| Symptoms | |
| Yes | 19 (39) |
| No | 30 (61) |
| Colonoscopy findings* | |
| Nil | 21 (45) |
| Piles | 13 (28) |
| Polyps | 10 (21) |
| Diverticular disease | 2 (4) |
| Cancer | 1 (2) |

*2 participants declined colonoscopy.

Clinicopathological characteristics of the participants who underwent colonoscopy are illustrated in Table I. The range of QFOBT values was 103–2,291 ng/ml, and there was no relation between QFOBT values and pathology in our series. In the cohort, 45% (21) had no abnormalities detected, 28% (13) were noted to have haemorrhoids, and 4% (2) had diverticular disease. 21% (10) had polyps and one case of colorectal cancer was detected. Of these participants with polyps and cancer, 82% (9) were located in the distal colon (Table II). 64% (7) had a solitary lesion, while the most number of polyps found was four, in two cases. 64% (7) of these cases had significant neoplasia (lesions ≥ 1 cm). Five of these cases had successful endoscopic polypectomies. Two cases required surgery and both underwent laparoscopic high anterior resections without any complications. In the cases who had polyps, 64% (7) had mild dysplasia, one case had moderate dysplasia and two had severe dysplasia, including the patient who required surgery. The final histology of the patient with cancer was a T2N1M0 cancer by the American Joint Committee on Cancer (AJCC) staging criteria.

**Table II. Pathological characteristics of colorectal neoplasia in quantitative faecal occult blood test positive patients.**

| Factor/Category | No. (%) of patients |
|---|---|
| Location of polyp/cancer | |
| Proximal | 2 (18) |
| Distal | 9 (82) |
| No. of lesions | |
| Solitary | 7 (64) |
| ≥ 2 | 4 (36) |
| Size of lesion (mm) | |
| ≤ 5 | 4 (36) |
| 6–9 | 0 |
| ≥ 10 | 7 (64) |
| Dysplasia | |
| Mild | 7 (64) |
| Moderate | 1 (9) |
| Severe | 2 (18) |
| Adenocarcinoma (T2N1M0) | 1 (9) |

## DISCUSSION

CRC is a leading cause of morbidity and mortality with huge human and financial costs. As a result, considerable efforts to evaluate effective screening tests to detect CRC at early curable stages have been made worldwide. Screening by FOBT has proven to be effective in decreasing mortality from CRC in both randomised trials[5-8] and case-control studies.[9,10] With the number of subjects enrolled in these four randomised controlled trials exceeding 320,000 and an average follow-up period ranging from 8 to18 years, a recent review by the Cochrane Library concluded that FOBT screening led to a reduction in CRC mortality of 16% (relative risk [RR] 0.84, 95% confidence interval [CI] 0.78–0.92). When adjusted for screening attendance, the reduction rises to 25% (RR 0.75, CI 0.66–0.84).[21]

A positive FOBT, however, is not intended to be a definitive diagnostic finding, but determines who is more likely to have colorectal neoplasia (adenoma ≥ 1 cm or colorectal cancer), and who should proceed for a colonoscopy. Thus, this is a classic example of the World Health Organisation concept of screening.[22] The selection process is advantageous in a healthy population as it is simple, convenient, and a non-invasive way to draw healthy persons into screening. It also focuses colonoscopical resources onto those more likely to have neoplasia, thus reducing healthcare costs. It is suggested that while colonoscopy alone as a one-step screening may reduce the miss rate for significant lesions, many may undergo screening for no gain because they do not have, or will never develop CRC in their lifetime.[23,24] These individuals are conversely subjected to harm that may counterbalance the benefit, but this is an issue that has never been tested by a randomised trial. Nonetheless, besides causing a modest reduction in CRC mortality, FOBT screening benefits include potentially reducing cancer incidence by the detection and removal of colorectal adenomas. Less invasive surgical options such as laparoscopic colectomy or transrectal excision may also be viable.[21]

However, multiple flaws remain. The harmful effects of FOBT screening include the psychosocial consequences of receiving false-positive results as well as false-negative results in patients and should be considered. It is also estimated that fewer than 10% of people who have occult blood positive in stool will actually have CRC, neither may it be suitable for adenoma screening in which bleeding often does not occur.[25] Hence, non-bleeding CRC or those not consistently discharging sufficient blood into the gut lumen will not be detected by either guaiac or immunological FOBTs. Furthermore, compliance to the test is often limited, thus restricting its effectiveness. Annual retesting is therefore necessary but may still be insufficient.

Successful efforts to reduce the disease burden from CRC depend on the implementation of effective screening practices in community settings. Screening events like these promote awareness but are not an accurate reflection of the disease burden of the population.[26] The results of this charity screening event retain an inherent bias found in any screening programme. Our study demonstrates a wide variation in the attitudes of participants who turned up for screening. On the one hand, we had several patients (34) who have had voluntary screening within the year but nonetheless sought a re-evaluation which was largely unnecessary, thus demonstrating the problem of selection bias. Participants with a positive family history may also be over-represented in this population (15%). In addition, many of the participants (21%, 222) had symptoms on screening and would in fact require proper clinical evaluation. This high proportion of symptoms detected could be due to the administration of a relatively detailed questionnaire by the doctors and nurses present on-site. For these symptomatic participants and participants with a family history, the appropriate investigation would probably have been a colonoscopy rather than screening with QFOBT. These participants were allowed to proceed largely due to the overwhelming numbers who turned up for the event and had queued for long hours to obtain the free kits. Nonetheless, the high turnout of first-time screening participants suggests that there remains a role for such screening events to provide reminders to the public. In addition, the overwhelming response in our event suggests that a vibrant and engaging method would serve as greater impetus for the public to participate. The carnival atmosphere was thought to be more inviting for the public despite the grim undertones of the disease, and

attract the younger generations to come forth. However, funding for such events remains a challenge. Aggressive marketing and canvassing for sponsors in both the healthcare and commercial sector is required in order to ensure the sustainability of future events.

Various countries have embraced the use of automated QFOBT testing as it provides a higher sensitivity and specificity as compared to the traditional guiaic FOBT. This includes the introduction of this facility in the authors' institution. Besides improved sensitivity and specificity, one additional advantage is the development of a fully automated procedure in the analysis of QFOBT. The instrument used for the development and quantification of the FIT (OC-Sensor μ, Eiken Chemical, Japan) is a desktop instrument and is self-containing with reagents, buffers, washing and fluid-disposal bottles. The collection of stool samples is easy with test kits provided by the manufacturer. Multiple faecal test sampling devices are able to be loaded concurrently in the instrument and mixing of faecal buffer solution with the latex-antihuman HbA antibody reagent is automatic. Multiple samples are thus analysed in a short period of time and allow for the exact quantification of the amount of occult blood in the sample ranging from less than 10 ng/ml to more than 1,000 ng/ml. However, there has been no conclusive evidence to date regarding the use of QFOBT in an average-risk population. More work would be required to define the optimal threshold levels for population-based screening programmes. While we were not able to provide sensitivity or specificity details from this screening event, the number of significant colorectal neoplasia (14%, 7) patients in those with positive QFOBT provide further evidence of the importance of screening with a potential reduction in CRC mortality.

The challenge remains of how to improve CRC detection rates. Novel multitarget DNA-based stools testing methods (mutations of k-ras, p53 and APC genes) as well as BAT-26 (microsatellite instability marker) have been proposed as future screening tools and have gained wide media and commercial attention.[27-29] These oncogene mutations that characterise colorectal neoplasia are detectable in exfoliated epithelial cells in the stool. In contrast to intermittent bleeding, shedding of the epithelial cells into the gut lumen is continual, thus improving sensitivity. However, when compared to FOBTs, this had major shortcomings[27-29] as it required tedious sample preparations, labour-intensive techniques, high costs as well as compliance issues as patients were required to provide an entire bowel movement (30g of stool) for analysis. These methods thus never gained prominence.

In conclusion, the myriad of screening tools exemplify the continued search for a more refined test. FOBT, despite its flaws, will remain an important tool as no other CRC screening procedure at present has been shown to reduce CRC mortality. It is appealing as initial costs are low, the test is widely available and FOBT does not pose an immediate risk to the screened population. While we are unable to comment on the accuracy of QFOBT, the ease with which the automated QFOBT could analyse large numbers of kits in a short period of time was certainly beneficial. To the best of our knowledge, this is the first such event reported in Asia and has highlighted that there is healthy demand for such screening events. The high number of participants with symptoms also demonstrates that an event held in a unique fashion such as this may prompt the public to come forward earlier for such health screening procedures. Continual education of the public at events like these are essential to improve attitudes towards screening as well as to ensure appropriate responses to test results. Improving screening rates would certainly go a long way to improve the CRC outcome.

## ACKNOWLEDGEMENTS

The authors would like to acknowledge the support of Nagase for the provision of QFOBT kits and reagents. We also thank staff nurses Miss Wee-Meng Ling and Miss Ariel Soo-Fern Ong for their invaluable contributions in the organisation and execution of the QFOBT screening event. In addition, we would like to acknowledge all volunteer SGH administrative staff, doctors, nurses and NUS medical students who contributed to the success of the event.

## REFERENCES

1. US Preventive Services Task Force. Screening for colorectal cancer. In: Guide to Clinical Preventive Services. 2nd ed. Baltimore: Williams & Wilkins, 1996: 89-103.
2. Guidelines for colorectal cancer screening and surveillance. Gastrointest Endosc 2000; 51:777-82.
3. Winawer SJ, Fletcher RH, Miller L, et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterol 1997; 112:594-642.
4. Winawer S, Fletcher R, Rex D, et al. Colorectal cancer screening and surveillance: clinical guidelines and rationale--Update based on new evidence. Gastroenterol 2003; 124:544-60.
5. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med 1993; 328:1365-71.
6. Hardcastle JD, Chamberlain JO, Robinson MHE, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996; 348:1472-7.
7. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996; 348:1467-71.
8. Kewenter K, Brevinge H, Engaråas B, Haglind E, Ahrén C. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult

blood testing. Results for 68,308 subjects. Scand J Gastroenterol 1994; 29:468-73.
9. Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst 1999; 91:434-7.
10. Faivre J, Tazi MA, EL Mrini T, et al. Faecal Occult blood screening and reduction of colorectal cancer morality: a case-control study. Br J Cancer 1999; 79:680-3.
11. Ministry of Health, Singapore. Clinical Practice Guidelines on Health Screening. Singapore: Minstry of Health, Singapore; July 2003.
12. Seow A, Koh WP, Chia KS, et al. Trends in cancer incidence in Singapore 1968-2002. Singapore Cancer Registry; 2004. Report no. 6.
13. Young GP, St John DJ, Winawer SJ, Rozen P. Choice of fecal occult blood test for screening: recommendations based on performance characteristics in population studies: a WHO (World Health Organization) and OMED (World Organization for Digestive Endoscopy) report. Am J Gastroenterol 2002; 97: 2499-507.
14. Petty MT, Deacon MC, Alexeyeff MA, St John DJ, Young GP. Readability and sensitivity of a new faecal occult blood test in a hospital ward environment. Comparison with an established test. Med J Aust 1992; 156:420-3.
15. Smith A, Young GP, Cole SR, Bampton P. Comparison of a brush-sampling fecal immunochemical test for haemoglobin with a sensitive guaiac-based fecal occult blood test in detection of colorectal neoplasia. Cancer 2006; 107:2152-9.
16. Morikawa T, Kato J, Yamaji Y, et al. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. Gastroenterology 2005; 129:422-8.
17. Castiglione G, Grazzini G, Miccinesi G, et al. Basic variables at different positivity thresholds of a quantitative immunochemical test for faecal occult blood. J Med Screen 2002; 9:99-103.
18. Vilkin A, Rozen P, Levi Z, et al. Performance characteristics and evaluation of an automated-developed and quantitative, immunochemical, fecal occult blood screening test. Am J Gastroenterol 2005; 100:2519-25.
19. Wong WM, Lam SK, Cheung KL, et al. Evaluation of an automated immunochemical fecal occult blood test for colorectal neoplasia detection in a Chinese population. Cancer 2003; 97:2420-4.
20. Levi Z, Rozen P, Hazazi R, et al. A quantitative immunochemical fecal occult blood test for colorectal neoplasia. Ann Intern Med 2007; 146:244-55.
21. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the fecal occult blood test. Hemoccult. Cochrane Database Syst Rev 2007; 1:CD001216.
22. Watson JMG, Jungner G. Principles and practice of screening for disease. Geneva: World Health Organization Public Health Papers 34, 1968.
23. Woolf SH. The best screening test for colorectal cancer-a personal choice. N Engl J Med 2000; 343:1641-3.
24. Fletcher RH. Screening colonoscopy: option or preference? Gastrointest Endosc 2000; 51:624-7.
25. Macrae FA, St John DJB. Relationship between patterns of bleeding and Hemoccult sensitivity in patients with colorectal cancers or adenomas. Gastroenterology 1982; 82:891-8.
26. Brawley OW, Kramer BS. Cancer screening in theory and in practice. J Clin Oncol 2005; 23:293-300.
27. Ahlquist DA, Skoletsky JE, Boynton KA, et al. Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. Gastroenterology 2000; 119:1219-27.
28. Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME; Coloectal Cancer Study Group. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med 2004; 351:2704-14.
29. Woolf SH. A smarter strategy? Reflections on fecal DNA screening for colorectal cancer. N Engl J Med 2004; 351:2755-8.