Colorectal cancer screening with faecal occult blood test within a multiple disease screening programme: an experience from Keelung, Taiwan

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SUPPLEMENT

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Background Given increasing rates of colorectal cancer (CRC) in countries with intermediate incidence rates, the decision to implement population-based screening must consider the trade-off between high costs and a relatively low yield. In Taiwan, we proposed community-based CRC screening using faecal occult blood tests (FOBT) within a multiple disease screening programme.

Aims Based on early results from the screening programme, we aimed to compare the projected efficacies, in terms of reductions in CRC mortality, achieved with multiple disease screening, single disease screening and no screening programmes.

Methods Annual FOBT has been included in the Keelung multiple disease screening programme. A total of 26,008 subjects were offered screening. Early indicators have been estimated to assess the potential effectiveness of this programme, including the Dukes' stage distribution of screen-detected cases, the proportionate incidence and the prevalence/incidence ratio. Transition rates according to adenoma size and Dukes' stage have been estimated from an eight-state Markov model. The projected mortality reductions based on this disease natural history have been estimated using Markov Chain Monte Carlo simulation for both multiple screening and single screening.

Results The overall attendance rate was 82% at the first screen and 87% at the second screen. At the first screen, 70% of screen-detected cases were localized (i.e. Dukes' stage A or B). The corresponding figure for the second screen was 80%. Approximately three-quarters of detected adenomas were smaller than 1 cm. The estimated mean transition times from diminutive adenoma to small adenoma, from small adenoma to large adenoma and from large adenoma to pre-clinical Dukes' A or B invasive carcinoma were 14.4, 5.4 and 5.6 years, respectively. Estimated reductions in CRC mortality, based on annual screening, are 23 and 33% for the single and multiple disease screening programmes, respectively. Multiple screening with an annual screening regime may lead to a further 13% reduction in mortality when compared to conventional single screening.

Conclusion Early indications suggest that population-based screening for CRC with FOBT, implemented through a multi-disease screening programme, is both feasible and efficacious. Further evaluation of the programme, through longer follow-up and cost-effectiveness analysis, is now required.

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INTRODUCTION

In Taiwan, colorectal cancer (CRC) remains the leading cause of cancer death. However, the removal of pre-cancerous lesions (adenomatous polyps) and the early detection of cancerous lesions (Dukes' A and Dukes' B stages) can effectively reduce both incidence of and mortality from the disease. Tools for early detection of colorectal neoplasm include periodical faecal occult blood testing (FOBT), flexible endoscopy including colonoscopy and sigomoidoscopy, and double-contrast barium enema (DCBE). The efficacy of FOBT screening has been demonstrated through several population-based randomized trials, with estimated mortality reductions of 33% for annual screening[1] and 15% for biennial screening.[2] However, the efficacy and cost effectiveness of FOBT may be different in countries with intermediate or low incidence rate of colon and rectum cancer.

The efficacy of a FOBT screening programme is dependent on a constellation of factors, including compliance rates (for both the initial test and the follow-up colonoscopies), disease natural history and the incidence rate of CRC in the underlying population. In countries with intermediate or low incidence rate, high costs may outweigh the benefits of screening if the yield of screen-detectable cases is low.

In Taiwan, screening for CRC started in 1992 with a selective programme called The Taiwan Multicenter Cancer Screening project (TAMCAS). This was a hospital-based project aimed at the early detection of three cancers (hepatocellular carcinoma, colorectal and breast cancers) in individuals who were considered to be at increased risk for each disease.[3] The high-risk group for CRC included individuals with a family history of CRC or other malignant diseases, as well as those with a personal history of familial polyposis, inflammatory bowel disease or cancer of the thyroid, breast or colorectum. The study estimated that screening of this cohort (using FOBT) reduced CRC mortality by approximately 25%.

Since then the incidence rate of CRC in Taiwan has increased dramatically, from 19.8 per 100,000 in 1995 to 36.3 per 100,000 in 2000. This has prompted central government to consider mass screening. The recently proposed Keelung multiple screening programme combines several screening programmes in a unified system with the

aim of reducing duplicate costs incurred in each separate programme (for example, resource use in field work of screening and referrals to medical care system). Moreover, as the Keelung Community-based Integrated Screening (KCIS) programme covers not only cancers but also some non-malignant chronic diseases, a reduction in chronic diseases that are associated with CRC risk (such as type 2 diabetes and hypertension) may indirectly affect CRC mortality. In addition, it is hoped that incorporating FOBT in a multi-disease screening programme may improve the rate of return of specimens, as well as attendance at follow-up colonoscopies.

The present study reports on early findings from CRC screening within the KCIS programme. The disease natural history of colorectal neoplasm according to adenoma size and Dukes' stage has also been estimated using the empirical data. Effectiveness, in terms of mortality reduction, has been estimated for multiple disease screening and single disease screening, as well as for different inter-screening intervals, and the results for different screening options have been compared.

MATERIALS AND METHODS

Study design and screened population

The Keelung programme commenced in 1999 and has been described in full elsewhere.[4] In brief, the programme focuses on five neoplastic diseases (breast cancer, liver cancer, colorectal neoplasm, cervical neoplasm and oral neoplasm) and three non-neoplastic diseases (type 2 diabetes mellitus, hypertension and hyperlipidemia). A sample of residents aged 30–79 years was selected from the population registry and invited to screening.

For CRC screening with FOBT, only people aged 50–79 years were included. Annual screening with an immunological, single session test (EIKEN, 1999–2003 and IKAGAKU LA – Hemochaser, 2004) was implemented. Each participant was instructed by public health nurses or technicians in how to accurately collect stool specimens and how to return specimens. Subjects with positive FOBT results were referred for colonoscopy. Cases with negative finding on colonoscopy were offered five-yearly colonoscopic screening. For cases with polyps, the surveillance strategy followed guidelines established by the US Preventive Service Task Force (USPSTF).[5,6]

Early indicators for evaluating the efficacy of CRC screening

Since the Keelung programme is still at an early stage, data on long-term outcomes such as mortality are not yet available. Thus early indicators for evaluating the efficacy of cancer screening were required.

First, the distribution of Dukes' stage for screen-detected cases was derived. The proportion of early-stage cancers will provide an indication of how effectively screening is advancing the time of diagnosis, and therefore the potential for mortality reduction.

Second, we calculated the ratio of interval cancers and expected cancers in the absence of screening,[7,8] where the latter was derived from the incidence of CRC in 1998 in Keelung, before the advent of KCIS. This quantity, known as the proportionate incidence or I/E ratio, is a function of both sojourn time and sensitivity, and is frequently used in the estimation of programme sensitivity. Using the traditional method, the test sensitivity can be estimated as $1–I/E$ ratio for interval cancers occurring within one year of a negative screening exam, and the programme sensitivity can be estimated as $1–I/E$ ratio for interval cancers occurring at any point during the programme.

The third indicator is the ratio of prevalence at first screen and expected annual incidence, known as the P/I ratio.[9,10] The P/I ratio is an alternative method for estimating the lead time gained through the early detection of CRC cases. Under the assumption of fixed sensitivity and constant pre-clinical incidence, the higher the ratio, the longer the sojourn time and the more the lead time gained. Again, the expected incidence was based on the incidence of CRC in 1998 in Keelung.

Stochastic process for estimating disease progression of colorectal neoplasm

A time-continuous, progressive Markov model was constructed for estimating the natural history of CRC. The model has eight states depicting the adenocarcinoma sequence according to adenoma size and Dukes' stage of invasive carcinoma (Figure 1). The techniques for modelling disease natural history using stochastic processes, including the formulation of the likelihood function and parameter estimation, are detailed in Duffy *et al.*[11] and Chen *et al.*[12] The mathematical details of estimation of mean sojourn times for pre-clinical Dukes' stage A and B and for pre-clinical Dukes' stage C and D are available from the authors.

Modelling and comparison of different screening regimes

Three screening regimes for CRC have been compared: screening as part of a multiple disease programme, single disease screening, and no screening programme. Decision trees for the three options were constructed and are

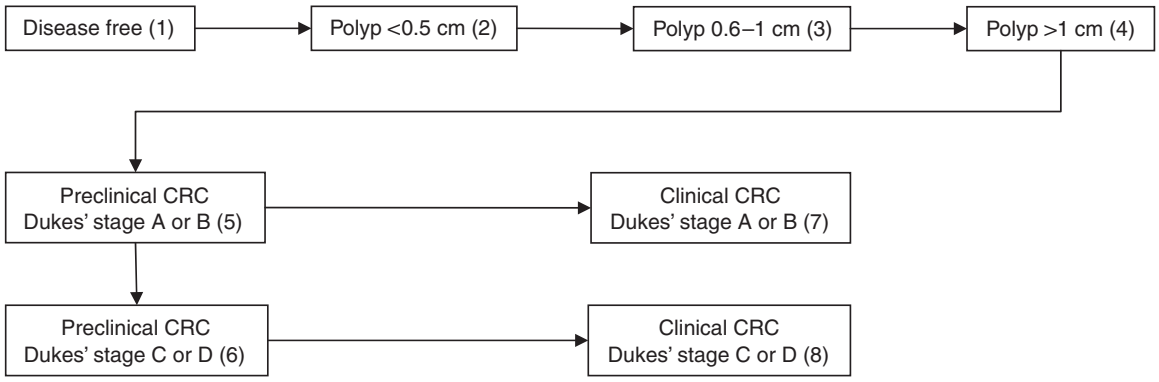

Figure 1 An eight-state Markov model for the natural history for CRC

available from the authors. The strategy of no screening follows the disease natural history of colorectal neoplasm as estimated in the model described above. Additionally, estimates of 10-year survival according to Dukes' stage and detection mode were taken from the literature.[1,2] For the other screening strategies, models were adjusted for compliance rates, referral rates, and the sensitivity and specificity of the tests. With the exception of sensitivity and specificity of screening for diabetes and hypertension, which were estimated from the literature,[13–15] base-case estimates were taken from the Keelung data. Finally, for the multiple screening regime, the probabilities of progression of CRC, given other co-morbidities diabetes or hypertension were estimated from the relative risks of CRC observed in association with these diseases (1.11 and 1.42) in the Keelung programme.[4] From this, the reduction in CRC mortality as a result of a reduction in these conditions could be estimated and applied to the multiple screening model. Markov Chain Monte Carlo (MCMC) simulation was applied to project the effectiveness, in terms of mortality reduction, of the different screening strategies.

RESULTS

Basic screening findings

The overall compliance rate was 82% at the first screen and 87% at the second screen. Rates did not differ substantially among age groups (Table 1). Rates of positive FOBT and of compliance following referral for colonoscopy are shown in Table 2. The overall positive rate was 5.6% and increased with age, from 4.5% for subjects aged 50–59 years to 7.3% for subjects aged 70–79 years. Similar findings were noted for subsequent screens. All subjects with positive FOBT were referred for colonoscopy, and the overall compliance with follow-up was 68% at first screen and 75% at the second screen. Variation across age groups was not substantial.

Table 3 shows the numbers of adenomas and invasive carcinomas detected through screening according to adenoma size and Dukes' stage. At the first screen, 70% of screen-detected invasive carcinomas were localized (i.e. Dukes' stage A or B). The corresponding figure for the second screen was 80%. Approximately three-quarters of detected adenomas were smaller than 1 cm at both first and second screens. Large proportions of small adenomas and localized invasive carcinomas suggest that CRC screening with FOBT in the KCIS programme may lead to significant reductions in invasive carcinoma and mortality from CRC in the future.

Table 1 Numbers of invitees and compliers by age groups in the Keelung programme, 2000–2002

	Number invited to screen	Number of compliers	Compliance rate (%)
First screening			
50–59	10,426	8750	84
60–69	9374	7736	83
70–79	6208	4835	78
Total	26,008	21,321	82
Subsequent screening			
50–59	2828	2505	89
60–69	3444	3032	88
70–79	2273	1857	82
Total	8545	7394	87

Table 2 Rates of positive FOBTs and compliance with follow-up colonoscopy in the Keelung programme, 2000–2002

	Number screened	Number of positive FOBT (%)	Number attending colonoscopy	Colonoscopy attendance rate (%)
First screening				
50–59	8750	393 (4.5%)	270	69
60–69	7736	448 (5.8%)	323	72
70–79	4835	353 (7.3%)	223	63
Total	21,321	1194 (5.6%)	816	68
Subsequent screening				
50–59	2505	83 (3.3%)	62	75
60–69	3032	140 (4.6%)	127	91
70–79	1857	119 (6.4%)	75	63
Total	7394	352 (4.8%)	264	75

Early indicators for evaluating the efficacy of CRC screening

Table 4 shows the estimated proportionate incidence of KCIS programme in 2000–2002. The overall sensitivity was estimated to be 70% (1–30%). The figures were 81, 80 and 66% for age groups 50–59, 60–69 and 70–79 years, respectively. Using the estimated sensitivity together with the estimated prevalence of 190.3 cases per 100,000 person-years and a compliance rate of 68% for follow-up colonoscopies, the estimated sojourn time was 3.07 years. Corresponding estimates by age group were 2.56, 2.91 and 3.29 years for subjects aged 50–59, 60–69 and 70–79 years, respectively.

Natural history of CRC

Table 5 shows the estimated transition rates derived from the eight-state Markov model. The annual incidence rate of diminutive adenoma was 130 per 100,000. The estimated mean times taken for the transitions from diminutive adenoma to small adenoma and from small adenoma to large adenoma were 14.4 years (1/0.07 per year) and 5.4 years (1/0.19 per year), respectively. The annual rate of malignant transformation from large adenoma to invasive carcinoma of pre-clinical Dukes' stages A and B was estimated as 0.18, yielding a mean dwelling time of 5.6 years for large adenomas. The estimated mean sojourn times for pre-clinical Dukes' stages C and D and for pre-clinical stages A and B were 1.1 and 3.76 years, respectively.

Co-morbidity of and death from type 2 diabetes and hypertension

Table 6 gives the proportions of CRC cases with type 2 diabetes, hypertension or various combinations of these diseases, along with the estimated probability of death from either CRC or causes related to the co-morbidities for each subgroup. The latter are based on figures from the UK Prospective Diabetes Study.[16]

Efficacy of CRC screening within a multiple screening programme compared with a single screening programme or no screening programme

Table 7 lists the base-case estimates used in Monte Carlo simulation for the comparison of the three screening

Table 3 Prevalence rates of adenomas and cancers by adenoma size and Dukes' stage

	Number screened	Adenomas (prevalence, %)	Adenoma size				CRC cases (prevalence, %)	Dukes' stage				
			0.5 cm	0.6~1 cm	>1 cm	Unknown		A	B	C	D	Unknown
First screening												
50–59	8750	48 (0.55)	28 (60%)	11 (23%)	8 (17%)	1	6 (0.07%)	0 (0%)	1 (25%)	3 (75%)	0 (0%)	2
60–69	7736	107 (1.38)	55 (52%)	24 (23%)	27 (25%)	1	18 (0.23%)	9 (60%)	3 (20%)	2 (13%)	1 (7%)	3
70–79	4835	80 (1.65)	39 (49%)	19 (24%)	21 (27%)	1	17 (0.35%)	6 (40%)	6 (40%)	3 (20%)	0 (0%)	3
Total	21321	235 (1.10)	122 (53%)	54 (23%)	56 (24%))	3	41 (0.19%)	15 (44%)	10 (24%)	8 (20%)	1 (2%)	7
Subsequent screening												
50–59	2505	21	9 (45%)	7 (35%)	4 (20%)	1	1 (0.04%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0
60–69	3032	49	25 (51%)	13 (27%)	11 (22%)	0	7 (0.23%)	1 (17%)	3 (50%)	2 (33%)	0 (0%)	1
70–79	1857	34	18 (53%)	7 (21%)	9 (26%)	0	6 (0.32%)	2 (67%)	1 (33%)	0 (0%)	0 (0%)	3
Total	7394	104	52 (50%)	27 (26%)	24 (23%)	1	14 (0.19%)	3 (30%)	5 (50%)	2 (20%)	0 (0%)	4

Table 4 Incidence rate of CRC after a negative screening result, as a percentage of the incidence rates in the absence of screening, Keelung programme

Age at entry (years)	Time since last negative screen	Interval cancers	Person-years	Interval cancer rate*	Expected incidence*	Proportionate incidence (%)
Overall (50–79)	0 to <1 year	11	28,282.71	38.89	130.93	30
	1 to <2 years	15	18,667.15	80.36	130.93	61
	2 to <3 years	7	8981.58	77.94	130.93	60
	3 to <4 years	3	3074.14	97.59	130.93	75
50–59	0 to <1 year	1	10,807.27	9.25	48.14	19
	1 to <2 years	4	7090.79	56.41	48.14	117
	2 to <3 years	2	3470.99	57.62	48.14	120
	3 to <4 years	1	1279.83	78.14	48.14	162
60–69	0 to <1 year	3	10,642.00	28.19	138.44	20
	1 to <2 years	2	6950.34	28.78	138.44	21
	2 to <3 years	5	3282.64	152.32	138.44	110
	3 to <4 years	2	1090.49	183.40	138.44	132
70–79	0 to <1 year	7	6833.44	102.44	273.16	38
	1 to <2 years	9	4626.02	194.55	273.16	71
	2 to <3 years	0	2227.95	0.00	273.16	0
	3 to <4 years	0	703.82	0.00	273.16	0

*Per 100,000 person-years

Table 5 Estimated transition rates in the progression of CRC: Results from the eight-state Markov model

Transition	Estimated transition rate	95% confidence interval	Mean transition time (years)
Normal → diminutive adenoma	0.0013	0.0010–0.0016	—
Diminutive adenoma → small adenoma	0.0696	0.0498–0.0895	14.37
Small adenoma → large adenoma	0.1854	0.1163–0.2545	5.39
Large adenoma → pre-clinical CRC Dukes' stage A or B	0.1772	0.1099–0.2444	5.64
Pre-pre-clinical CRC Dukes' stage A or B → clinical CRC Dukes' stage C or D	0.3079	0.1568–0.4590	3.25
Pre-pre-clinical CRC Dukes' stage A or B → clinical CRC Dukes' stage A or B	0.2455	0.1200–0.3709	4.07
Pre-clinical CRC Dukes' stage C or D → clinical CRC Dukes' stage C or D	0.9241	0.2531–1.5951	1.08

Table 6 Probability of CRC death according to chronic disease status

Chronic disease status	Proportion of all CRC cases	Probability of CRC death		
		Multiple screen	Single screen	No screen
Previous type 2 diabetes+previous hypertension	0.0312	0.0066	0.0066	0.0086
Previous type 2 diabetes+asymptomatic hypertension	0.0119	0.0050	0.0066	0.0086
Previous diabetes	0.0259	0.0048	0.0048	0.0063
Asymptomatic type 2 diabetes+previous hypertension	0.0078	0.0060	0.0066	0.0086
Asymptomatic type 2 diabetes+asymptomatic hypertension	0.0099	0.0045	0.0066	0.0086
Asymptomatic hypertension	0.0144	0.0056	0.0048	0.0063
Previous hypertension	0.1152	0.0058	0.0058	0.0076
Asymptomatic hypertension	0.1465	0.0045	0.0058	0.0076
No diabetes or hypertension	0.6372	0.0043	0.0043	0.0056

regimes: multiple screening, single screening and no screening. Table 8 shows the estimated efficacy of CRC screening with FOBT in the KCIS programme by screening modality (multiple or single) and by inter-screening interval. Mortality reduction is negatively associated with the length of inter-screening interval. Within a single disease screening programme, the simulation predicted that annual screening with FOBT leads to a 23% reduction in CRC mortality

Table 7 Parameters used in the computer simulation

Parameter	Base-case estimate	Sources
1. Transition rates		
Normal →Pre-clinical CRC Dukes' stage A or B	0.0014	Keelung empirical data
Pre-clinical CRC Dukes' stage A or B →pre-clinical CRC Dukes' stage C or D	0.24	
Pre-clinical CRC Dukes' stage A or B →clinical CRC Dukes' stage A or B	0.19	
Pre-clinical CRC Dukes' stage C or D →clinical CRC Dukes' stage C or D	0.72	
2. Distribution of CRC cases by chronic disease status	Empirical estimates (Table 6)	Keelung data
3. 10-year survival rates		
Pre-clinical Dukes' A and B	80.40%	Literature
Pre-clinical Dukes' C and D	28.48%	
Clinical Dukes' A and B	77.23%	
Clinical Dukes' C and D	17.26%	
4. Efficacy of reducing CRC		
Type 2 diabetes	14.53%	Keelung data
Hypertension	33.30%	
Type 2 diabetes+hypertension	42.99%	
5. Sensitivity (Sen) and specificity (Spe) of		
• FOBT for CRC	Sen: 60%	Keelung data and literature
• Multiple screening for type 2 diabetes	Sen: 80% Spe: 96%	
• Multiple screening for hypertension	Sen: 93% Spe: 95%	

Table 8 Projected efficacy of multiple and single screening by inter-screening interval in a screened population (n=22,176)

Screening regime	CRC (A or B)	CRC (C or D) or CRC death	CRC death	RR*	95% CI
Multiple screening					
Annual	278.30	167.87	102.82	0.67	0.52–0.86
Biennial	253.48	192.69	113.94	0.74	0.58–0.94
Three-yearly	241.88	204.29	119.02	0.77	0.61–0.98
Four-yearly	234.96	211.21	121.91	0.79	0.62–1.00
Five-yearly	231.17	215.00	124.25	0.81	0.64–1.02
Single screening					
Annual	329.54	195.22	118.22	0.77	0.60–0.97
Biennial	300.17	224.58	131.24	0.85	0.67–1.07
Three-yearly	286.43	238.33	137.18	0.89	0.71–1.12
Four-yearly	278.20	246.55	140.57	0.91	0.73–1.15
Five-yearly	273.70	251.05	143.35	0.93	0.74–1.17
Control	250.50	274.25	154.17		

*RR = relative rate of CRC mortality

compared with a 15% reduction with biennial screening. Annual screening with FOBT in multiple screening may lead to a 33% reduction in mortality from CRC and causes related to type 2 diabetes and hypertension. Thus, annual screening within a multiple screening programme is predicted to lead to a 13.5% greater mortality reduction than seen in a single screening programme.

DISCUSSION

Early assessment of effectiveness

This study has demonstrated the feasibility of implementing population-based CRC screening using FOBT within a community-based multi-disease screening programme. Compliance rates for both the initial test and for follow-up colonoscopies were high; and a high proportion of the screen-detected cases at both the first and subsequent screen were cancers of Dukes' stage A or B (68 and 80%, respectively). These rates are slightly higher than seen in the Nottingham FOBT trial.[2] In that study, the proportion of clinically detected cases (consisting of cancers in refusers, interval cancers and control arm cancers) that were Dukes' stage A or B cancers was 47%. This suggests that the Keelung screening programme is leading to the early detection of many CRCs.

In our study, the programme sensitivity was estimated to be 70%. This is higher than the estimated sensitivity in the Nottingham study. This difference is likely to be due to the fact that our study is using an immunological FOBT rather than a guaic-based test, which is thought to be less sensitive. The prevalence-to-expected incidence ratio, an empirical estimate of mean sojourn time, was 3.07 years, which lies between the mean sojourn times estimated from the eight-state Markov model of 1.1 years for pre-clinical Dukes' stage C or D and 3.76 years for pre-clinical Dukes' stage A or B. This estimate is only slightly longer than the estimate of 2.8 years given for a group of high-risk individuals in the TAMCAS project[3] and comparable with those from other studies addressing mass screening for CRC.[2,17]

Comparisons of different screening modalities

Simulation results suggest that annual mass screening for CRC using FOBT could lead to a 23% mortality reduction, decreasing to 15% for biennial screening. Annual screening within a multiple disease screening programme could lead to a 13.5% greater mortality reduction due to inclusion of screening for chronic diseases which are risk factors for CRC, such as type 2 diabetes and hypertension. One could argue that the simulation study is speculative. However, the parameters assumed in the study were all estimated from empirical data either in Taiwan or elsewhere. The most debatable assumption is that control of hypertension and impaired glucose tolerance will in turn reduce the risk of CRC. While there is no doubt that these conditions are risk factors for CRC,[18–20] the mechanisms of association are not clear, and it may be that both are markers for damage already suffered. Thus, the confirmation or otherwise of this remains a target for empirical research. Also, the incorporation of testing and treatment of these non-neoplastic conditions will increase the cost of the programme. The pros and cons of multiple screening should be assessed, once further empirical data are available, through a cost-effectiveness analysis.

CONCLUSIONS

In conclusion, early indications suggest that population-based screening for CRC using FOBT, implemented through a multi-disease screening programme, is both feasible and efficacious. Further evaluation of the programme, through longer follow-up and cost-effectiveness analyses, is now required.

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