

**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.

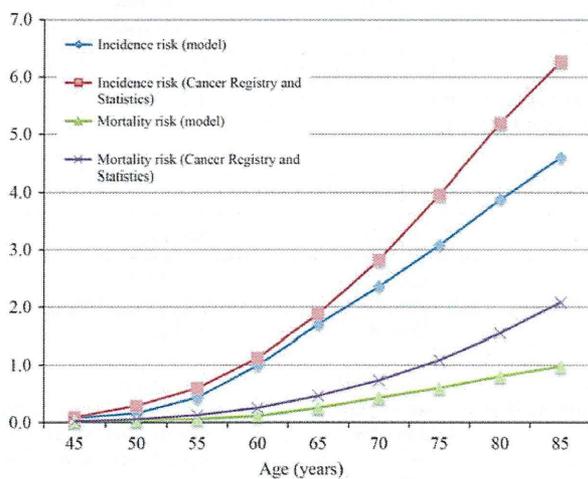
screening, there would be 9541 CRC cases among the cohort of 100 000 individuals, and the calculated QALYs and total cost per person were 22.8 and JPY 156 125, respectively. Compared with no screening, all three screening strategies (Strategies 1, 2 and 3) experienced fewer CRC cases, gained more QALYs,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



**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.

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.

### 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 <sup>a</sup>	Dominates	Dominates <sup>a</sup>
vs. Strategy 1	Dominated <sup>b</sup>	—	293 616	Dominates <sup>a</sup>
vs. Strategy 2	Dominated <sup>b</sup>	see Strategy 2 vs. 1	—	see Strategy 2 vs. 3
vs. Strategy 3	Dominated <sup>b</sup>	Dominated <sup>b</sup>	781 342	—

<sup>a</sup>‘Dominates’ denotes a strategy (column) that is less costly and more effective than its comparator (row).

<sup>b</sup>‘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 <sup>a</sup>	Dominates <sup>a</sup>	Dominates <sup>a</sup>
vs. Strategy 1	Dominated <sup>b</sup>	—	126 810	Dominated <sup>b</sup>
vs. Strategy 2	Dominated <sup>b</sup>	see Strategy 2 vs. 1	—	see Strategy 2 vs. 3
vs. Strategy 3	Dominated <sup>b</sup>	Dominates <sup>a</sup>	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 <sup>a</sup>	Dominates <sup>a</sup>	See No screening vs. 3
vs. Strategy 1	Dominated <sup>b</sup>	—	Dominates <sup>a</sup>	see Strategy 1 vs. 3
vs. Strategy 2	Dominated <sup>b</sup>	Dominated <sup>b</sup>	—	Dominated <sup>b</sup>
vs. Strategy 3	218 464	77 010	Dominates <sup>a</sup>	—
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 <sup>a</sup>	Dominates <sup>a</sup>	Dominates <sup>a</sup>
vs. Strategy 1	Dominated <sup>b</sup>	—	87 804	Dominates <sup>a</sup>
vs. Strategy 2	Dominated <sup>b</sup>	see Strategy 2 vs. 1	—	see Strategy 2 vs. 3
vs. Strategy 3	Dominated <sup>b</sup>	Dominated <sup>b</sup>	125 953	—

<sup>a</sup>'Dominates' denotes a strategy (column) that is less costly and more effective than its comparator (row).

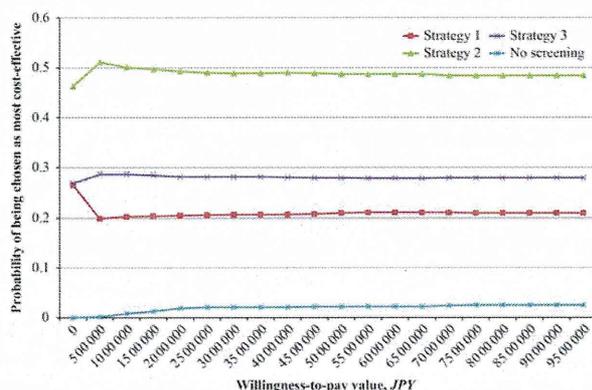
<sup>b</sup>'Dominated' denotes a strategy (column) that is more costly and less effective than its comparator (row).

**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 <sup>a</sup>	Dominates <sup>a</sup>	Dominates <sup>a</sup>	Dominates <sup>a</sup>
vs. 45 years	Dominated <sup>b</sup>	—	see 45 years vs. 50 years	see 45 years vs. 55 years	see 45 years vs. 60 years
vs. 50 years	Dominated <sup>b</sup>	420 284	—	Dominates <sup>a</sup>	see 50 years vs. 60 years
vs. 55 years	Dominated <sup>b</sup>	782 013	Dominated <sup>b</sup>	—	see 55 years vs. 60 years
vs. 60 years	Dominated <sup>b</sup>	564 055	1 400 462	206 113	—

<sup>a</sup>'Dominates' denotes a strategy (column) that is less costly and more effective than its comparator (row).

<sup>b</sup>'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  $\leq 65$  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 uptake 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 (UMIN00016093). 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 from 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.

## References

1. Matsuda A, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H; Japan Cancer Surveillance Research Group<. Cancer incidence and

- incidence rates in Japan in 2008: a study of 25 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) project. *Jpn J Clin Oncol* 2014;44:388–96.
2. Saito H. Screening for colorectal cancer: current status in Japan. *Dis Colon Rectum* 2000;43:S78–84.
  3. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993;328:1365–71.
  4. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;348:1472–7.
  5. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996;348:1467–71.
  6. Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2000;343:1603–7.
  7. Faivre J, Dancourt V, Lejeune C, et al. Reduction in colorectal cancer mortality by fecal occult blood screening in a French controlled study. *Gastroenterology* 2004;126:1674–80.
  8. Hiwatashi N, Morimoto T, Fukao A, et al. An evaluation of mass screening using fecal occult blood test for colorectal cancer in Japan: a case-control study. *Jpn J Cancer Res* 1993;84:1110–2.
  9. Saito H, Soma Y, Koeda J, et al. Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case-control study. *Int J Cancer* 1995;61:465–9.
  10. Saito H. Screening for colorectal cancer by immunochemical fecal occult blood testing. *Jpn J Cancer Res* 1996;87:1011–24.
  11. Zappa M, Castiglione G, Grazzini G, et al. Effect of faecal occult blood testing on colorectal mortality: results of a population-based case-control study in the district of Florence, Italy. *Int J Cancer* 1997;73:208–10.
  12. Saito H, Soma Y, Nakajima M, et al. A case-control study evaluating occult blood screening for colorectal cancer with hemoccult test and an immunochemical hemagglutination test. *Oncol Rep* 2000;7:815–9.
  13. Nakajima M, Saito H, Soma Y, Sobue T, Tanaka M, Munakata A. Prevention of advanced colorectal cancer by screening using the immunochemical faecal occult blood test: a case-control study. *Br J Cancer* 2003;89:23–8.
  14. Lee KJ, Inoue M, Otani T, Iwasaki M, Sasazuki S, Tsugane S; Japan Public Health Center-based Prospective Study. Colorectal cancer screening using fecal occult blood test and subsequent risk of colorectal cancer: a prospective cohort study in Japan. *Cancer Detect Prev* 2007;31:3–11.
  15. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013;369:1095–105.
  16. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012;366:687–96.
  17. Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. *JAMA* 2000;284:1954–61.
  18. Sonnenberg A, Delcò F, Inadomi JM. Cost-effectiveness of colonoscopy in screening for colorectal cancer. *Ann Intern Med* 2000;133:573–84.
  19. Pignone M, Saha S, Hoerger T, Mandelblatt J. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002;137:96–104.
  20. Tappenden P, Chilcott J, Eggington S, Patrick J, Sakai H, Karnon J. Option appraisal of population-based colorectal cancer screening programmes in England. *Gut* 2007;56:677–84.
  21. Vijan S, Hwang I, Inadomi J, et al. The cost-effectiveness of CT colonography in screening for colorectal neoplasia. *Am J Gastroenterol* 2007;102:380–90.
  22. Tsoi KK, Ng SS, Leung MC, Sung JJ. Cost-effectiveness analysis on screening for colorectal neoplasm and management of colorectal cancer in Asia. *Aliment Pharmacol Ther* 2008;28:353–63.
  23. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. *Epidemiol Rev* 2011;33:88–100.
  24. Sharaf RN, Ladabaum U. Comparative effectiveness and cost-effectiveness of screening colonoscopy vs. sigmoidoscopy and alternative strategies. *Am J Gastroenterol* 2013;108:120–32.
  25. Tsuji I, Fukao A, Shoji T, Kuwajima I, Sugawara N, Hisamichi S. Cost-effectiveness analysis of screening for colorectal cancer in Japan. *Toboku J Exp Med* 1991;164:269–78.
  26. Shimbo T, Glick HA, Eisenberg JM. Cost-effectiveness analysis of strategies for colorectal cancer screening in Japan. *Int J Technol Assess Health Care* 1994;10:359–75.
  27. Sekiguchi M, Matsuda T, Tamai N, et al. Cost-effectiveness of total colonoscopy in screening of colorectal cancer in Japan. *Gastroenterol Res Pract* 2012;2012:728454.
  28. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;13:322–38.
  29. Hamilton SR, Bosman FT, Boffetta P, et al. Carcinoma of the colon and rectum. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, editors. *WHO Classification of Tumors of the Digestive System*. 4th ed. Lyon: IARC, 2010;134–46.
  30. Winawer SJ, Zauber AG. The advanced adenoma as the primary target of screening. *Gastrointest Endosc Clin N Am* 2002;12:1–9. v.
  31. Ministry of Health, Labor and Welfare, Japan. Comprehensive Survey of Living Conditions 2013 [in Japanese]. Health, Labor and Welfare Statistics Association, Tokyo, Japan, 2013.
  32. Kitagawa S, Miyagawa K, Iriguchi Y, et al. Nationwide survey on gastrointestinal cancer screening 2012. *Journal of Gastrointestinal Cancer Screening* 2015;53:60–101.
  33. Hamashima C, Sobue T, Muramatsu Y, Saito H, Moriyama N, Kakizoe T. Comparison of observed and expected numbers of detected cancers in the research center for cancer prevention and screening program. *Jpn J Clin Oncol* 2006;36:301–8.
  34. Sano Y, Fujii T, Matsuda T, et al. Study design and patient recruitment for the Japan Polyp Study. *Open Access Journal of Clinical Trials* 2014;6:37–44.
  35. Morikawa T, Kato J, Yamaji Y, Wada R, Mitsuhashi T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. *Gastroenterology* 2005;129:422–8.
  36. Morikawa T, Kato J, Yamaji Y, et al. Sensitivity of immunochemical fecal occult blood test to small colorectal adenomas. *Am J Gastroenterol* 2007;102:2259–64.
  37. Yoshino J, Igarashi Y, Ohara H, et al. 5th report of endoscopic complications: results of the Japan Gastroenterological Endoscopy Society. *Gastroenterol Endosc* 2010;52:95–103. (in Japanese).
  38. Japanese Society for Cancer of the Colon and Rectum. *JSCCR Guidelines 2014 for the Treatment of Colorectal Cancer*. Tokyo, Japan: Kanehara & Co., Ltd., 2014. (in Japanese).
  39. Sweet A, Lee D, Gairy K, Phiri D, Reason T, Lock K. The impact of CT colonography for colorectal cancer screening on the UK NHS: costs, healthcare resources and health outcomes. *Appl Health Econ Health Policy* 2011;9:51–64.
  40. Segnan N, Patrick J, von Karsa L, editors. *European guidelines for quality assurance in colorectal cancer screening and diagnosis*, 1st edn. Luxembourg: Publication Office of the EU, 2010.
  41. Hol L, van Leerdam ME, van Ballegooijen M, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. *Gut* 2010;59:62–8.
  42. Siegel JE, Torrance GW, Russell LB, Luce BR, Weinstein MC, Gold MR. Guidelines for pharmacoeconomic studies. Recommendations from the panel on cost effectiveness in health and medicine. Panel on cost Effectiveness in Health and Medicine. *Pharmacoeconomics* 1997;11:159–68.
  43. Shiroywa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY

- gained: what is the threshold of cost effectiveness? *Health Econ* 2010; 19:422–37.
44. Niv Y, Hazazi R, Levi Z, Fraser G. Screening colonoscopy for colorectal cancer in asymptomatic people: a meta-analysis. *Dig Dis Sci* 2008;53:3049–54.
  45. Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. *Ann Intern Med* 2009; 150:849–57.
  46. Bokemeyer B, Bock H, Hüppe D, et al. Screening colonoscopy for colorectal cancer prevention: results from a German online registry on 269000 cases. *Eur J Gastroenterol Hepatol* 2009;21:650–5.
  47. Rutter CM, Johnson E, Miglioretti DL, Mandelson MT, Inadomi J, Buist DS. Adverse events after screening and follow-up colonoscopy. *Cancer Causes Control* 2012;23:289–96.
  48. Hamdani U, Naeem R, Haider F, et al. Risk factors for colonoscopic perforation: a population-based study of 80118 cases. *World J Gastroenterol* 2013;19:3596–601.
  49. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. *Gastroenterology* 2010;138:2088–100.
  50. Kashida H, Kudo SE. Early colorectal cancer: concept, diagnosis, and management. *Int J Clin Oncol* 2006;11:1–8.

