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Optimal use of colonoscopy and fecal immunochemical test for population-based colorectal cancer screening: a cost-effectiveness analysis using Japanese data

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Abstract

Objective: There have been few cost-effectiveness analyses of population-based colorectal cancer screening in Japan, and there is no consensus on the optimal use of total colonoscopy and the fecal immunochemical test for colorectal cancer screening with regard to cost-effectiveness and total colonoscopy workload. The present study aimed to examine the cost-effectiveness of colorectal cancer screening using Japanese data to identify the optimal use of total colonoscopy and fecal immunochemical test.

Methods: We developed a Markov model to assess the cost-effectiveness of colorectal cancer screening offered to an average-risk population aged 40 years or over. The cost, quality-adjusted life-years and number of total colonoscopy procedures required were evaluated for three screening strategies: (i) a fecal immunochemical test-based strategy; (ii) a total colonoscopy-based strategy; (iii) a strategy of adding population-wide total colonoscopy at 50 years to a fecal immunochemical test-based strategy.

Results: All three strategies dominated no screening. Among the three, Strategy 1 was dominated by Strategy 3, and the incremental cost per quality-adjusted life-years gained for Strategy 2 against Strategies 1 and 3 were JPY 293 616 and JPY 781 342, respectively. Within the Japanese threshold (JPY 5–6 million per QALY gained), Strategy 2 was the most cost-effective, followed by Strategy 3; however, Strategy 2 required more than double the number of total colonoscopy procedures than the other strategies.

Conclusions: The total colonoscopy-based strategy could be the most cost-effective for population-based colorectal cancer screening in Japan. However, it requires more total colonoscopyprocedures than the other strategies. Depending on total colonoscopy capacity, the strategy of adding total

colonoscopy for individuals at a specified age to a fecal immunochemical test-based screening may be an optimal solution.

Key words: colorectal cancer screening, cost-effectiveness analysis, fecal immunochemical test, total colonoscopy

Introduction

Colorectal cancer (CRC) has markedly increased and is now the second most commonly diagnosed cancer and the third leading cause of cancer-related mortality in Japan (1). For the secondary prevention of CRC, a Japanese population-based CRC screening system has used the 2-day fecal immunochemical test (FIT) as a primary screening procedure on the basis of the evidence regarding its effectiveness for CRC screening (2). The effectiveness of the fecal occult blood test (FOBT) for reducing CRC-associated mortality has been clearly shown in several randomized controlled trials (3–7), whereas other case–control or cohort studies have shown the effectiveness of FIT for CRC screening and the superior sensitivity of FIT for CRC compared with that of FOBT (8–14). Japanese population-based CRC screening is offered to the entire population aged 40 years and over, and total colonoscopy (TCS) is performed for those with a positive FIT result. Recently, however, it has been reported that TCS-based CRC screening, in which TCS is performed as a primary screening procedure, is effective for reducing CRC incidence and mortality, based on long-term follow-up data in cohort studies (15,16). In this context, an analysis of the optimal combination of TCS and FIT for population-based CRC screening is required because there is yet no consensus regarding the issue.

Cost-effectiveness analysis is an essential part of the evaluation of screening strategies. Several cost-effectiveness analyses of CRC screening have been reported from the USA and several other countries (17–24). In Japan, however, there have been only limited analyses (25,26). Recently, by analyzing the TCS screening database of our institution's cancer screening division and the Japanese nationwide survey data of CRC screening, we reported that not only FIT but also TCS might be cost-effective for primary screening (27). However, the study retrospectively evaluated only the cost of identifying a CRC patient; further study using a Markov model analysis is necessary to evaluate the true cost-effectiveness of Japanese CRC screening.

In the present study, we aimed to identify the optimal combination of TCS and FIT for population-based CRC screening in the Japanese setting from the perspective of cost-effectiveness. To evaluate cost-effectiveness, we performed a Markov model analysis using Japanese clinical and cost data. To determine the optimal screening strategy, we also considered the number of TCS procedures required.

Patients and methods

Decision analytic model

We developed a state-transition Markov model that simulated the natural history of CRC development, and the actual cost-effectiveness was analyzed by Monte Carlo simulation using Tree Age Pro 2014 (TreeAge Software Inc., Williamstown, MA, USA) (28). In a Markov model, clinical situations are described in terms of discrete health states, 'Markov states,' that individuals can be in; an individual is always in one of these states, and all events of interest are modeled as transitions from one state to another. In this study, the natural history of CRC development was simulated as a transition from normal epithelium to low-risk adenomatous polyps sized 1–4 and 5–9 mm, to high-risk polyps, to CRC (from Dukes' A to Dukes' D), and ultimately to death from CRC, with reference to previous studies (17–24). Therefore, the Markov states were set as shown in Fig. 1. In addition, the detection status of colorectal polyps and CRC ('detected' or 'undetected') was considered, with CRC screening affecting the transition from 'undetected' to 'detected.' CRC was defined, according to the international classification, as a malignant epithelial tumor originating in the large bowel with invasion beyond the muscularis mucosae (29). High-risk polyps included intramucosal cancers and adenomas with a diameter ≥10 mm, with high-grade dysplasia, or with villous histology (≥25%) (30). The study setting was Japan and the initial population comprised 100 000 individuals aged 40 years who were at an average risk of CRC. The screening and analysis continued through the lifetime of the cohort. The time frame of the analysis was divided into 1 year, during which individuals were in the same health state before having the opportunity to transition to another state. The transition was governed by transition probability values mostly estimated from Japanese literature as described later. Japanese data for age-specific CRC incidence rates was the basis for determining the number of individuals in the population would develop CRC without any screening or intervention (1).

The validity of the model was assessed by comparing the lifetime cumulative risks for CRC incidence and mortality for the 40-year-old Japanese population estimated from the model of this study with those estimated from Japan's Cancer Registry and Statistics (http://gdb.ganjoho.jp/graph_db/gdb1?smTypes=67, Cancer Information Service, National Cancer Center, Japan) (1). When estimating these risks using the model, CRC screening with FIT (primary screening) and TCS (for those with a positive FIT) were considered with uptake rates set at 37 and 55% for FIT and TCS, respectively, based on the data of current Japanese uptake rates (31,32).

CRC screening strategies

To evaluate the optimal use of TCS and FIT for CRC screening, a total of three CRC screening strategies with TCS and/or FIT, including a

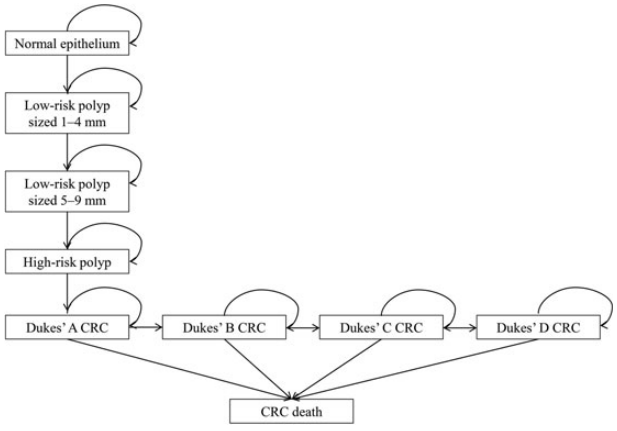

Figure 1. The natural history model of colorectal cancer. CRC, colorectal cancer.

FIT-based strategy which mostly corresponded to the current strategy of Japanese population-based CRC screening and other two strategies which used TCS more actively than the current strategy, were examined in this study (Fig. 2).

Strategy 1: a FIT-based screening strategy
The population is offered FIT at the age of 40 years. When the test is negative, it is repeated annually. Individuals with a positive FIT result are invited for TCS examination; any polyps found are removed and surveillance TCS is repeated every 3 years until no more polyps are found. When the results on TCS are normal, FIT is resumed 5 years after the TCS (Fig. 2a).

Strategy 2: a TCS-based screening strategy
The population is offered TCS as primary screening at the age of 40 years. When the test is negative, TCS is repeated 10 years later. If polyps are found, they are removed and surveillance TCS is repeated every 3 years until no more polyps are found. When the TCS results are normal, TCS is resumed 10 years later (Fig. 2b).

Strategy 3: a strategy of adding population-wide TCS for 50-year-old individuals to a FIT-based screening
This screening strategy is the same as Strategy 1 for individuals aged 40–49 years. The difference is that at the age of 50 years the whole population undergoes TCS, apart from those who underwent TCS in their 40s. After TCS, the screening continues according to the TCS results as with Strategy 1 (Fig. 2c).

Model parameters

Model parameters, including transition probabilities, test characteristics and cost, are summarized in Table 1. Most data were based on Japanese data (1,33–38), except for some data that were only available from foreign studies (20,39). The disease progression parameters from normal epithelium to colorectal polyps and cancer were calculated on the basis of the CRC incidence data from a study of 25 population-based cancer registries for the Monitoring of Cancer Incidence in Japan project (1), and the polyp prevalence data at Cancer Screening Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan (33). The possibility of new polyps developing after endoscopic removal of polyps was estimated with reference to the data from the Japan polyp study (34). The references for the data regarding other transition probabilities are provided in Table 1 (20,38,39).

With regard to the parameters of test characteristics, the sensitivities and specificities of FIT for colorectal polyps and cancer were set on the basis of data from detailed previous studies by Morikawa et al. (35,36). The sensitivities and specificities of TCS for colorectal polyps and cancer were set according to the data from the Japan polyp study (34). The possibility of complication (perforation and bleeding) following TCS were estimated from the nationwide report from the Japan Gastroenterological Endoscopy Society (37).

The cost included the screening-related cost and CRC treatment-related cost. The screening-related cost was set on the basis of Japanese national reimbursement tables. The CRC treatment-related cost was calculated from the cost of the treatment procedure, hospitalization, adjuvant chemotherapy and follow-up care on the basis of Japanese national reimbursement tables and expert discussion.

The uptake rate of each test (FIT and TCS) was also built into this analysis. The CRC screening uptake rate in Japan has been increasing, but the current rate (~30–40%) is lower than the Japanese government's target values (50%) and the cut-off value for the desirable level of the uptake rate (65%) provided in the European guidelines (31,40). These guidelines based their evidence on performance indicators for FIT on data with a FIT uptake rate of 61.5% (41). From this, it ideally appears that an uptake rate of at least 60% is required for population-based CRC screening. Thus, in the present study, all uptake rates were first set at 60% in the base case analysis and then changed in the sensitivity analyses.

Cost-effectiveness analysis

The cost-effectiveness analysis was performed from a healthcare payer's perspective. The effectiveness of screening was measured in terms of the quality-adjusted life-years (QALYs) gained. Costs and QALYs were discounted at an annual rate of 3% (42). Strategies that were more costly and less effective than other strategies were ruled out by simple dominance. Among the remaining strategies, the incremental cost-effectiveness ratio (ICER) was evaluated. ICER was determined for a strategy by comparing the additional cost and effectiveness of the strategy with those of a less costly and less effective strategy; ICER was calculated as the difference in costs divided by the difference in effectiveness.

To compare the demand for endoscopic resources between different screening strategies, the number of TCS procedures performed in each strategy was also calculated.

Sensitivity analyses

In addition to the base case analysis, scenario analyses were performed with regard to the uptake rates (10% and 100%), the initial age of screening (50 years), and the age for population-wide TCS in Strategy 3 (40–60 years). A probabilistic sensitivity analysis was performed for the parameters of transition probabilities, costs, test characteristics, uptake rates and quality of life scales. In a probabilistic sensitivity analysis, these multiple parameters were varied simultaneously. We used β distributions for the parameters for which we could acquire raw data (the denominator and numerator of parameters), including the sensitivities of FIT and TCS, the probability of perforation after TCS, and that of new polyps developing after polyp resection, and gamma distributions for the other variables with a range of ±25%. A cost-effectiveness acceptability curve was drawn to show the correlation between the probability of being chosen as the most cost-effective scenario for each strategy and the willingness-to-pay (WTP) values for one additional QALY gained. The WTP value is the maximum cost that an individual is willing to pay to gain one additional QALY, and the value varies according to country; the Japanese threshold is reported to be JPY 5–6 million per QALY gained (43).

Results

Validity of the model

The cumulative risks for CRC incidence and mortality for the Japanese 40-year-old population estimated from the Cancer Registry and Statistics and those estimated from the model are shown in Fig. 3. The risks estimated from the model generally matched those from the Cancer Registry and Statistics, particularly ≤65 years of age. After the age of 65 years, the risks estimated from the model were slightly lower than those estimated from the Cancer Registry and Statistics.

Base case analysis

The outcomes for the three screening strategies and for no screening in the base case analysis are summarized in Table 2. Without any

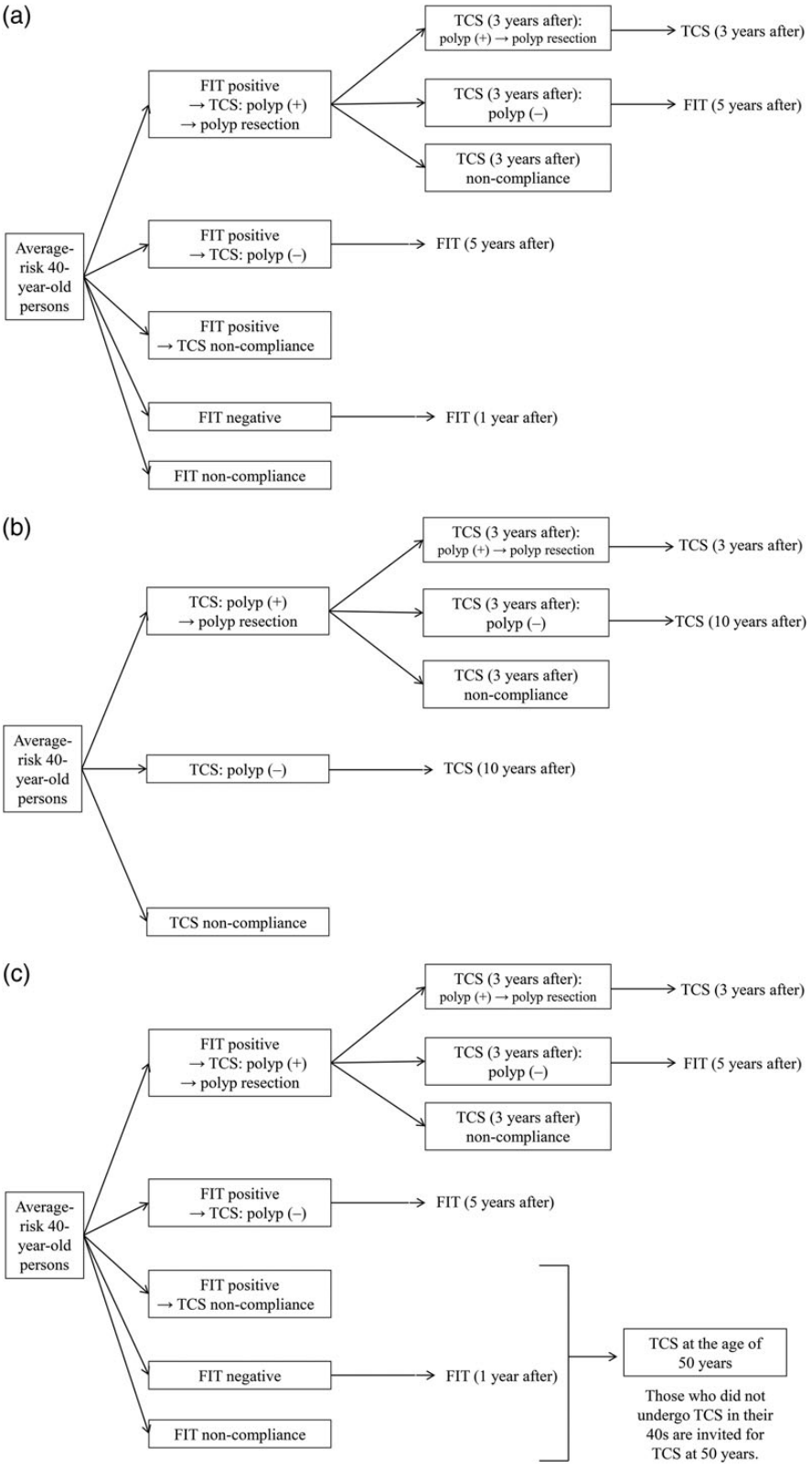

Figure 2. Three screening strategies analyzed in this study. (a) Strategy 1: A fecal immunochemical test-based screening strategy. FIT, fecal immunochemical test; TCS, total colonoscopy. (b) Strategy 2: A total colonoscopy-based screening strategy. (c) Strategy 3: A strategy of adding population-wide total colonoscopy for 50-year-old individuals to a fecal immunochemical test-based screening. During the first 10 years (40–49 years), individuals follow Strategy 1. All of those who did not undergo total colonoscopy during the first 10 years undergo total colonoscopy at the age of 50 years.

Table 1. Model parameters in the cost-effectiveness analysis

Model parameters	Baseline value	References
Transition probabilities (per year)		
Probability of progression to CRC		
From normal epithelium to 1–4 mm sized low-risk polyp	3.4–6.6% (different by age)	33
From 1–4 mm low-risk polyp to 5–9 mm low-risk polyp	1.4–5.6% (different by age)	33
From 5–9 mm low-risk polyp to high-risk polyp	1.3–5.6% (different by age)	33
From high-risk polyp to Dukes' A CRC	3.4%	20, 39
From Dukes' A CRC to Dukes' B CRC	58.3%	20, 39
From Dukes' B CRC to Dukes' C CRC	65.6%	20, 39
From Dukes' C CRC to Dukes' D CRC	86.5%	20, 39
Probability of death from CRC		
Dukes' A	1.7%	38
Dukes' B	3.2%	38
Dukes' C	7.2%	38
Dukes' D	28.4%	38
Probability of symptomatic presentation of CRC		
Dukes' A	6.5%	20, 39
Dukes' B	26.0%	20, 39
Dukes' C	46.0%	20, 39
Dukes' D	92.0%	20, 39
Probability of developing polyps following endoscopic polyp resection		
Developing low-risk polyp (1–4 mm) after endoscopic polyp resection	10.0%	34
Developing low-risk polyp (5–9 mm) after endoscopic polyp resection	5.3%	34
Developing high-risk polyp after endoscopic polyp resection	0.7%	34
Probability of recurrence after treatment of colorectal cancer		
Dukes' A	0.8%	38
Dukes' B	2.8%	38
Dukes' C	7.1%	38
Test characteristics		
FIT		
Sensitivity for 1–4 mm low-risk polyp	6.3%	35, 36
Sensitivity for 5–9 mm low-risk polyp	7.9%	35, 36
Sensitivity for high-risk polyp	26.5%	35, 36
Sensitivity for Dukes' A CRC	52.8%	35, 36
Sensitivity for Dukes' B CRC	70.0%	35, 36
Sensitivity for Dukes' C and D CRC	78.3%	35, 36
Specificity for colorectal polyp and CRC	94.6%	35, 36
TCS		
Sensitivity for 1–4 mm low-risk polyp	74.1%	34
Sensitivity for 5–9 mm low-risk polyp	86.5%	34
Sensitivity for high-risk polyp	97.6%	34
Sensitivity for CRC (Dukes' A–D)	99.9%	34
Specificity for colorectal polyp and CRC	100.0%	34
Probability of perforation after TCS without endoscopic polyp resection	0.01%	37
Probability of perforation after TCS with endoscopic polyp resection	0.06%	37
Probability of death following perforation	6.7%	37
Probability of bleeding after TCS with endoscopic polyp resection	0.5%	37
Cost (JPY)		Japanese national reimbursement tables
FIT	1600	
TCS	15 500	
Endoscopic resection of low-risk polyp	50 000	
Endoscopic resection of high-risk polyp	157 114	
Annual cost of CRC management by Dukes classification		
Dukes' A (1 year)	1 319 816	
Dukes' A (2–5 years)	35 570	
Dukes' B (1 year)	1 399 034	
Dukes' B (2–5 years)	35 570	
Dukes' C (1 year)	2 340 416	
Dukes' C (2–5 years)	44 972	
Dukes' D (1 year)	2 687 125	
Dukes' D (2–5 years)	2 544 972	

CRC, colorectal cancer; FIT, fecal immunochemical test; TCS, total colonoscopy.

screening, there would be 9541 CRC cases among the cohort of 100 000 individuals, and the calculated QALYs and total cost per person were 22.8 and JPY 156 125, respectively. Compared with no screening, all three screening strategies (Strategies 1, 2 and 3) experienced fewer CRC cases, gained more QALYs, and were less costly; i.e. all three strategies dominated no screening.

Among the three strategies, simple dominance of Strategy 3 over Strategy 1 was observed: Strategy 3 resulted in more QALYs and less cost than Strategy 1. Compared with Strategies 1 and 3, Strategy 2 yielded more QALYs, but involved greater cost. The ICERs per QALY gained for Strategy 2 against Strategies 1 and 3 were JPY 293 616 and JPY 781 342, respectively.

With regard to the number of TCS procedures, Strategy 2 required the most procedures (294 322 procedures per 100 000 population), followed by Strategy 3 (126 171 procedures per 100 000), and Strategy 1 (100 740 procedures per 100 000).

Scenario analyses

When the uptake rates decreased to 10%, Strategy 2 showed simple dominance over no screening and the other two screening strategies, whereas the ICER per QALY gained for no screening against Strategy 3 was JPY 218 464 (Table 3). When the uptake rates increased to 100%, all three screening strategies showed simple dominance over no screening, and the ICERs per QALY gained for Strategy 2 against Strategies 1 and 3 were JPY 126 810 and JPY 19 475, respectively (Table 3).

When the initial age of screening changed to 50 years, all three screening strategies dominated no screening, and the ICERs were JPY 87 804 and JPY 125 953 per QALY gained for Strategy 2 against Strategies 1 and 3 (Table 3).

The results for QALYs, costs and required number of TCS procedures when the age for population-wide TCS in Strategy 3 was changed between 40 and 60 years are shown in Table 4. Compared with the base case scenario of Strategy 3 with TCS at 50 years, the strategy with population-wide TCS at the age of 40 years resulted in fewer QALYs and higher cost. In contrast, when the population-wide TCS was performed at 55 years, more QALYs were gained with lower cost than when the TCS was performed at 50 years. The ICER per QALY gained for the strategy with TCS at 55 years against the strategy with TCS at 60 years was JPY 206 113. Against the strategy with TCS at 55 years, the ICER per QALY gained for the strategy with TCS at 45 years was JPY 782 013. The strategy with TCS at 45 years yielded more QALYs and was less costly than Strategy 2, and the ICER per QALY gained for this strategy against Strategy 1 was JPY 151 856. The required number of TCS procedures decreased as the age for population-wide TCS increased.

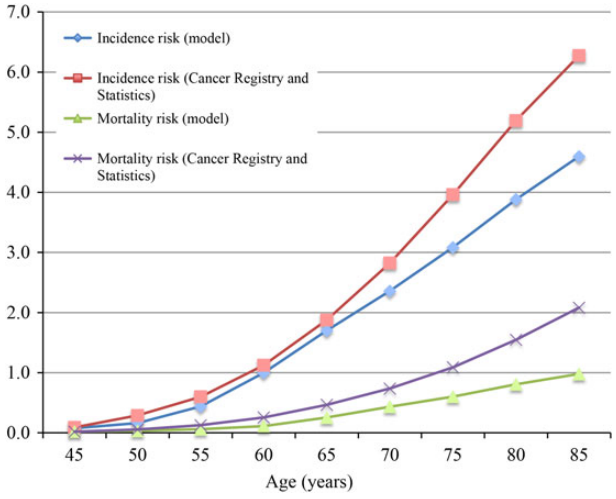

Figure 3. Comparison between cumulative risks for colorectal cancer incidence and mortality estimated from the study model and those estimated from the Cancer Registry and Statistics.

Probabilistic sensitivity analysis

The probabilistic sensitivity analysis performed for no screening and the three strategies (Strategies 1, 2 and 3) and the cost-effectiveness acceptability curve showed a correlation between the probability of being chosen as the most cost-effective scenario for each strategy and the WTP values (Fig. 4). In the figure, the horizontal axis represents the WTP value for one additional QALY, with a range of JPY 0–10 000 000, and the vertical axis represents the probability of being chosen as the most cost-effective scenario for each strategy. When the WTP value was set at JPY 5 000 000, the probability of being chosen as the most cost-effective scenario was 2.2% for no screening, 21.0% for Strategy 1, 48.7% for Strategy 2 and 28.1% for Strategy 3. When the age for population-wide TCS was changed to 45 years in Strategy 3, the probability resulted in 2.4% for no screening, 21.8% for Strategy 1, 53.2% for Strategy 2, and 22.6% for Strategy 3.

Table 2. Results of the base case analysis

	No screening	Strategy 1	Strategy 2	Strategy 3
Cost (per person, JPY)	156 125	94 733	99 930	93 523
QALYs (per person)	22.7986	23.0001	23.0178	23.0096
CRC cases (per 100 000 persons)	9541	3926	2989	3625
TCS procedures (per 100 000 persons)	—	100 740	294 322	126 171
Incremental cost per QALY gained (JPY)				
vs. No screening	—	Dominates[a]	Dominates	Dominates[a]
vs. Strategy 1	Dominated[b]	—	293 616	Dominates[a]
vs. Strategy 2	Dominated[b]	see Strategy 2 vs. 1	—	see Strategy 2 vs. 3
vs. Strategy 3	Dominated[b]	Dominated[b]	781 342	—

[a]'Dominates' denotes a strategy (column) that is less costly and more effective than its comparator (row).
[b]'Dominated' denotes a strategy (column) that is more costly and less effective than its comparator (row).
QALY, quality-adjusted life-years.

Table 3. Results of the scenario analyses on the uptake rates and initial age of screening

	No screening	Strategy 1	Strategy 2	Strategy 3
Uptake rates: 100%				
Cost (per person, JPY)	154 694	99 382	104 961	103 789
QALYs (per person)	22.8026	23.0770	23.1210	23.0608
Incremental cost per QALY gained (JPY)				
vs. No screening	—	Dominates[a]	Dominates[a]	Dominates[a]
vs. Strategy 1	Dominated[b]	—	126 810	Dominated[b]
vs. Strategy 2	Dominated[b]	see Strategy 2 vs. 1	—	see Strategy 2 vs. 3
vs. Strategy 3	Dominated[b]	Dominates[a]	19 475	—
Uptake rates: 10%				
Cost (per person, JPY)	153 653	152 928	137 289	151 710
QALYs (per person)	22.8209	22.8278	22.8753	22.8120
Incremental cost per QALY gained (JPY)				
vs. No screening	—	Dominates[a]	Dominates[a]	See No screening vs. 3
vs. Strategy 1	Dominated[b]	—	Dominates[a]	see Strategy 1 vs. 3
vs. Strategy 2	Dominated[b]	Dominated[b]	—	Dominated[b]
vs. Strategy 3	218 464	77 010	Dominates[a]	—
Starting age: 50 years				
Cost (per person, JPY)	154 107	99 793	104 069	99 043
QALYs (per person)	22.8194	23.0845	23.1332	23.0933
Incremental cost per QALY gained (JPY)				
vs. No screening	—	Dominates[a]	Dominates[a]	Dominates[a]
vs. Strategy 1	Dominated[b]	—	87 804	Dominates[a]
vs. Strategy 2	Dominated[b]	see Strategy 2 vs. 1	—	see Strategy 2 vs. 3
vs. Strategy 3	Dominated[b]	Dominated[b]	125 953	—

[a]'Dominates' denotes a strategy (column) that is less costly and more effective than its comparator (row).
[b]'Dominated' denotes a strategy (column) that is more costly and less effective than its comparator (row).

Table 4. Results of the scenario analyses on the age for population-wide total colonoscopy in Strategy 3

	40 years	45 years	50 years	55 years	60 years
Cost (per person, JPY)	99 602	97 679	93 523	92 049	91 142
QALYs (per person)	22.9979	23.0195	23.0096	23.0123	23.0079
TCS procedures (per 100 000 persons)	138 687	133 193	126 171	123 659	123 106
Incremental cost per QALY gained (JPY)					
vs. 40 years	—	Dominates[a]	Dominates[a]	Dominates[a]	Dominates[a]
vs. 45 years	Dominated[b]	—	see 45 years vs. 50 years	see 45 years vs. 55 years	see 45 years vs. 60 years
vs. 50 years	Dominated[b]	420 284	—	Dominates[a]	see 50 years vs. 60 years
vs. 55 years	Dominated[b]	782 013	Dominated[b]	—	see 55 years vs. 60 years
vs. 60 years	Dominated[b]	564 055	1.400 462	206 113	—

[a]'Dominates' denotes a strategy (column) that is less costly and more effective than its comparator (row).
[b]'Dominated' denotes a strategy (column) that is more costly and less effective than its comparator (row).

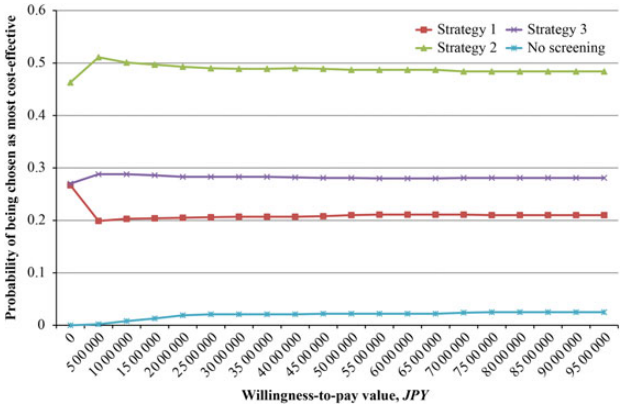

Figure 4. Probabilistic sensitivity analysis performed for the three strategies (1, 2 and 3) and no screening.

Discussion

This study examined in detail the cost-effectiveness of CRC screening with FIT and/or TCS in the Japanese settings by performing a simulation model analysis. For this analysis, we constructed a model of CRC using Japanese clinical data. The validity of the model was indicated by the finding that the cumulative risks for CRC incidence and mortality estimated from the model and the Cancer Registry and Statistics matched mostly, particularly for people ≤65 years of age. Although these risk estimates differed slightly after the age of 65 years, we believe that it does not matter in this study. On the contrary, the difference strengthens the evidence for the favorable cost-effectiveness of CRC screening indicated by the model analysis because the lower CRC incidence and mortality estimated from the model means that it may be more difficult to prove the (cost-)effectiveness of screening using the model than with real-life data.

Our results indicate that CRC screening with FIT and/or TCS was superior to no screening from the perspective of cost-effectiveness in most cases. This finding agrees with previous foreign cost-effectiveness studies on CRC screening (17–24). However, when the uptake rates decreased to 10%, the ICER per QALY gained for no screening against Strategy 3 was well below JPY 5-6 million. Considering that this amount is the upper limit of the WTP value for one additional QALY in Japan (43), it is postulated that the superiority of CRC screening to no screening in terms of cost-effectiveness will be more difficult to maintain when uptakes rates are low. To maintain the superior cost-effectiveness of CRC screening, it will be essential to achieve high screening uptake rates.

Despite a number of previous cost-effectiveness studies on CRC screening, there has been no consensus on the optimal use in terms of cost-effectiveness of FIT and TCS for population-based CRC screening (17–26). In the base case analysis of this study, the ICER per QALY gained for Strategy 2 against Strategy 1 was lower than the upper limit of the WTP value in Japan and Strategy 3 showed simple dominance over Strategy 1, which suggests that the strategies that use TCS more actively (Strategies 2 and 3) could be more cost-effective than the FIT-based screening strategy (Strategy 1). Furthermore, the sensitivity analyses showed that the strategies with greater use of TCS (Strategies 2 and 3) could be more cost-effective than the FIT-based screening strategy (Strategy 1) in most cases. This finding may largely be due to the much lower fee per TCS procedure in Japan than in other countries. Comparing cost-effectiveness between Strategies 2 and 3, the base case and sensitivity analyses showed that Strategy 2 was more cost-effective than Strategy 3 in many cases. However, the sensitivity analyses showed that the superiority of Strategy 2 against Strategy 3 with regard to cost-effectiveness was not always the case and that Strategy 3 could be more cost-effective than Strategy 2 under certain sets of model parameters and the age for population-wide TCS in Strategy 3.

If TCS is to be used more actively for population-based CRC screening, its safety and the availability of TCS resources require discussion. First, with regard to the safety of TCS, recent foreign studies have reported that the perforation rate of TCS without polypectomy was 0.01–0.03%, which is a very low rate that indicates the safety of screening TCS (44–48). Similarly, in Japan, the corresponding rate has been reported to be low, as shown in Table 1 (37). Given the safety of screening TCS, it may be possible to use it more actively than the currently performed FIT-based CRC screening. However, the risk of perforation associated with TCS cannot be completely ignored at present, particularly for the elderly population (44–48). Second, the capacity for screening TCS in Japan has not been clarified, with some surveys currently in progress, including the Japan endoscopy database project (UMIN000016093). Nevertheless, it is obvious that TCS capacity is limited in Japan and that we must arrange the CRC screening system to meet this limitation. Considering the limited TCS capacity, the TCS-based screening (Strategy 2), which requires more than double the number of TCS procedures than the other strategies in this study (Strategies 1 and 3), is likely to be the most difficult to implement.

From the cost-effectiveness aspect only, the TCS-based strategy may be the best; however, considering cost-effectiveness, safety, and the TCS capacity issue together, we postulate that the strategy of adding population-wide TCS at a specific age to the FIT-based strategy (Strategy 3) may be an optimal option for population-based CRC screening in Japan. With regard to the optimal age for population-wide TCS in Strategy 3, TCS at 45 years was the most cost-effective under the condition of the upper limit of WTP being JPY 5-6 million, according to the scenario analyses in this study. Considering that it is necessary to set the age for population-wide TCS as a range rather than one specific age to achieve a higher uptake rate, it appears that TCS within the age range 45–55 years would be acceptable from the perspective of cost-effectiveness on the basis of the study results. This would also be expected to improve the safety of the procedure because of the relatively younger age. With regard to the TCS capacity, although more TCS procedures may be required than with the FIT-based strategy, the increase is considered not to be too great; the number of TCS procedures required in Strategy 3 (TCS at 45–55 years) compared with those required in Strategy 1 was 123 659–133 193 vs. 100 740 per 100 000 individuals, whereas Strategy 2 required 294 322 TCS procedures per 100 000 individuals.

This study had several limitations. First, the natural history model of CRC in this study was based on currently available Japanese data; as a result, it was completely based on the concept of the adenoma-carcinoma sequence on which the previously reported cost-effectiveness analyses were based (17–24). However, other CRC pathways, such as the serrated pathway and the *de novo* pathway, have been reported, and it may be necessary to include these in the natural history model of CRC in future analyses, after the collection of a sufficiently large body of data on serrated polyps or *de novo* cancers (49,50). Second, the values of model parameters set in the base case analysis could vary case by case in the real world. However, sensitivity analyses, including probabilistic sensitivity analyses, were performed for the parameters. Third, indirect costs such as productivity loss cost due to CRC treatment were not considered in this study. Because limited data are available on indirect costs in Japan at present, it is currently difficult to include these costs in the cost-effective analysis. However, the cost-effective analyses in this study were performed form the healthcare payer's perspective in Japan, and thus we believe that no inclusion of indirect cost was appropriate for the analyses. For future cost-effectiveness analyses that include other perspectives, inclusion of data on the indirect costs associated with CRC in Japan would be warranted.

In conclusion, the present study examined the cost-effectiveness of population-based CRC screening in Japan. The CRC screening strategies with more active use of TCS could be more cost-effective than the FIT-based screening strategy. The TCS-based screening strategy could be the most cost-effective; however, considering the safety and limited capacity of TCS resources in addition to cost-effectiveness, the strategy of adding population-wide TCS for individuals in the age range 45–55 years to the FIT-based screening may be an optimal solution.

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Conflict of interest statement

None declared.

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