ORIGINAL ARTICLE

Cost-effectiveness analysis for determining optimal cut-off of immunochemical faecal occult blood test for population-based colorectal cancer screening (KCIS 16)

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Objectives We aimed to determine the optimal cut-off of the immunochemical faecal occult blood test (iFOBT) by using cost-effectiveness analysis.

Methods A total of 22,672 subjects aged 50 years or older were invited to have an uptake of iFOBT. We collected data from screen-detected cases for the cut-off above 100 ng/mL and obtained interval cancers from a nationwide cancer registry for a cut-off below 100 ng/mL. We found a total of 65 colorectal cancer (CRC) cases, including 43 detected by screen and 22 diagnosed between screens (interval cases). The optimal cut-off was first determined by receiver operating characteristics (ROC) curve analysis. Formal economic evaluation was further applied to identifying the optimal cut-off by assessing the minimum incremental cost-effectiveness ratio (ICER), an indicator for cost per life year gained (effectiveness), given a series of cut-offs of iFOBT, ranging from 30 to 200 ng/mL compared with no screening.

Results ROC curve analysis found the optimal cut-off of iFOBT to be 100 ng/mL at which the sensitivity, false-positive and odds of being affected given a positive result were 81.5% (70.2%–89.2%), 5.7% (5.4%–6.0%) and 1.24 (1.19–1.32), respectively. The area under ROC curve was 0.87 (0.81–0.93). In economic appraisal, the screening programme irrespective of any cut-off dominated (less cost and more effectiveness) over the control group. The optimal cut-off (the lowest ICER) was 110 ng/mL at which an average of 0.054 life year was gained and that of 950 ($US) was saved.

Conclusions We used cost-effectiveness to identify 110 ng/mL as the optimal cut-off of iFOBT in a Taiwanese population-based screening for CRC. Our model provides a useful approach for health policy-makers in designing population-based screening for CRC to determine the optimal cut-off of iFOBT when cost and effectiveness need to be taken into account.

INTRODUCTION

The efficacy of population-based screening with faecal occult blood test (FOBT) with up to 33% mortality reduction from colorectal cancer (CRC) has been demonstrated in several randomized trials.[1–3] However, in most studies, FOBT was based on a chemical method that has approximately 55–66% sensitivity for CRC and was even worse for adenomas.[4]

To improve the performance of FOBT, immunochemical faecal occult blood test (abbreviated as iFOBT hereafter) has been developed and is reported to have higher sensitivity up to 82% (95% confidence interval [CI], 67%–92%) for people aged 50–70 years.[5] Since iFOBT evolved gradually from qualitative to quantitative assay, there is a trade-off relationship between sensitivity and specificity. Given a lower cut-off, higher sensitivity is accompanied by lower specificity and *vice versa*. A nationwide programme in Japan has demonstrated the feasibility of iFOBT with higher sensitivity but lower specificity.[6] From the viewpoint of clinical decision-making, the optimal cut-off of iFOBT based on a quantitative assay is worthy of being investigated.

As far as population-based screening is concerned, how to convert the loss resulting from false-negative cases and unnecessary false-positive cases to the relative contribution between cost and effectiveness given different cut-offs of iFOBT requires economic appraisal because the occurrence of false-negative cases affects life years gained and false-positive cases cause false alarm, both of which may also raise direct and indirect costs. However, few studies have been conducted to address the optimal cut-off value for identifying asymptomatic subjects through a population-based screening for CRC on the basis of cost-effectiveness analysis. In the present study, the optimal cut-off of iFOBT applied to a Taiwanese population-based screening for CRC was first determined by receiver operating characteristics (ROC) curve and further assessed by cost-effectiveness analysis.

MATERIALS AND METHOD

Study subjects

Data used for producing ROC curve analysis were derived from a multiple disease screening programme in Keelung, the northernmost county of Taiwan, between 1 January 2001 and 31 December 2003, conducted by the Keelung Community-based Integrated Screening (KCIS). The details of study design, implementation and results have been described in full elsewhere.[7] In brief, a total of 56,968 subjects (including 21,502 men and 35,466 women) were enrolled in the KCIS programme until the end of 2003. Out

of 56,968 subjects, 22,672 subjects aged 50 years or older were invited annually to have an uptake of iFOBT.

Screening procedure and stool sample collection

Two-stage screening procedure was used to ascertain asymptomatic adenoma and invasive carcinoma of the colon and rectum. One day iFOBT method with a brush-type sampler was given to each eligible subject while he/she was invited to out-reaching screening. How to collect a stool sample with a standard procedure as shown in Figure 1 was instructed by a trained public health nurse. The brush-type sampler for haemoglobin achieved the best participation rates by simplifying sampling and removing the need for restrictions of diet and drugs.[8] The participant returned the collected stool sample within 3–5 days to each health centre in the vicinity where the screening activity was held. The stool sample was uploaded to the automated machine to yield a series of quantitative readings of iFOBT value. The reagents of iFOBT were supplied by EIKEN Chemical Co., Japan. All subjects with iFOBT levels $\geqslant 100$ ng/mL were defined as positive iFOBT.

Study design

Although positive result of iFOBT was defined as 100 ng/mL in the current screening programme, a quantitative value of iFOBT was reported after the collected stool sample was analysed (see below). Figure 1 shows the study design for a quantitative assay for the relationship between the value of iFOBT and the ascertainment of CRC. The value of iFOBT was determined at baseline screen. For positive subjects, namely $\geqslant 100$ ng/mL, CRC cases were either ascertained by confirmatory diagnosis with colonoscopy ('a' in Figure 1) or identified through the linkage of a nationwide cancer registry for positive subjects but refused to be referred for confirmatory diagnosis (rejected CRC cases) during the follow-up period ('b' in Figure 1). For subjects with the value of iFOBT below 100, CRC cases were also identified through the linkage of the nationwide cancer registry during the follow-up period ('c' in Figure 1). The concurrent validity for the given cut-off regarding iFOBT against CRC in relation to sensitivity and specificity is arrayed as a cross-table like the following:

	True CRC	
Cut-off	Yes	No
$\geqslant 100$	a	b
<100	c	d

In population-based screening, it is very hard to estimate sensitivity $(a/(a+c))$ and specificity by different cut-off values unless all subjects with negative results of iFOBT receive confirmatory diagnosis. In addition, as mentioned above, among screening positives $(a+b)$, a fraction of subjects refused to receive colonoscopy (rejected screening positives). To tackle these two problems, we followed subjects with negative results of iFOBT $(c+d)$ or rejected screening positives to ascertain CRC by linking these persons with nationwide cancer registry with their personal identifier number. These CRC cases were defined as interval or rejected cancer under the assumption that all these cases were ascribed to false-negative cases at screen or rejected screening positives.

ROC analysis

The ROC curve was derived by plotting 1−specificity (X) against sensitivity (Y) given a series of cut-offs of iFOBT based on the study design mentioned above. The closer the ROC curve to the upper-left corner, the higher the predictive power for predicting CRC. The optimal cut-off

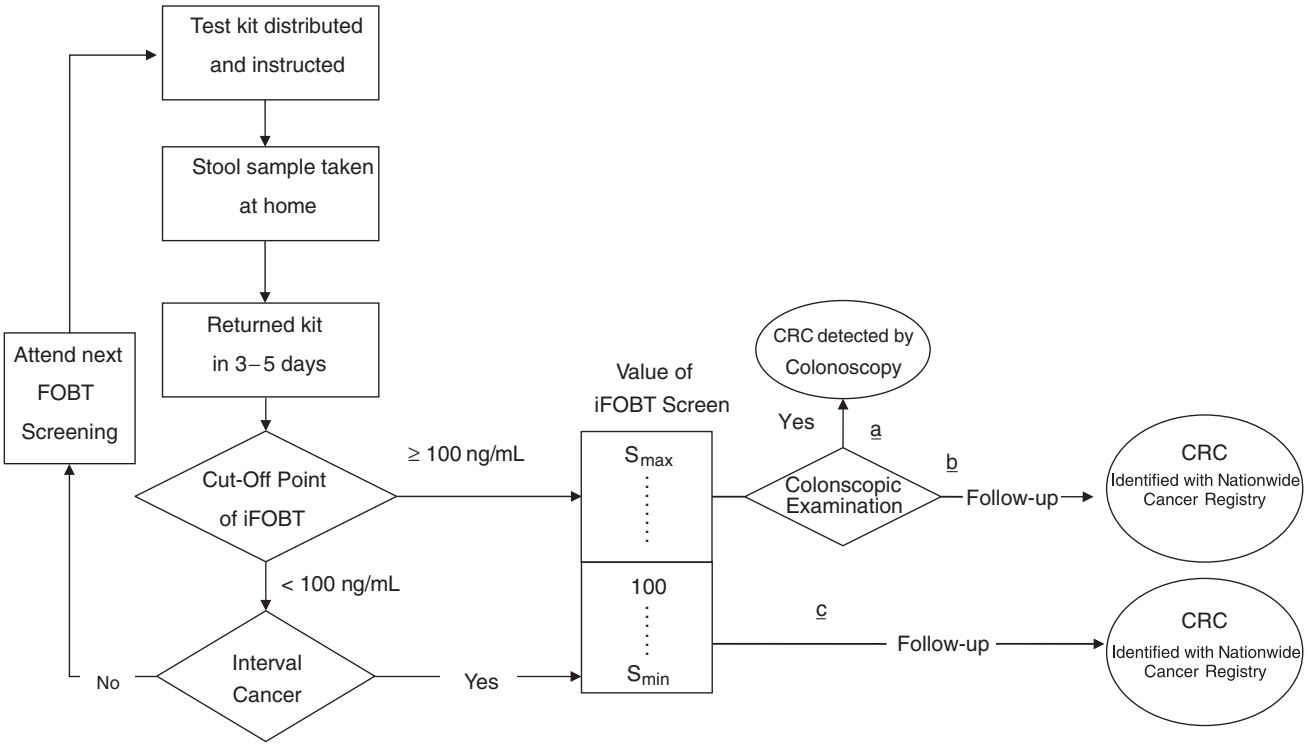

Figure 1 Study design for collecting iFOBT sample and relating the value of iFOBT to CRC

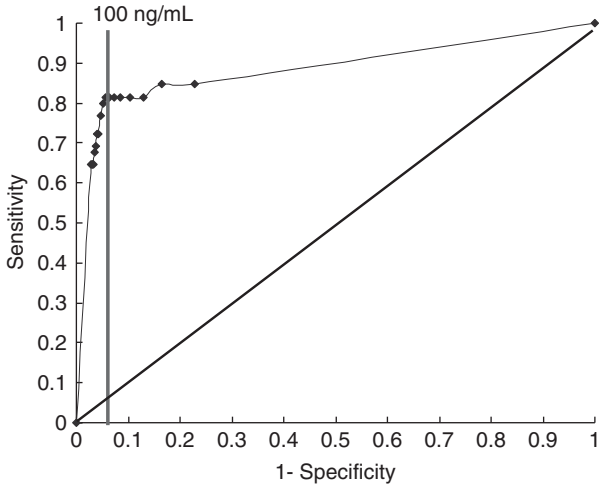

Figure 2 Empirical data-based receiver operation characteristic (ROC) curve for various cut-off values of iFOBT. Note: Area under ROC curve is 0.87

based on ROC curve was also ascertained by identifying the value closest to the upper-left corner (Figure 2).

Cost-effectiveness analysis

To determine the optimal cut-off based on cost-effectiveness analysis, alternative screening programmes given a series of cut-offs, as opposed to no screening, were compared by using a Markov decision model, which is shown in Figure 3. The detailed descriptions on the structure of the Markov decision model is given in the Appendix. Parameters used in the Markov decision model are listed in Table 1. Briefly, for no screening (baseline group), the natural history part is followed until occurrence of clinical cancer whose prognosis follows the annual death rate for clinical cancer. Age-specific pre-clinical incidence rates in the five-year category, shown in Table 1, were based on the annual incidence rate of CRC in Keelung city obtained from the Taiwan cancer registry system. Annual transition rate from the pre-clinical screen-detectable phase to the clinical phase, estimated by a three-state Markov model using data from the KCIS programme, which is very similar to the method used in the previous study,[9] was 0.1974. Annual death rate, also estimated from the KCIS data, was 0.092 for clinical cancer after surgery in conjunction with adjuvant therapy. For each cycle, the probability of death from competing causes is also considered.

For alternative screening programmes given different cut-offs, the transitions between states are characterized by whether to have uptake of screen (attendance rate), result of screen and compliance with colonoscopy (compliance). The progressions of true-negative, false-positive cases who refused to undergo colonoscopy or refusers who had not progressed to the occult pre-clinical screen-detectable phase (PCDP) at screen followed the natural history of the disease starting from the normal state, whereas the false-negative, true-positive cases who refused to undergo colonoscopy or refusers who had already progressed to the occult PCDP at screen followed the natural history of the disease starting from the occult PCDP as in the baseline group. Subjects who had stayed in the occult PCDP and were detected by screen would be classified as true-positive cases. They would be treated and defined as 'treated PCDP'. Note that those false-positive cases after being confirmed by colonoscopy will enter into surveillance mode. In addition to the annual death rate for clinical cancer mentioned in the baseline group, the annual death rate was 0.0357 for the treated PCDP cases after surgery in conjunction with adjuvant therapy (see Table 1). Annual death probabilities for competing causes used in the baseline group were also applied in the screened group.

Unit cost or annual cost associated with different states staying at each cycle is also specified in Table 1. As the societal perspective was adopted in current economic analysis, direct costs and indirect costs were included. Direct costs consist of iFOBT, colonoscopy for iFOBT positive, and polypectomy, biopsy, surgery, hospitalization, continued oncological care and terminal care. Indirect costs were related to production loss due to screen, colonoscopy, biopsy and treatment. As our medical care system has been covered by national health insurance since 1995, base-case estimates regarding the direct cost of iFOBT and medical costs were quoted from the price reimbursed by the Bureau of National Health Insurance (BNHI). All these costs were converted to US dollars using an exchange rate of 32 New Taiwan dollar (NTD) for each $1 in 2000. The production loss per day was imputed according to Accounting and Statistics issued by the Directorate General of Budget in Taiwan.

We used a Markov cohort simulation method to follow a hypothetical cohort from people aged 50–80 years with population size and the make-up of demographic characteristics identical to subjects in the KCIS programme. The calculation of expected cost and outcome (CRC death) in each cycle (a year) for alternative screening programmes given a series of cut-off points and no screening involves summing the costs and outcomes of all possible consequences weighted by the probability of consequence in the light of the model in Figure 3. Adding the costs of each state weighted by the proportion in each state and then adding across cycles yields the total costs in each programme. Adding the proportion of living cohorts for each cycle and adding across cycles gives the total life years. For each screening programme given a specific cut-off of iFOBT, the incremental cost (the difference in total costs between screening programme and no screening) divided by incremental effectiveness (the difference in total life years between screening programme and no screening, defined as life year gained) give an indicator of the incremental cost-effectiveness ratio (ICER). The optimal cut-off point of iFOBT was defined as the value with the minimum ICER. Since time horizons for estimating costs and effectiveness were different between the screen and no screen arms, all costs and effectiveness were discounted at an annual rate of 5%.

RESULTS

Descriptive findings

Among 22,672 participatants, 58% were women. The mean age was 63.36 (±9.20) years, with 64.87 (±9.51) years for men and 62.27 years (±8.82) for women. Table 2 shows positive results of iFOBT value larger than 100 ng/mL, compliance, screen-detected colorectal neoplasm and interval cancer or rejected after follow-up by age and gender. The subjects were distributed evenly across four age groups: 8650 (38.2%) were 50–59 years old, 7839 (34.6%) were 60–69 years old, 5126 (22.6%) were 70–79 years old and 1057 (4.7%) were 80 or older (Table 2).

The proportion of positive iFOBT test was 5.5%. The positive result of iFOBT in men (6.4%) was higher than that in women (4.8%). The proportion of positive iFOBT test increased with advancing age. The age distribution with

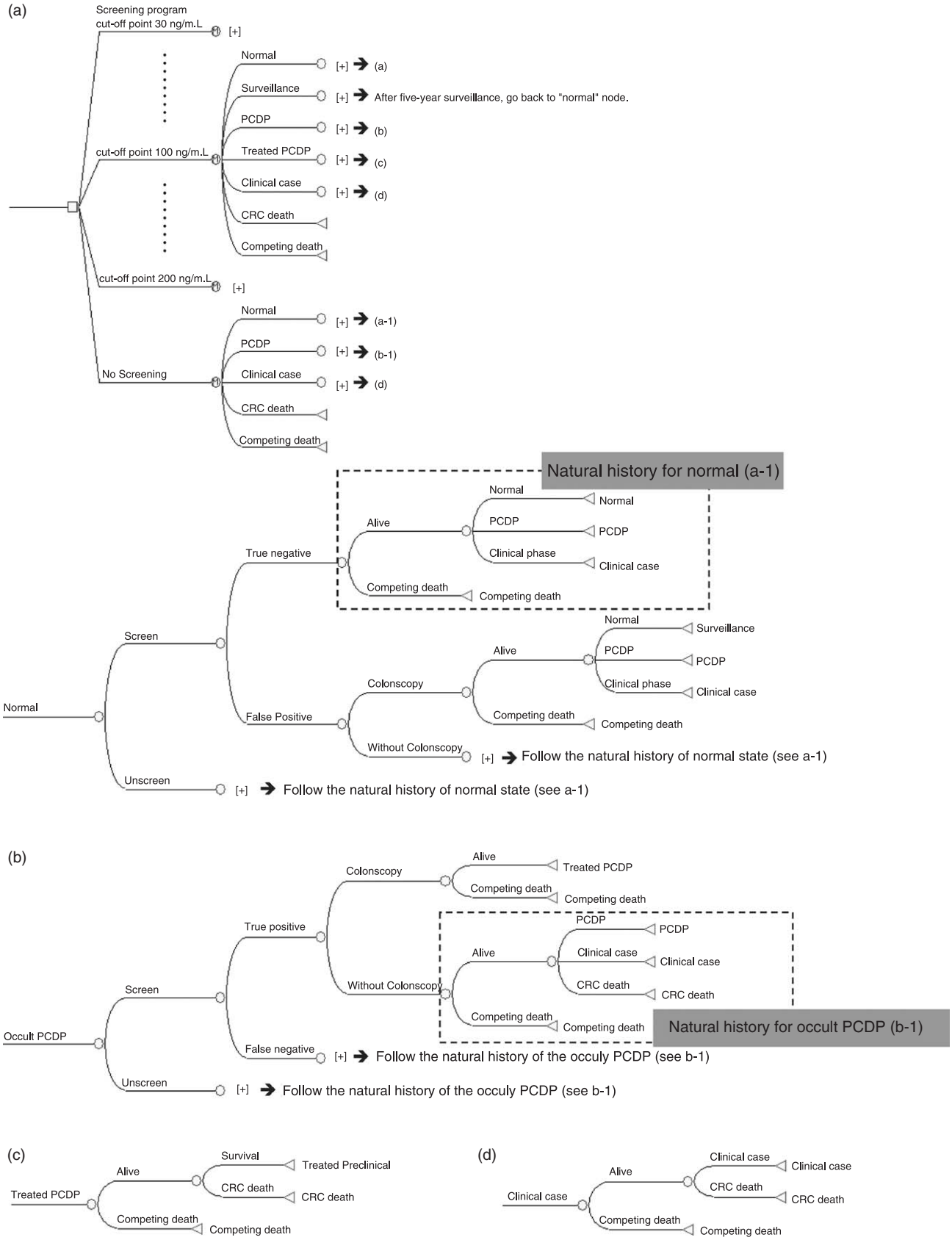

Figure 3 Decision tree used to evaluate the cost-effectiveness of alternative screening for CRC given different cut-off points of iFOBT as opposed to no screening. Symbols: □, decision node; ⓜ, Markov cycle; ◯, chance node (the assignment of probability); ◁, back to Markov cycle

screening positives in five broad categories included 50–59 years: 308 (3.6%); 60–69 years: 419 (5.4%); 70–79 years: 416 (8.1%) and 80+ years: 94 (8.9%). All screening positives ($N=1237$) were further referred to undergo colonoscopy. The compliance decreased from 72% for age group 50–59 years to 48% for subjects aged 80 years or older. The inverse relationship between age and compliance was more remarkable in women than in men. Of 1237 subjects, 811 (65.6%) were confirmed with colonoscopy, yielding 492 normal, 276 screen-detected adenomatous

Table 1 Base-case estimates for cost-effectiveness analysis

Variable	Base-case estimates	Reference
Natural history		
(1) Age-specific pre-clinical incidence rate (normal to the occult PCDP)	Annual rate	
50–54 years	0.001229	Incidence rate of Keelung city obtained from CRS, Taiwan
55–59 years	0.002232	
60–64 years	0.003253	
65–59 years	0.004702	
70–74 years	0.006664	
75–79 years	0.007957	
80+ years	0.007740	
(2) Occult PCDP→clinical phase	0.1974 (annual rate)	Estimated from KCIS data
Prognosis of death		
Treated PCDP→CRC death	0.0357 (annual rate)	Estimated from KCIS data
Clinical cases→CRC death	0.092 (annual rate)	Estimated from KCIS data
Compliance with colonoscopy	0.6556	KCIS
Costs		
(1) Direct cost		
Immunochemical FOBT	$2.2	KCIS
Colonoscopy	$70.3	BNHI
Colonoscopic polypectomy	$45	BNHI
Biopsy and pathology	$35.9	BNHI
Treatment cost (including surgery and hospitalization) for CRC	$8188	BNHI
Continued care cost for CRC	$188	BNHI
Terminal care for CRC	$11,031	BNHI
(2) Indirect cost		
Production loss	$6.5	DGBAS
Time for iFOBT	20 min	
Time for colonoscopy	4 h	
Time for polypectomy	4 h	
Length of stay in hospital (days)	15	BNHI
Number of accompanies (average)	0.25	
Continuing care per day	4 h	

CRS, Cancer Registry System, Taiwan; KCIS, Keelung Community Integrated Screening Program; BNHI, Bureau of National Health Insurance, Taiwan; DGBAS, Directorate General of Budget, Accounting and Statistics, Taiwan

Table 2 The proportion of positive iFOBT test (100 ng/mL cut-off), compliance with colonoscopy, and follow-up finding by gender and age group

				Colonoscopy						
	iFOBT			Accepted			Rejected			
Age group (years)	Negative (%)	Positive (%)	Compliance with colonoscopy (%)	*N*	Adenoma	CRC	*N*	CRC	Interval cancer	Total CRC
Men										
50–59	2941 (96.2)	117 (3.8)	70.9	83	28	4	34	2	0	6
60–69	2955 (93.5)	205 (6.5)	75.1	154	69	11	51	2	4	17
70–79	2416 (91.1)	237 (8.9)	67.9	161	72	9	76	1	4	14
>79	562 (92.1)	48 (7.9)	58.3	28	14	3	20	0	0	3
Subtotal	8874 (93.6)	607 (6.4)	70.2	426	183	27	181	5	8	40
Women										
50–59	5401 (96.6)	191 (3.4)	72.3	138	31	4	53	0	0	4
60–69	4465 (95.4)	214 (4.6)	63.6	136	31	5	78	2	3	10
70–79	2294 (92.8)	179 (7.2)	52.5	94	25	7	85	3	1	11
>79	401 (89.7)	46 (10.3)	37.0	17	6	0	29	0	0	0
Subtotal	12561 (95.2)	630 (4.8)	61.1	385	93	16	245	5	4	25
All Attendees										
50–59	8342 (96.4)	308 (3.6)	71.8	221	59	8	87	2	0	10
60–69	7420 (94.7)	419 (5.4)	69.2	290	100	16	129	4	7	27
70–79	4710 (91.9)	416 (8.1)	61.3	255	97	16	161	4	5	25
>79	963 (91.1)	94 (8.9)	47.9	45	20	3	49	0	0	3
Subtotal	21435 (94.5)	1237 (5.5)	65.6	811	276	43	426	10	12	65

Table 3 Sensitivity (%), false-positive (%) and odds of being affected by positive result (OAPR) at different cut-offs of iFOBT

Cut-off	Sensitivity (95% CI)	False-positive rate (95% CI)	OAPR (95% CI)
30	84.6 (73.7–91.5)	22.9 (22.4–23.4)	1:94 (1:72–1:123)
40	84.6 (73.7–91.5)	16.5 (16.1–17.0)	1:68 (1:52–1:89)
50	81.5 (70.2–89.2)	12.9 (12.5–13.4)	1:55 (1:42–1:72)
60	81.5 (70.2–89.2)	10.3 (9.9–10.7)	1:44 (1:34–1:57)
70	81.5 (70.2–89.2)	8.5 (8.2–8.9)	1:36 (1:28–1:47)
80	81.5 (70.2–89.2)	7.4 (7.0–7.7)	1:31 (1:24–1:41)
90	81.5 (70.2–89.2)	6.4 (6.1–6.8)	1:27 (1:21–1:36)
100	81.5 (70.2–89.2)	5.7 (5.4–6.0)	1:24 (1:19–1:32)
110	80.0 (68.5–88.0)	5.2 (4.9–5.5)	1:23 (1:17–1:29)
120	76.9 (65.2–85.6)	4.7 (4.4–5.0)	1:21 (1:16–1:28)
130	72.3 (60.3–81.8)	4.3 (4.1–4.6)	1:21 (1:16–1:27)
140	72.3 (60.3–81.8)	4.1 (3.8–4.3)	1:20 (1:15–1:26)
150	69.2 (57.1–79.2)	3.8 (3.5–4.0)	1:19 (1:15–1:25)
160	67.7 (55.5–77.9)	3.5 (3.3–3.8)	1:18 (1:14–1:24)
170	64.6 (52.3–75.2)	3.3 (3.1–3.5)	1:18 (1:14–1:23)
180	64.6 (52.3–75.2)	3.1 (2.9–3.4)	1:17 (1:13–1:22)
190	64.6 (52.3–75.2)	3.0 (2.8–3.2)	1:16 (1:12–1:21)
200	64.6 (52.3–75.2)	2.9 (2.6–3.1)	1:15 (1:12–1:20)

CI, confidence interval; OAPR, odds of being affected given a positive result

polyps and 43 screen-detected CRC. For subjects with negative results of iFOBT or subjects who were positive but did not undergo colonoscopy, we identified 22 invasive cases (10 rejected and 12 interval cases).

ROC curve analysis

Table 3 shows a series of sensitivity, false-positive and odds of being affected given a positive result (OAPR) and a series of cut-offs of iFOBT from 30 to 200 (ng/mL). The area under ROC curve was 0.87 (95% CI: 0.81–0.93). The optimal cut-off was 100 ng/mL at which the corresponding sensitivity, false-positive and OAPR for detection of CRC were 81.5% (95% CI: 70.2–89.2%), 5.7% (95% CI: 5.4–6.0%) and 1.24 (1.19–1.32), respectively (Table 3 and Figure 2). By the stratification of gender, the threshold value was 110 ng/mL for women with the area under ROC curve equal to 0.89 (95% CI: 0.80–0.98). In men, the corresponding threshold value was 100 ng/mL. The area under ROC curve was 0.87 (95% CI: 0.80–0.95). The overlapping of 95% CIs of the area under ROC curve between men and women suggests that the selection of cut-off does not vary significantly with gender.

Economic analysis

Figure 4a shows the relationship between average discounted life years and discounted costs and different cut-offs of iFOBT. The average discounted life years decreased with the increased cut-off of iFOBT. The average discounted costs showed an increase from 30 to 50, then had a slight drop until 100, and started to rise after 100. Figure 4b shows the corresponding results of ICER. For 'no screening' (the baseline group), the average discounted life years and costs were 13.7797 and 2005.40. Compared with the baseline group, the screening programme irrespective of any cut-off dominated over the control group indicated by minus ICER (less cost and more effectiveness). Given 100% attendance rate, ICER had the lowest value at 110 ng/mL at which average discounted life years and costs were 13.83 and 1100.10, which yielded an average of 0.054 life year gained and that of cost-saving by 905.30 ($US).

DISCUSSION

While iFOBT with a quantitative assay has been extensively applied to population-based screening for CRC, a concern about the optimal cut-off was raised. At the lower cut-off value, unnecessary colonoscopies resulting from higher false-positive cases with iFOBT but high utility as a result of lower false-negative cases would be expected. By contrast, at a higher cut-off value, false-positive and superfluous colonoscopies were reduced but false-negative cases were increased. The determination of cut-off point for iFOBT, particularly based on a quantitative assay, is of paramount importance to population-based screening for identifying asymptomatic CRC cases. ROC curve analysis and cost-effectiveness analysis was therefore applied to determining the optimal cut-off point.

To the best of our knowledge, this is the first study to show how the optimal cut-off point has been determined using formal ROC curve analysis on the basis of empirical data from a population-based screening for CRC. At the standard cut-off (100 ng/mL), sensitivity was 81.5 % (95% CI: 70.2–89.2), false-positive was 5.7% (95% CI: 5.4–6.0%) and OAPR was 1.24 (1.19–1.32). If the cut-off value was raised to 130 ng/mL, the sensitivity was decreased to 72.3% (95% CI: 60.3–81.8%), but the specificity was increased to 95.7%. Using ROC curve analysis, the overall optimal cut-off point was 100 ng/mL. This confirmed that the standard cut-off point 100 ng/mL that used to be adopted in clinical setting for early detection of CRC is also reproducible from population-based screening for CRC.

Very few previous studies can be compared with our results because most of the previous studies reporting sensitivity and specificity were based on qualitative assay. Our sensitivity estimate using the current standard cut-off, i.e 100 ng/mL, was consistent with Zappa *et al.*'s[5] or Greenberg *et al.*'s[10] findings that showed 82–83% sensitivity using reverse passive haemagglutination test, an iFOBT method, but higher than 53.8% sensitivity in Saito's study[11] and 68% sensitivity in Allison *et al.*'s study.[12] Compared with other cut-off point studies, while cut-off point was at 150 ng/mL, our results showed lower sensitivity (69%) than those of Nakama *et al.* study (81%).[13] In addition to technical reasons such as laboratory variation or different kits, the disparity between our study and other studies may be attributed to the adoption of different inter-screening intervals, as our estimates on sensitivity are highly dependent on interval cancer, which is strongly affected by the inter-screening interval. This suggests that the optimal cut-off point identified in our study may only be applicable to our KCIS study.

Our current study has two major strengths. The first merit is to use a good study design to identify interval CRC cases

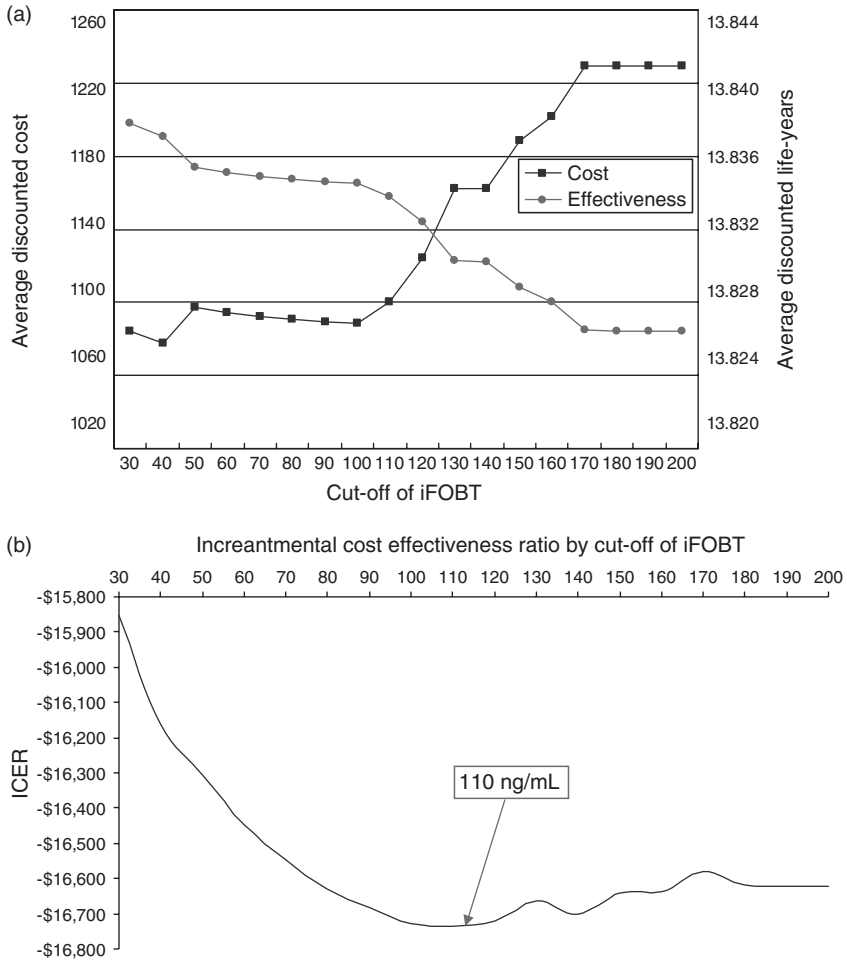

Figure 4 The change of average discount cost ($US) and life years and ICERs by cut-off values of iFOBT

missed at previous screen to capture false-negative cases for iFOBT value below 100 ng/mL. Moreover, since not all subjects with positive iFOBT were referred, these subjects were therefore followed over time to identify CRC cases. A total of 22 cases were ascertained, including 10 patients who were offered but rejected a colonoscopy and 12 interval cases. Although this method is not perfect, it is an expedient because it is not feasible to identify asymptomatic CRC below 100 ng/mL or cases refusing to take colonoscopy, as mentioned above, unless all subjects below 100 ng/mL undergo confirmatory diagnosis or the programme has 100% referral rate, both of which cannot be carried out in reality.

The second unique character is that our study adopted two methods to determine the optimal cut-off for iFOBT. Both methods have considered the relative harm between false-negative and false-positive. However, the ROC curve analysis to ascertain the optimal cut-off value is only based on the trade-off between sensitivity and specificity. This may be adequate provided that the screening policy is not contingent on cost. However, since false-positive cases are highly related to the cost of confirmatory procedure and false-negative cases are strongly related to the efficacy and costs involved in treating advanced cancer, and both are also related to indirect cost, economic appraisal is therefore required to determine the optimal cut-off. Very few studies have been conducted to convert loss as a result of both false-negative cases and false-positive cases into increased cost or the reduction of effectiveness. In our study, we exploited conventional cost-effectiveness analysis, including direct and indirect costs, to identify 110 ng/mL as the optimal cut-off for population-based screening when attendance rate is 100% and other parameters are identical to the KCIS programme. One study in Hong Kong recommends 150 ng/mL as the optimal cut-off.[14] However, it is very difficult to make a comparison between two studies because only direct cost was considered in that study. The relationship in Figure 4 also clearly indicated the evolution of average discounted life years and average discounted costs with the change in cut-off values of iFOBT. The average discounted life years decreased with the raised cut-off values of iFOBT, whereas the average discounted costs had a conspicuous increase from 30 to 50 ng/mL, crept down from 50 until 100 ng/mL and had a remarkable increase beyond 110 ng/mL. This change parallels the trade-off between false-positive and false-negative cases. The increased cost from 30 to 50 ng/mL may suggest that the increased cost due to false-positive cases contribute more to the cost related to false-negative cases in a lower cut-off. A slight decrease between 50 and 100 ng/mL is a reflection of the fact that the reduced costs due to the reduced false-positive cases outweigh the direct and indirect costs involved with false-negative cases in the range. False-negative cases play a more crucial role in costs than false-positive cases when the cut-off is raised to 100 ng/mL or higher.

There are two limitations in our study. The first is that the optimal cut-off point for detecting adenoma had not been

determined because adenoma due to false-negative cases or subjects who were offered but rejected a colonoscopy cannot be known in the absence of registered data.

The second limitation is that the determination of optimal cut-off may be subject to uncertainty of parameters used in the Markov decision model. For example, if attendance rate is changed from 100% to 70%, the optimal cut-off value is changed to 100 ng/mL. To tackle this problem, the parameters used in the Markov decision model are derived from the KCIS programme that is exactly the underlying population we want to apply. In addition, different inter-screening intervals may also affect sensitivity and specificity estimates used in ROC analysis as mentioned above. This strongly suggests that our results of cost-effectiveness for determining the optimal cut-off value may be applied only to the current population-based screening data, the KCIS programme, but may not be adequate for other population-based screening programmes. We strongly suggest that such a cost-effectiveness analysis used in our study should be repeated to determine the optimal cut-off value given a different scenario.

In conclusion, we demonstrate how to apply conventional cost-effectiveness to determine the optimal cut-off value for population-based screening for CRC with iFOBT. The optimal cut-off value recommended for subjects aged 50 years or older in our community-based screening programme was 110 ng/mL. Our model provides a useful approach for health policy-makers to determine the optimal cut-off value for population-based screening for CRC with iFOBT when cost and effectiveness need to be taken into account.

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REFERENCES

1 Mandel JS, Bond JH, Church TR, *et al.* Reducing mortality from colorectal cancer by screening for fecal occult blood. *N Engl J Med* 1993;**328**:1365–71
2 Hardcastle JD, Chamberlain JO, Robinson MHE, *et al.* Randomized controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;**348**:1472–7
3 Kronborg O, Fenger C, Olsen J, *et al.* Randomized study as of screening for colorectal cancer with faecal occult blood test. *Lancet* 1996;**348**:1467–71
4 Ahlquist D, Wieand H, Moertal C, *et al.* Accuracy of fecal occult blood screening for colorectal neoplasia: a prospective study using Hemoccult and Hemoquant. *JAMA* 1993;**269**:1262–7
5 Zappa M, Castiglione G, Paci E, *et al.* Measuring interval cancers in population-based screening using different assays of fecal occult blood testing: the District of Florence experience. *Int J Cancer* 2001;**92**:151–4
6 Saito H. Screening for colorectal cancer by immunochemical fecal occult blood testing. *Jpn J Cancer Res* 1996;**87**:1011–24
7 Chen THH, Chiu YH, Luh DL, *et al.* Community-based multiple screening model: design, implementation, and analysis of 42,387 participants. Taiwan Community-based Integrated Community Screening Group. *Cancer* 2004;**100**:1734–43
8 Cole SR, Young GP, Esterman A, Cadd B, Morcom J. A randomized trial of the impact of new faecal haemoglobin test technologies on population participation in screening for colorectal cancer. *J Med Screen* 2003; **10**:117–22
9 Yang KC, Liao CS, Chiu YH, Yen AMF, Chen THH. Colorectal cancer screening with faecal occult blood test within a multiple disease screening programme: an experience from Keelung, Taiwan. *J Med Screen* 2006; **13**:S8–13
10 Greenberg PD, Bertario L, Gnauck R, *et al.* A prospective multicenter evaluation of new fecal occult blood tests in patients undergoing colonoscopy. *Am J Gastroenterol* 2000;**95**:1331–8
11 Saito H. Sensitivity of immunochemical occult blood testing in detecting early colorectal cancer. *Nippon Rinsho* 1996;**54**:1421–4
12 Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med* 1996; **334**:155–9
13 Nakama H, Zhang B, Zhang Y. Evaluation of the optimum cut-off point in immunochemical occult blood testing in screening for colorectal cancer. *Eur J Cancer* 2001;**37**:398–401
14 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

APPENDIX

Markov decision model

To assess how cost and effectiveness are affected by a series of cut-offs of iFOBT used in population-based screening programmes for CRC, a Markov decision model is constructed and shown in Figure 3. The details regarding the structure and Markov model are delineated as follows.

(1) Decision: A series of decision nodes are assigned by considering a series of alternative screening programmes given the different cut-offs of iFOBT, ranging from 30 to 200 ng/mL, as opposed to no screening.
(2) Markov cycle tree: A Markov cycle process is used to capture multi-state outcomes, including normal, the PCDP phase (treated or occult), clinical phase, competing causes of death and death from CRC in each cycle that is taken as one year in our study. The details for the progression of each state are described as follows.

    (1) Normal (part (a) in Figure 3): Given that true disease is normal, an individual may be detected as true negative or false-positive as a result of first round of screen. Before entering into the second round of screen, it is possible for a true negative to stay in the normal state or to evolve to the occult PCDP or to the clinical phase via the occult PCDP, which is governed by annual transition probabilities converted from age-specific pre-clinical incidence rate and annual transition rate from the occult PCDP to clinical phase, as shown in Table 1, to annual transition probabilities using conventional backward Kolmogorov equation. Not that such a transition is also conditioned on the fact that he/she is still alive and not susceptible to other causes of death. Given that true disease status is normal, the other possibility for an individual is false-positive after the uptake of screen. Whether and when he/she returns to periodical iFOBT screen is dependent on whether it is confirmed by colonoscopy. Those false-positives confirmed by colonoscopy return to normal and may enter the pool of screen programme by five-year inter-screening interval (surveillance mode). During the five-year period, transitions to all possible states in each cycle are still governed by annual transition probabilities. The evolution for false-positives who do not comply with colonoscopy follows the natural history of the disease (similar to the part (a-1) in Figure 3) until they return to the next round of screen. Subjects who refused to have the uptake of screen followed the normal state of natural history as seen in (a-1) of Figure 3.
    (2) The occult PCDP (the part (b) in Figure 3): The uptake of screen for those whose true disease status has already been in the occult PCDP may yield two possible outcomes, true-positive and false-negative. An individual confirmed as CRC by colonoscopy would be treated (treated PCDP).

Subjects who have been in the PCDP phase and are screened as positive but reluctant to undergo colonoscopy follow the natural history of the disease (see the part (b-1) in Figure 3). As times to the occurrence of PCDP in these cases are not exactly known but the time to occurrence of clinical cancers is known, the annual transition probability of death from CRC for such occult PCDP cases is therefore a function of both annual transition rate from the occult PCDP to clinical phase and annual death rate for clinical cancers.

(3) Treated PCDP: The treated PCDP follows the part (c) in Figure 3, which requires annual death rate of treated PCDP and other competing causes following life-table information obtained from vital statistics from Taiwan.

(4) Clinical case: Clinical cases will follow part (d), which indicates the prognosis of death from other causes or CRC.

(5) Death: Both deaths from CRC and other competing causes are absorbing states.

Assumptions required for decision analysis include the following:

(1) Since a cycle is taken as one-year annual transition, probabilities are assumed constant.

(2) Progressive assumption: Each invasive carcinoma of CRC and death from CRC follows a four-state progressive model.

$$\text{Normal} \rightarrow \text{PCDP} \rightarrow \text{Clinical Phase} \rightarrow \text{CRC death}$$

No regression is allowed. Subject with progression from normal through PCDP and finally to clinical phase is said to follow the natural history of the disease. The unscreened subjects or screen positive but without being confirmed by colonoscopy will follow this process to surface to clinical cases in the presence of symptoms or signs. Those who are in the state of PCDP while screened are detected as true positive would be treated, and the transition of natural history from the PCDP to the clinical phase would be interrupted. This is called 'treated PCDP'.

(3) Lack of memory is assumed to be due to Markov property.