BMJ Open

Optimising colorectal cancer screening in Shanghai, China: a modelling study

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To cite: Cenin D, Li P, Wang J, *et al*. Optimising colorectal cancer screening in Shanghai, China: a modelling study. *BMJ Open* 2022;**12**:e048156. doi:10.1136/bmjopen-2020-048156

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-048156).

Received 18 December 2020
Accepted 31 March 2022

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ABSTRACT

Introduction To reduce the burden of colorectal cancer (CRC) in Shanghai, China, a CRC screening programme was commenced in 2013 inviting those aged 50–74 years to triennial screening with a faecal immunochemical test (FIT) and risk assessment. However, it is unknown whether this is the optimal screening strategy for this population. We aimed to determine the optimal CRC screening programme for Shanghai in terms of benefits, burden, harms and cost-effectiveness.

Methods Using Microsimulation Screening Analysis-Colon (MISCAN-Colon), we estimated the costs and effects of the current screening programme compared with a situation without screening. Subsequently, we estimated the benefits (life years gained (LYG)), burden (number of screening events, colonoscopies and false-positive tests), harms (number of colonoscopy complications) and costs (Renminb (¥)) of screening for 324 alternative screening strategies. We compared several different age ranges, screening modalities, intervals and FIT cut-off levels. An incremental cost-effectiveness analysis determined the optimal strategy assuming a willingness-to-pay of ¥193 931 per LYG.

Results Compared with no screening, the current screening programme reduced CRC incidence by 40% (19 cases per 1000 screened individuals) and CRC mortality by 67% (7 deaths). This strategy gained 32 additional life years, increased colonoscopy demand to 1434 per 1000 individuals and cost an additional ¥199 652. The optimal screening strategy was annual testing using a validated one-sample FIT, with a cut-off of 10 µg haemoglobin per gram from ages 45 to 80 years (incremental cost-effectiveness ratio, ¥62 107). This strategy increased LY by 0.18% and costs by 27%. Several alternative cost-effective strategies using a validated FIT offered comparable benefits to the current programme but lower burden and costs.

Conclusions Although the current screening programme in Shanghai is effective at reducing CRC incidence and mortality, the programme could be optimised using a validated FIT. When implementing CRC screening, jurisdictions with limited health resources should use a validated test.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Microsimulation Screening Analysis-Colon (MISCAN-Colon) is a well-established microsimulation model for colorectal cancer that has been extensively validated.
⇒ In this analysis, we assessed 324 alternative screening strategies to determine the optimal colorectal cancer screening programme for Shanghai in terms of benefits, burden, harms and cost-effectiveness.
⇒ There is some uncertainty about the accuracy of the test characteristics of the faecal immunochemical tests, and therefore their performance, in the Chinese population.
⇒ Given conflicting advice in China about the post diagnostic colonoscopy pathway, (including when to return to screening and the surveillance pathway), we simulated surveillance in our main analysis consistent with European Society of Gastrointestinal Endoscopy Guidelines, which may not be an accurate reflection of clinical practice in Shanghai.
⇒ The limited information on complications arising from colonoscopy in China likely means our results provide an underestimate of complications and their associated costs.

INTRODUCTION

Colorectal cancer (CRC) is a global health issue with significant incidence and mortality, however, this burden is unevenly distributed. Due to its large population, China is a noteworthy contributor to the global burden of CRC and is expected to account for approximately 28% of CRC cases and deaths in 2018.[1 2] Moreover, CRC incidence and mortality has been steadily increasing in China: between 2003 and 2011, incidence rose from 12.8 to 16.8 per 100 000, while mortality rose from 5.8 to 7.8.[3] This, coupled with a steadily ageing population[4] suggests the large burden of CRC is set to remain in the foreseeable future[5] and represents a significant public health challenge for the country.

Although screening has long been established as an effective method to reduce CRC incidence and mortality, it has not yet been universally implemented. While a diverse range of CRC screening programmes have been established throughout Europe, North America and Australia, to date, very few countries in Asia have implemented such programmes.[6] In an effort to reduce the

burden of CRC, there is a growing trend for lower incidence countries to implement organised population CRC screening,[6] as is the case in China, where region-specific programmes are currently being implemented.[7 8] However, despite the rising CRC incidence and mortality, the first consensus on organised CRC screening in China was not available until 2014.[9]

Shanghai, one of the largest and most developed cities in China, experiences some of the highest CRC incidence and mortality in China.[10] CRC incidence rates have increased significantly from 1973 to 2010, with the age-adjusted incidence rates increasing from 13.6 to 28.2 per 100 000 in men and 11.9 to 22.3 per 100 000 in women.[10–12] To address this, the Shanghai Municipal Government implemented a community-based CRC screening programme in 2013.[7] The programme invited individuals aged 50–74 to participate in CRC screening, offering triennial screening with a locally produced faecal immunochemical test (FIT) and a risk questionnaire. This strategy was decided on after comprehensive evaluation of the capacity of health resources of the region.[7] The initial results of the screening programme in Shanghai[7] and the Pudong New Area (the largest district of Shanghai)[13] have recently been published. These results highlight several challenges for the implemented screening programme, including poor uptake of initial offer of screening, suboptimal attendance at diagnostic colonoscopy and low rates of cancer detection.

Such results call into question whether the implemented CRC screening programme is optimal for the population. Therefore, the aim of this research is to determine the optimal CRC screening programme for Shanghai in terms of benefits, burden, harms and costs. Using microsimulation modelling, we compared and assessed the performance of the current screening strategy against standardised and validated FITs, varying programme characteristics including screening interval and screening start-age and stop-age.

METHODS

We used the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model to simulate a cohort of citizens of Shanghai aged 45 years in 2013. We assessed 324 different screening strategies to determine the benefits, burden, harms and costs of screening compared with the same population without screening. Subsequently, we performed an incremental cost-effectiveness analysis to identify strategies that provide good value for money and to determine the optimal strategy from a cost-effectiveness perspective.

MISCAN-Colon

MISCAN-Colon is a well-established microsimulation model for CRC developed at the Department of Public Health, Erasmus University Medical Center.[14] The model has been extensively described previously and is described in the model description (online supplemental file 1).[15 16]

In brief, the model simulates the life-histories of a large population of individuals from birth to death, first without and then with screening for CRC. As each simulated person ages, one or more adenomas may arise and some can progress in size from small (<5 mm) to medium (6–9 mm) to large (>10 mm). Some adenomas develop into preclinical cancer and subsequently progress through cancer stages I to IV. At any time during the development of the disease, symptoms may present and CRC may be diagnosed. The introduction of screening may alter the simulated life-histories through detection and removal of adenomas or through detection of CRC at an earlier stage with a more favourable survival. By comparing the life-histories of a simulated population being screened to the corresponding life-histories in a simulated population not screened, MISCAN-Colon quantifies the effectiveness and the costs of screening.

MISCAN-Colon was adjusted to match age-specific incidence of CRC in China before the introduction of screening in 2013.[17] Stage distribution,[18] localisation of cancers in the colorectum[19] and 5-year relative survival[18] after clinical diagnosis of a cancer were based on Chinese literature (online supplemental file 2, table 1). Additional assumptions of the MISCAN-Colon model are presented in the Supplementary Methods (online supplemental file 2).

Screening strategies

In this analysis, we assessed four screening modalities: the FIT as currently offered in the Shanghai screening programme (Shanghai FIT), the Shanghai FIT coupled with the risk assessment (Shanghai FIT+RA) and a standardised and validated FIT taking either one-sample (FIT 1) or two-samples (FIT 2, at least one-sample positive). For the validated tests, we considered five different cut-off values—10, 15, 20, 30 and 40 micrograms of haemoglobin per gram faeces (µg Hb/g, table 1).

For each modality and cut-off value, we assessed multiple start ages (45, 50 or 55 years), stop ages (70, 75 or 80 years) and intervals (annual, biennial and triennial). Individuals with a positive screening test were invited to a diagnostic colonoscopy. Surveillance was based on findings at diagnostic colonoscopy in accordance with the European Society of Gastrointestinal Endoscopy Guidelines.[20] We elected to simulated surveillance consistent with these guidelines because there is conflicting advice in China about the post diagnostic colonoscopy pathway (including when to return to screening and the surveillance pathway),[13 21–24] and the Asia Pacific Consensus Group did not provide precise guidelines on surveillance intervals, other than to suggest that such intervals should be tailored to the risk level.[25] In a sensitivity analysis, we assessed a surveillance pathway derived from Chinese literature (online supplemental file 2, figure 1).[21 22]

We assumed 100% adherence to all screening, diagnostic and surveillance tests because this allows for the determination of the optimal benefit of CRC screening.

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Table 1 Test characteristics of the faecal immunochemical tests and colonoscopy

Test	Sensitivity (%)					Specificity (%)
	Adenoma ≤5 mm	Adenoma 6–9 mm	Adenoma ≥10 mm	CRC early preclinical*	CRC late preclinical*	
Shanghai FIT†	0.0	8.7	20.3	44.6	78.9	87.4
Shanghai FIT+RA†	0.0	9.4	33.0	74.2	93.1	79.3
One-sample FIT10‡	0.0	11.0	39.4	65.5	90.0	96.1
One-sample FIT15‡	0.0	6.5	33.3	58.5	87.0	97.3
One-sample FIT20‡	0.0	5.0	29.3	52.0	83.5	97.9
One-sample FIT30‡	0.0	3.3	26.6	50.5	83.0	98.4
One-sample FIT40‡	0.0	2.6	22.1	50.0	82.5	98.7
Two-sample FIT10‡§	0.0	16.2	63.3	75.0	93.5	94.1
Two-sample FIT15‡§	0.0	8.9	52.7	71.0	92.0	95.7
Two-sample FIT20‡§	0.0	7.1	46.9	66.0	90.0	96.7
Two-sample FIT30‡§	0.0	4.6	42.5	66.5	90.5	97.4
Two-sample FIT40‡§	0.0	4.9	12.5	66.0	90.0	97.7
Colonoscopy¶**	75.0	85.0	95.0	95.0	95.0	86.0

*It was assumed that the probability that a CRC bleeds and thus the sensitivity of a FIT for CRC depends on the time until clinical diagnosis.[61]
†Specificity and sensitivity are based on the positivity rates and detection rates of advanced neoplasia observed in the first screening round in Pudong, Shanghai. This data for this was provided by Pudong Centre for Disease Control. Sensitivity for adenomas smaller than 5 mm was assumed to be 0% for all tests.
‡Specificity and sensitivity are based on the positivity rates and detection rates of advanced neoplasia observed in the first screening round of two Dutch randomised trials.[28–31] Sensitivity for adenomas smaller than 5 mm was assumed to be 0% for all tests, at any cut-off level.
§A two-sample FIT is considered positive when at least one-sample contains detectable blood at the specified cut-off value.
¶Specificity for colonoscopy is based on Schroy *et al* 2013.[36] The lack of specificity with endoscopy reflects the detection of non-adenomatous lesions, which, in the case of colonoscopy, leads to unnecessary polypectomy, which is associated with an increased risk complications.
**Sensitivity of colonoscopy for the detection of adenomas and CRC within the reach of the endoscope was obtained from a systematic review on miss rates observed in tandem colonoscopy studies.[35]
CRC, colorectal cancer; FIT, faecal immunochemical test; FIT10, faecal immunochemical test, 10 µg Hb/g faeces cut-off value; FIT15, faecal immunochemical test, 15 µg Hb/g cut-off value; FIT20, faecal immunochemical test, 20 µg Hb/g faeces cut-off value; FIT30, faecal immunochemical test, 30 µg Hb/g cut-off value; FIT40, faecal immunochemical test, 40 µg Hb/g cut-off value; µg Hb/g, micrograms of haemoglobin per gram faeces; RA, risk assessment.

All strategies were compared with a situation without screening.

In total, 324 unique strategies were evaluated. For each strategy, we simulated a population of 10 million 45-year-olds, with life expectancy as observed in China in 2010.[26] It was assumed that no screening occurred before or after the screening start and stop ages. Individuals were followed for life, until a maximum age of 100 years, commencing in 2015.

Test characteristics

Although the Shanghai screening programme reports that it is using a qualitative FIT with a pre-set cut-off of 100 nanograms of haemoglobin per millilitre of faeces (equivalent to 20 µg Hb/g faeces),[7] laboratory tests have shown that the quantity of faeces in samples and diluents of the test were not standardised, with the actual cut-off being lower than the pre-set cut-off.[27] Consequently, the characteristics and actual cut-off of the Shanghai FIT remain unknown. Therefore, the test characteristics of the Shanghai FIT and the Shanghai FIT+RA (table 1 and online supplemental file 2, table 2) were fitted to the positivity and detection rates observed in the first three years of screening in Pudong New Area, the largest district of Shanghai (online supplemental file 2, table 3). Data were provided by the Pudong Centre for Disease Control (Pudong CDC).

The test characteristics of the validated FIT 1 and FIT 2 were fitted to the positivity and detection rates of advanced neoplasia observed in the first screening round of two Dutch randomised trials, which used the OC-Sensor micro (Eiken Chemical, Tokyo, Japan, table 1).[28–31] To estimate the two-sample FIT test characteristics, we followed the approach described in Goede and colleagues.[32] The characteristics differ to those previously presented as the natural history of the MISCAN-Colon model has been updated since this publication.[33]

In all instances, the sensitivity and specificity of the test characteristics were estimated so that simulated positivity rates and detection rates for (non-)advanced adenomas and cancer matched the observed rates to within 1%. The test characteristics were adjusted to take into account the effect of systematic false-positive and false-negative results

(individuals who always test positive but do not have adenomas and/or who test negative because of adenomas which do not bleed).[34]

For colonoscopy, test characteristics were based on a systematic review of polyp miss rates in tandem colonoscopy studies.[35] The lack of specificity of colonoscopy reflects the detection of benign hyperplastic polyps, which are not cancer precursors.[36] Complications of colonoscopy were measured as the number of perforations arising from colonoscopy.[37]

Costs of screening, surveillance and CRC care

Costs associated with colonoscopy, polypectomy, complications from colonoscopy and costs of cancer treatment were obtained from Chinese literature (table 2).[19 38–40] The costs of the Shanghai FIT, FIT 1, FIT 2 and the RA were provided by Pudong CDC. The costs of all of the FITs were based on the current reimbursement funding arrangement. These costs include the test kits, their distribution, return and analysis and expenses in marketing. We also included costs associated with colonoscopy, such as costs for following-up individuals with a positive screening test to encourage them to attend diagnostic colonoscopy and general outpatient costs.[19] All costs are presented in Chinese Renminbi (RMB, ¥) and where necessary are standardised to 2019 prices using the Consumer Price Index.[41]

Outcomes

For all strategies, the model estimated CRC incidence, the number of CRC deaths and the number of screening, diagnostic and surveillance tests required between ages 45 and 80 years per 1000 individuals. The benefits of screening were measured as the reduction in CRC incidence and mortality and the number of life years gained (LYG) per 1000 individuals. The number of screening events and colonoscopies were taken as measures of the burden of screening and for colonoscopy, both diagnostic and surveillance colonoscopies were included. Harms of screening were measured as the number of perforations arising from colonoscopy and the number of false-positive tests (which is defined as a positive screening test followed by a colonoscopy with no clinical findings).

Cost-effectiveness analysis

We conducted a cost-effectiveness analysis from the healthcare sector perspective, and discounted both future costs and life-years using a standard annual rate of 3%[42] (undiscounted results and results discounted at 5% were also assessed). We plotted all of the screening strategies in a cost-effectiveness plane and performed an incremental cost-effectiveness analysis to see which strategies were efficient. The efficient strategy with the highest incremental cost-effectiveness ratio (ICER) below the willingness-to-pay (WTP) threshold was considered optimal. The WTP threshold was set at three times the Chinese gross domestic product per capita in 2018 (¥193 931 RMB which is equal to US$29 313)[43] for one LYG.

Table 2 Costs associated with colorectal cancer screening and treatment*

Cost parameter	¥	Probabilistic sensitivity analysis, ranges†
		Gamma-distribution
Per quantitative FIT—one-sample‡, §	15.00	7.50 to 30.00
Per quantitative FIT—two-sample‡, §	25.00	12.50 to 50.00
Per qualitative FIT—two-sample‡, §	13.00	6.50 to 26.00
Per risk assessment‡	3.48	1.74 to 6.96
Per positive screening test‡, ¶	15.00	7.50 to 30.00
Per colonoscopy**	375.30	187.65 to 750.60
Per polypectomy††	654.83	327.42 to 1309.66
Per perforation of colonoscopy‡‡	19 761.04	9880.52 to 39 522.08
Treatment by stage and location§§		
Stage I CRC	35 227.92	17 613.96 to 70 455.84
Stage II CRC	37 342.58	18 617.29 to 74 685.58
Stage III CRC	37 481.16	18 740.58 to 74 962.32
Stage IV CRC	38 472.04	19 236.02 to 76 944.08
General outpatient cost¶¶	23.30	11.65 to 46.60

*Costs are from a health system perspective and do not include patient time costs. All costs are presented in Chinese Renminbi (¥) and are indexed to 2019 prices.[41]
†Ranges of 95% CIs for the costs in the probabilistic sensitivity analysis were obtained by halving and doubling the base case values. Using these ranges, the shape parameter k and the scale parameter θ are calculated as input for the gamma-distributions.
‡Costs provided by Pudong Centre for Disease Control and are based on the current reimbursement funding arrangement.
§Costs include the test kits, their distribution, return and analysis and expenses in marketing.
¶These costs are provided to encourage those with positive screening test to attend diagnostic colonoscopy, as well as support other activities related to colonoscopy.
**Costs for colonoscopy are based on sources from China[38] and includes cost of bowel preparation.[40]
††Costs for polypectomy is based on sources from China[38] and includes costs of biochemical and pathological testing.[40] This cost is in addition to the cost for colonoscopy.
‡‡Costs for perforation during colonoscopy is based on sources from China.[38]
§§Costs of cancer treatment are taken from the Chinese setting.[19 39]
¶¶Co-payment made by patients when seeing a doctor and undergoing a colonoscopy.[19]
CRC, colorectal cancer; FIT, faecal immunochemical test.

Sensitivity analyses

We conducted a series of sensitivity analyses to assess the robustness of our assumptions. First, due to uncertainty about the performance of the validated FIT in the Chinese population, we conducted an analysis where we adjusted the characteristics such that the sensitivity and specificity were halfway between the calibrated Shanghai FIT and the validated FITs (online supplemental file 2, table 4). Second, due to uncertainty about the actual

cost of the validated FITs, we explored the impact of varying its cost by assuming a 50% reduction and a twofold increase. All other costs were held constant. Third, quality-adjusted life years were excluded from the main analysis because at present there is no available information on these measures in the Chinese setting. Therefore, we assessed the impact of using international quality of life measurements in a sensitivity analysis (online supplemental file 2, table 5).[44] Fourth, we assessed the impact of an alternative surveillance pathway, derived from Chinese literature (online supplemental file 2, figure 1).[21 22] Finally, we assessed the impact of reducing the WTP threshold to the Chinese gross domestic product per capita in 2018 (¥64 644 RMB which is equal to US$9771) for one LYG.

Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis, we assessed the uncertainty of the test characteristics and costs for four strategies: the current programme using the Shanghai FIT+RA, the current programme using a validated two-sample FIT, the strategy that was found to be cost-effective at the WTP threshold and the strategy on the efficient frontier with similar colonoscopy demand as the existing programme. For every strategy, we performed 1000 simulations each containing different parameter values drawn from corresponding probability distributions. The test characteristics were drawn from a beta distribution and costs from a gamma distribution (table 2 and online supplemental file 2, table 6).

RESULTS

Benefits of screening

MISCAN-Colon predicted that, compared with no screening, all screening strategies reduced CRC incidence and mortality (online supplemental file 3, table S1). Undiscounted results and results discounted to 5% are presented in (online supplemental file 3, table S2A,B) and (online supplemental file 4, figure S1A,B). In a situation without screening, CRC incidence was 49 per 1000 individuals while CRC mortality was 11 per 1000 individuals. Screening reduced CRC incidence by 16%–53% (8–26 cases) and CRC mortality by 41%–79% (4–9 deaths), depending on intensity of screening (online supplemental file 3, table S1). In addition, screening gained an additional 20–39 life years (LYs). The current screening programme (triennial screening with Shanghai FIT+RA from ages 50 to 75 years) reduced CRC incidence by 19 cases (40%) and mortality by 7 deaths (67%) and gained an additional 32 LY.

Annual screening with the Shanghai FIT+RA, from ages 45 to 80 years was the most effective strategy at reducing CRC incidence, while annual screening with the FIT 2 with a cut-off of 10 µg Hb/g from ages 45 to 80 years was the most effective at reducing CRC mortality.

Screening burden

In general, screening strategies with a shorter screening interval and a greater number of years of screening required more screening tests than strategies with longer screening interval for fewer years. For example, annual screening with FIT 1, with a cut-off of 40 µg Hb/g, from 45 to 80 years required the greatest number of screening tests (29 329 tests), while triennial screening with the Shanghai FIT +RA, from ages 55 to 70 years required the least number of screening tests (3706 tests). The current screening programme required 5346 tests.

This pattern did not hold for the number of required colonoscopies. Although triennial screening with FIT 1, with a cut-off of 40 µg Hb/g, from ages 55 to 70 years required the least number of colonoscopies (265 colonoscopies) and annual screening with the Shanghai FIT+RA, from 45 to 80 years required the greatest number of colonoscopies (2609 colonoscopies), the order of strategies between this varied greatly. The current screening programme required 1434 colonoscopies. In general, the screening strategies that used the Shanghai FIT had a substantially greater colonoscopy requirement than those using the validated tests.

Screening harms

Overall, the risk of screening related perforations was very low—ranging between 0.01 and 0.09 per 1000 individuals. Complications were proportional to the number of colonoscopies, such that those strategies with fewer colonoscopies had fewer complications. The number of false-positive tests ranged from 21 to 1917 and was generally highest for the Shanghai FITs, particularly with risk assessment.

Costs and cost-effectiveness

Without screening, the cost of diagnosing and treating colorectal cancer was ¥869 648 per 1000 individuals. Screening increased costs by 1%–66% (¥884 095–¥1 443 352). The current screening programme cost an additional ¥152 565, an increase of 18% (¥1 022 213).

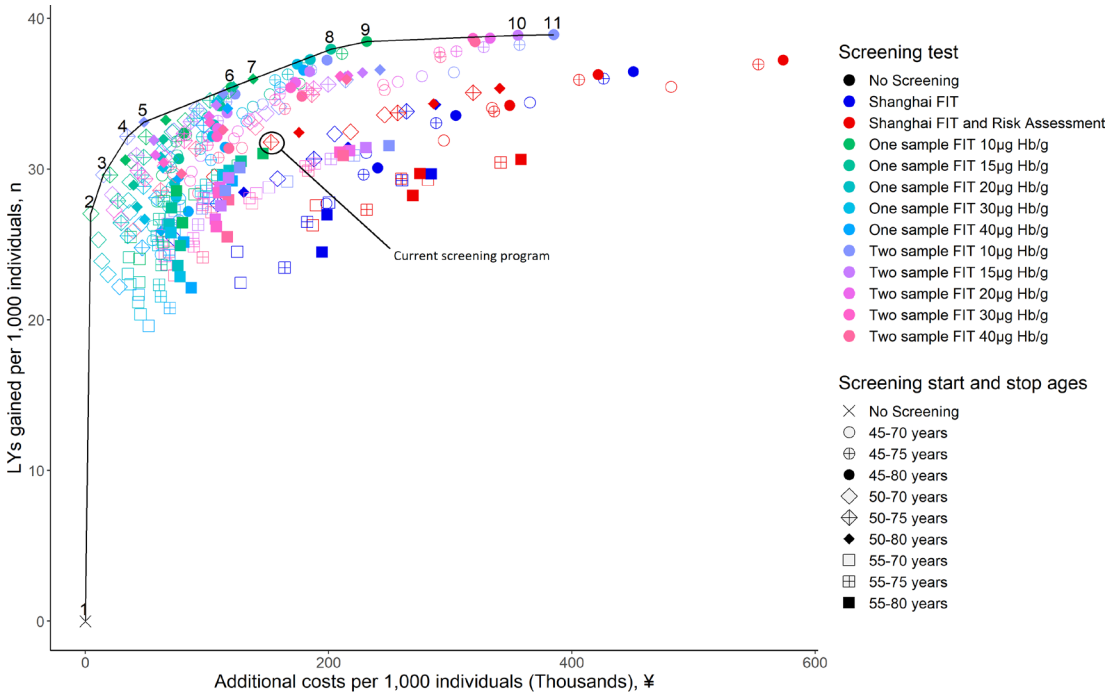
Of the 324 screening strategies, 10 were on the efficient frontier (ie, considered to provide good value for money, table 3, figure 1). The efficient strategies all had a low cut-off (10–15 µg Hb/g), and were an even mix of validated one-sample and two-sample tests. Screening start age varied from a relatively short-time period (50–70) years to the longest assessed period (45–80 years), and the screening interval ranged from 1 to 3 years. All screening strategies using the Shanghai FIT, either with or without the risk assessment, were dominated.

Using a WTP threshold of ¥193 931 per LYG, the optimal screening strategy was annual testing with FIT 1, using a cut-off of 10 µg Hb/g from ages 45 to 80 years (ICER, ¥59 218). Annual screening with FIT 2, using a cut-off of 10 µg Hb/g from ages 45 to 80 years was also on the efficient frontier, but with an ICER, ¥739 677 per LYG, it would not be considered as cost-effective.

Table 3 Costs and effects (discounted at 3%) per 1000 simulated 45-year-olds for a situation without screening, the current screening programme in Shanghai and screening strategies on the efficient frontier

Screening strategy											
Test	Start-stop age	Interval	FITs	Colonoscopies	False positives	Complications	CRC incidence	CRC mortality	Life years*	Total costs*†	ICER*†
No screening			0	49	0	0.01	49	11	21 482	869 648	
Current screening programme in Shanghai											
Shanghai FIT+RA	50–75	3	5346	1434	890	0.07	30	4	21 514	1 022 213	Dominated
Cost-effective screening strategies											
FIT-1–10	50–70	3	5901	514	151	0.03	36	5	21 509	874 095	164
FIT-2–10	50–70	3	5645	652	239	0.04	33	5	21 511	884 484	4027
FIT-2–10	50–75	3	6884	744	294	0.04	31	4	21 514	904 162	7778
FIT-2–10	50–80	3	7768	795	327	0.05	30	3	21 515	917 846	14 254
FIT-1–10	45–80	2	13 519	801	334	0.05	31	3	21 517	989 444	31 130
FIT-1–10	50–80	1	20 134	986	476	0.05	28	3	21 518	1 007 490	31 660
FIT-1–15	45–80	1	26 112	846	359	0.05	29	3	21 520	1 071 462	32 309
FIT-1–10‡	45–80	1	24 054	1104	572	0.06	27	2	21 520	1 101 071	59 218
FIT-2–15	45–80	1	23 434	1186	635	0.06	26	2	21 521	1 225 260	302 900
FIT-2–10	45–80	1	21 214	1456	867	0.07	24	2	21 521	1 254 847	739 677

*Results are discounted at an annual rate of 3%.
†Costs are presented in Chinese Renminbi (¥).
‡Optimal screening strategy at the willingness-to-pay threshold
CRC, colorectal cancer; FIT, faecal immunochemical test; FIT-1-10, one sample faecal immunochemical test, 10 µg Hb/g cut-off value; FIT-1-15, one sample faecal immunochemical test, 15 µg Hb/g cut-off value; FIT-2-10, two sample faecal immunochemical test, 10 µg Hb/g cut-off value; FIT-2-15, two sample faecal immunochemical test, 15 µg Hb/g cut-off value; ICER, incremental cost-effectiveness ratio.



	1	2	3	4	5	6	7	8	9	10	11
Screen test	NoScr	FIT-1-10	FIT-2-10	FIT-2-10	FIT-2-10	FIT-1-10	FIT-1-10	FIT-1-15	FIT-1-10	FIT-2-15	FIT-2-10
Screen ages	-	50-70	50-70	50-75	50-80	45-80	50-80	45-80	45-80	45-80	45-80
Screen frequency	-	3	3	3	3	2	1	1	1	1	1
ICER (¥)	-	164	4027	7778	14254	31130	31660	32309	59218	302900	739677

Figure 1 Costs and life years (discounted at 3%) per 1000 45-year-olds of all 324 colorectal cancer screening strategies and a strategy without screening, with the efficient frontier connecting the economically efficient strategies.

Note: Black circle highlights current screening programme in Shanghai.

* Discounted costs and life years gained reflect total costs and life years gained of a screening programme, accounting for time preference for present over future outcomes. Life years gained are plotted on the y-axis, and total costs are plotted on the x-axis. Each possible screening strategy is represented by a point. Strategies that form the solid line connecting the points lying left and upward are the economically rational subset of choices. This line is called the efficient frontier. The inverse slope of the line represents the incremental cost-effectiveness ratio of the connected strategies. Points lying to the right and beneath the line represent the dominated strategies.

FIT, faecal immunochemical test; ICER, incremental cost-effectiveness ratio; LYs, life years; μg Hb/g, micrograms of haemoglobin per gram faeces.

Sensitivity analyses

Our results were robust to changes in the validated FIT characteristics, costs, the use of international quality of life measurements and the adoption of a Chinese surveillance pathway. For all of these analyses, the validated FITs outperformed the Shanghai FIT, both with and without the risk assessment (online supplemental file 3, table S1A–E and online supplemental file 4, figure S2A–E). At the WTP threshold, the cost-effective strategies varied in terms of the test (FIT 1 and FIT 2) and cut-off, however all strategies required annual testing from ages 45 to 80 years (table 4). The Shanghai FIT+RA was on the efficient frontier when the Chinese surveillance pathway was assessed, however, with an ICER of ¥750 686, it would not be considered cost-effective. When assessed against a lower WTP threshold, the optimal screening strategy remained the same (annual testing with FIT 1, using a cut-off of 10 μg Hb/g from ages 45 to 80 years).

Probabilistic sensitivity analysis

The probabilistic sensitivity analysis suggests that at the WTP threshold of ¥193 931, of the four considered strategies, the optimal screening strategy (annual screening with FIT 1, with a cut-off of 10 μg Hb/g from 45 to 80 years) is the cost-effective strategy in more than 50% of the simulations (online supplemental file 4, figure S3). Above the WTP threshold, a strategy with similar colonoscopy demand to the existing programme (annual screening with FIT 2, with a cut-off of 10 μg Hb/g from 45 to 80 years) has the highest likelihood of being cost-effective. The current programme was not cost-effective in any of the 1000 simulations.

DISCUSSION

This microsimulation analysis assessed the performance of the Shanghai FIT, with and without the use of a risk assessment, compared with the use of validated one-sample and two-sample FITs. Our results suggest that the screening tests currently used in the Shanghai screening programme are not the most cost-effective as in all instances they were outperformed by validated screening tests. Although the Shanghai tests performed similarly terms of reductions in incidence and mortality

Table 4 Cost-effective strategies (discounted at 3%) for the sensitivity analyses. Outcomes are per 1000 45-year-olds

Screening strategy											
Test	Start-stop age	Interval	FITs	Colonoscopies	False positives	Complications	CRC incidence	CRC mortality	Life years*	QALYs*	Total costs*†	ICER*†
(A) Assuming adjusted FIT characteristic's												
FIT-1–10	45–80	1	18 630	1758	1144	0.08	26	3	21 519	–	1 242 210	60 319
(B) Assuming a 50% reduction in the costs of the validated FITs												
FIT-2–30	45–80	1	26 476	807	320	0.05	29	2	21 520	–	1 018 114	66 922
(C) Assuming a 200% increase in the costs of the validated FITs												
FIT-1–10	45–80	1	24 054	1104	572	0.06	27	2	21 520	–	1 288 058	62 198
(D) Assuming Chinese surveillance guidelines												
FIT-2–10	45–80	1	29 675	2123	1499	0.08	22	2	21 524		1 487 932	164 958
(E) Assuming international quality of life estimates												
FIT-2–10	45–80	1	867	1456	867	0.07	24	2	21 521	20 277	1 254 847	3374

*Results are discounted at an annual rate of 3%.
†Costs are presented in Chinese Renminbi (¥).
CRC, colorectal cancer; FIT, faecal immunochemical test; FIT-1-10, one sample faecal immunochemical test, 10 µg Hb/g cut-off value; FIT-2-10, two sample faecal immunochemical test, 10 µg Hb/g cut-off value; FIT-2-30, two sample faecal immunochemical test, 30 µg Hb/g cut-off value; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

and gains in LYs, they were generally more expensive. In addition, they required substantially more colonoscopies. Based on our results, the Shanghai screening programme could be optimised by using a validated, one-sample FIT, with a cut-off of 10 µg Hb/g, with screening occurring annually from ages 45 to 80 years (table 3). Although this strategy increases the number of screening tests and costs compared with the screening programme currently implemented in Shanghai, these increases are outweighed by the reductions in colonoscopy demand and associated harms, and CRC incidence and mortality, and the increase in the number of LYG. The probabilistic sensitivity analysis suggests that this strategy has a greater than 50% probability of being cost-effective at the WTP threshold (online supplemental file 4, figure S3). Furthermore, this strategy has the highest probability of being cost-effective at a wide range of WTP thresholds.

Shanghai is one of the only regions in the world to implement a triennial screening programme.[6] This strategy was chosen after the completion of a comprehensive evaluation of the capacity of health resources of the region.[7] This suggests that an alternative programme could be implemented if it did not exceed the demand of health services such as colonoscopy. According to our analysis, the current programme requires a colonoscopy capacity of 1434 per 1000 individuals, while our proposed cost-effective strategy reduces colonoscopy demand by approximately 30% (to 1104 colonoscopies). If colonoscopy demand was a key driver of the selection of a triennial screening programme, there are several alternatives that could be implemented. For example, while not considered to be cost-effective (ICER: ¥739 677), annual screening of individuals from 45 to 80 years with a validated, two-sample FIT, with a cut-off of 10 µg Hb/g results in a similar colonoscopy demand (1456 colonoscopies). The probabilistic sensitivity analysis shows that above the current WTP threshold, this strategy has the highest probability of being cost-effective. Alternatively, to achieve the same number of LYG (21 514 per 1000), a programme of triennial screening from 50 to 75 years with a validated, two-sample FIT, with a cut-off of 10 µg Hb/g could be implemented. This strategy would half the colonoscopy demand (to 744 colonoscopies) at an ICER of ¥7778. Other strategies could also be selected depending on desired outcomes, however, all of these alternatives use a validated FIT.

The suboptimal performance of the Shanghai screening tests is not surprising given their characteristics (table 2). Although the sensitivity of the Shanghai screening tests is comparable to the validated screening tests, the specificity is considerably lower, especially when the risk assessment is included. Low specificity increases the rate of false-positive tests[45] and consequently, greater numbers of individuals are unnecessarily sent for colonoscopy. This impacts the cost-effectiveness of the screening programme by increasing the burdens, harms and costs of screening. Shifting to a validated, quantitative FIT could help alleviate these issues while also providing an

opportunity to assess stool haemoglobin concentrations which have been demonstrated to be a strong predictor for future cancer risk.[46]

The high rate of false positivity of the screening tests used in the Shanghai screening programme has been suggested as an explanation for the low uptake of diagnostic colonoscopy.[7 13] Although failure to complete an appropriate follow-up test after a positive result further undermines the benefits of screening, the situation is not unique to the Shanghai screening programme - suboptimal compliance to diagnostic colonoscopy after a positive FIT has been noted in several screening programmes.[47] Compliance to diagnostic colonoscopy is complex and multidimensional.[48–50] In China, the results of primary screening test, perceived severity of the disease, personal or others experiences with colonoscopy and healthcare provider recommendation have also been shown to influence compliance.[49] Cultural beliefs may also play a significant role.[51] This suggests that health literacy related to CRC screening could be improved.

With compliance to diagnostic colonoscopy, and participation in screening in general, already demonstrated to be low in Shanghai and other locations in China,[8] the optimal screening strategy suggested by this investigation may not be optimal in practice. Screening programmes have to consider their 'real world' application and as the effectiveness of a FIT screening programme relies heavily on participation, the implementation of an annual screening programme over an extended 35-year period may further diminish this already low participation rate. Participation may be further diminished as a result of 'screening fatigue'—where motivation to participate is reduced due to a false perception of decreased CRC risk after several negative screening test results.[52 53] As CRC risk increases with age[1 2 54] participation of older individuals is important. With Shanghai being one of the most ageing cities in China,[55] it has been suggested that offering screening to those aged 75–80 is potentially warranted. Therefore, it may be pertinent to consider an alternative cost-effective strategy such as annual screening from 50 to 80 years, using a validated, one-sample FIT, with a cut-off of 10 µg Hb/g (ICER: ¥31 660) or triennial screening from 50 to 80 years, using a validated, two-sample FIT, with a cut-off of 10 µg Hb/g (ICER: ¥14 254). Choosing either of these strategies would substantially reduce both the screening burden and costs, while still achieving comparable benefits.

There are four noteworthy limitations to our research. First, there remains some uncertainty about the accuracy of test characteristics and therefore the performance of the validated FITs in the Chinese population. We therefore conducted a sensitivity analysis where we reduced the performance of the validated FITs. Our results were robust to this change in test characteristics, although there was less difference in effectiveness, the analysis produced similar results as base case. Second, we simulated surveillance in our main analysis consistent with European Society of Gastrointestinal Endoscopy Guidelines,[20] because there is conflicting advice in China about the post diagnostic colonoscopy pathway, (including when to return to screening and the surveillance pathway).[13 21–24] When we assumed surveillance guidelines derived from Chinese literature, our results did not change significantly. Although annual screening from 45 to 80 years with the Shanghai FIT+RA was on the efficient frontier, it was still not cost-effective. Third, we did not assess screening using colonoscopy. While colonoscopy screening could be considered advantageous over FIT screening, providing at least 10 years of screening coverage, compared with FIT, it is expensive, invasive and not without risk. Moreover, it is unlikely to become the test of choice in Shanghai for primary screening, given the very low colonoscopy uptake, even after a positive FIT, and the lack of colonoscopy capacity. Finally, there is limited information on complications arising from colonoscopy in China which likely means our results provide an underestimate of complications and their associated costs. However, given that the Shanghai FIT, both with and without the risk assessment, had higher numbers of colonoscopy, we do not feel that this would significantly alter our results. Fortunately, there is research underway to address this gap in knowledge.[56]

Despite these limitations, our research has important implications. First, our results suggest that the CRC screening programme in Shanghai could achieve better outcomes and costs could be reduced if the programme was to switch to using a validated screening test. Based on our results the most cost-effective strategy is annual testing with the validated one-sample FIT, using a cut-off of 10 µg Hb/g and screening from ages 45 to 80 years. Second, although the current screening programme is not considered optimal based on our results, our findings support the implementation of screening in Shanghai; even the use of suboptimal screening tests result in a reduction of CRC incidence and mortality in a cost-effective way compared with no screening (cost-effectiveness ratio=¥4801). Given the recent trend of rising CRC incidence and mortality,[10–12] coupled with the expectation that the burden is set to increase as the Chinese economy grows,[5 57] efforts to reduce the impact of CRC are important. Moreover, despite the use of these tests, the programme already appears to be having an impact on survival—individuals diagnosed with CRC who participated in the screening programme and were compliant with the screening policy experienced better survival outcomes compared with those who did not participate.[58] While this finding should be interpreted with caution given the short follow-up time and the potential for lead time and length bias,[45] it adds support to the benefits of screening in this population. Finally, our results demonstrate that screening for CRC is a highly cost-effective method of reducing the burden of CRC in Shanghai. This is particularly salient in China where out-of-pocket expenses for treating cancer have been described as 'catastrophic' (defined as out-of-pocket expenditure in access of 40% of annual household income) for both

newly diagnosed and end stage cancer.[59 60] This finding may be relevant to other jurisdictions with limited health resources who are considering implementing CRC screening.

CONCLUSION

Screening for CRC in Shanghai is an attractive and cost-effective option for reducing the burden of CRC. Although the current screening programme reduces both the incidence and mortality of CRC, a programme using a standardised, validated FIT could save more lives at a lower cost. In addition, addressing barriers to screening, such as poor health literacy and financial concerns, may increase participation and therefore improve the effectiveness of the screening programme.

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Contributors DC, IL-V and JW participated in the conceptualisation of the study. PL, JW, BY and ST performed data collection and provided expertise in the Chinese setting. DC and LdJ conducted the analysis and interpreted the outputs. DC drafted the manuscript. IL-V supervised the study. All authors participated in revising the article and approved the final version of the manuscript. DC is the guarantor.

Funding This research benefitted from our participation in the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET) (grant number: U01-CA199335) and was supported by funding from the Research Grant for Health Science and Technology of Pudong Health and Family Planning Commission of Shanghai, China (grant number: PW2017A-7). The funding sources had no role in the design, conduct or reporting of the study.

Competing interests IL-V and DC report grants from National Cancer Institute, during the conduct of the study.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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