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*Original Article*

# Opportunistic screening versus mass screening for colorectal neoplasms in China: a cost-benefit analysis

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**Abstract:** Opportunistic screening has been recommended for colorectal cancer detection and early diagnosis in China. This study compared the cost-effectiveness of opportunistic screening and mass screening. One hundred thousand individuals, aged 50-80 years, undergoing opportunistic screening or mass screening, were simulated in a state-transition Markov model. Colorectal adenomas found during colonoscopies were removed and a colonoscopy was repeated every three years until no additional adenomas were found. For individuals with negative findings, colonoscopies were repeated within 10 years. Direct costs included screening tests and the treatment of cancer and complications. This study excluded indirect costs from the model and used an incremental cost-benefit ratio to evaluate the cost-effectiveness of the two screening strategies. Incidence of colorectal cancer was reduced by opportunistic screening and mass screening by 56.79% and 74.85%, respectively. Incremental cost-effectiveness ratio for opportunistic screening (-730 Renminbi Yuan [RMB]) was lower than the ratio for mass screening (-594 RMB). Opportunistic screening was more cost-effective than mass screening in detecting and managing colorectal neoplasms. It was not sensitive to the cost of colonoscopies or treatment for advanced colorectal cancer. Therefore, it may be recommended in clinical practice.

**Keywords:** Cost-benefit, opportunistic screening, mass screening, colorectal cancer

## Introduction

Rising incidence of colorectal cancer (CRC) has become a major public health concern in China. Colorectal adenomas (CRAs) and particularly advanced colorectal adenomas (ACRAs) are precursors of CRC. More than 80% of CRC cases develop from CRA and the less-benign ACRA. Prevalence of CRA and ACRA in patients older than 50 has been reported in China as 20.6% and 3.0%, respectively [11]. Early diagnosis through screening is central to reducing CRC incidence and mortality rates [15].

In China, physicians use two strategies for colorectal neoplasm screening, opportunistic screening (OS) and mass screening (MS). OS has been recommended for CRC screening and early diagnosis because of its simplicity and practicality [4]. However, a health economics evaluation has not been performed for OS and MS. This present study, therefore, evaluated the cost-effectiveness of OS and MS in colorectal neoplasm screening.

## Methods

### *Markov model construction*

A state-transition Markov model was constructed to compare the cost-effectiveness of OS and MS. This model simulated disease pro-

gression in a population of 100,000 Chinese individuals, aged 50-80 years, that had been invited to participate in a screening and management program. This study modeled nine colorectal health states: Normal, non-advanced CRA (NACRA), NACRA post-polypectomy, ACRA, ACRA post-polypectomy, early CRC (Duke A and Duke B stages) (ECRC), ECRC post-curative resection, advanced CRC (Duke C and Duke D stages) (ACRC), and CRC-related death. ACRA was defined as 10-mm polyps, high-grade dysplasia, or significant villous components. Each year, subjects could move from one state to another through predefined probability transitions. The model estimated the number of subjects in each state. At the end of the study period, the model yielded the estimated cumulative number of CRC-related deaths, cumulative number of life-years saved, and cumulative cost of screening and management strategies.

*Screening strategies in Markov model*

Subjects underwent either OS or MS.

Strategy 1 (MS): A colorectal neoplasm questionnaire was designed. High-risk and low-risk individuals underwent a colonoscopy (CSPY) examination and a faecal occult blood test (FOBT), respectively. A CSPY would be carried on FOBT-positive individuals. CRA found during CSPY was removed by polypectomy and the subject underwent a follow up CSPY every three years until no additional CRA was found. Subjects diagnosed with ECRC underwent curative resection and a follow up CSPY four years later. Those with confirmed ACRC underwent enlarged radical resection and chemotherapy with the drug combination FOLFOX. Individuals with a normal CSPY were scheduled for another CSPY within 10 years.

Strategy 2 (OS): FOBT was performed only in planned-screening individuals. CSPY would be carried on FOBT-positive individuals. FOBT-negative individuals were excluded from the Markov model. Treatment for CSPY-positive subjects followed the procedures in Strategy 1.

*Colorectal neoplasm questionnaire: high-risk and FOBT-positive criteria*

High-risk criteria: OS involved patients aged 50-80 with ACRAs that were diagnosed between November 1, 2014 and August 1, 2015 at Shanghai Dachang Hospital. A high-risk individual was a patient with one of the following characteristics: (1) Gastrointestinal symptoms such as blood or mucus in stool, abdominal pain, or unexplained anaemia or weight loss; (2) History of CRC; (3) History of colorectal precancerous diseases (e.g. CRAs, ulcerative colitis, Crohn's disease, schistosomiasis); (4) Immediate family members with a history of CRC; (5) Immediate family members with a history of colorectal polyps; and (6) History of pelvic radiotherapy.

FOBT-positive criteria: In this study, immunochemical FOBT was performed. Immunochemical FOBT (Instant-view, Alfa Scientific Designs, Poway, CA, USA) was performed by taking a faecal sample from the first two consecutive stools. The faecal test sampling device was shaped like a small test tube with the faecal probe inserted and sealing it. The probe had a serrated tip which was poked into five different areas of the stool, according to manufacturer recommendations, and then pushed back into the tube to seal it. The probe tip with the faecal sample was suspended in a standard volume of haemoglobin-stabilising buffer. After sealing, the tube was shaken vigorously to mix the specimen and extraction buffer. In the laboratory, the ferrule at the extremity of the test tube was snapped off and four drops of the supernatant in the test tube were put into the round well of the testing device. The specimen migrated by capillary action through the test strip. This assay is a one-step lateral flow chromatographic immunoassay. Interpretation was made after 5-10 minutes. Appearance of one pink line on the test strip indicated that no blood was detected. If two pink lines developed, then the test was classified as positive. If blood was present in either sample, the concentration of haemoglobin in the specimen was over 50 μg of haemoglobin/g of faeces.

*Clinical data*

Key parameters in the screening and management of disease progression in this model were acquired from publications or clinical assumptions (**Table 1**). When screening information was not available, annual age-specific incidence rates of NACRA, ACRA, ECRC, and ACRC in the population were taken as 15.35%, 3.3%, 1.6%, and 1.0%, respectively.

**Table 1.** Clinical transition rates used to model colorectal neoplasm screening and management

| Rate (per annum) | Baseline value % (95% confidence interval) | Reference |
|---|---|---|
| Compliance rate of first time CSPY | 100 | Assumed |
| Compliance rate of repeat CSPY after positive finding | 38.87 (34.46-43.41) | [13] |
| Compliance rate of repeat CSPY after negative finding | 15.35 (14.45-16.29) | [11] |
| Prevalence of non-advanced CRA over age 50 | 3.3 (2.89-3.82) | [11] |
| Prevalence of advanced CRA over age 50 | 1.6 | [11] |
| Prevalence of early CRC over age 50 | 1 | [10] |
| Normal to non-advanced CRA without screening | 0.22 (0.14-0.3) | [10] |
| Non-advanced CRA to advanced CRA without screening | 5.7 (0.55-11) | [2] |
| Advanced CRA to early CRC without screening | 6.3 (2.9-15) | [2] |
| Early CRC to advanced CRC without screening | 30 | [5] |
| Mortality rate from early CRC without screening | 18 | [17] |
| Mortality rate from diagnosed early CRC | 4 | [17] |
| Mortality rate from advanced CRC without screening | 46 | [17] |
| Mortality rate from diagnosed advanced CRC | 13 | [17] |
| Early CRC recurrence rate after curative resection | 11.37 (6.50-18.05) | [14] |
| Advanced CRC recurrence rate after curative resection | 14.39 (8.89-21.56) | [14] |
| Non-advanced CRA recurrence rate after non-advanced CRA post-polypectomy | 25 (18.34-32.66) | [6] |
| Advanced CRA recurrence rate after non-advanced CRA post-polypectomy | 3.95 (1.46-8.39) | [6] |
| Early CRC incidence rate after non-advanced CRA post-polypectomy | 1.3 (0.5-2.2) | [12] |
| Advanced CRC incidence rate after non-advanced CRA post-polypectomy | 0.8 (0.4-1.2) | [12] |
| Non-advanced CRA recurrence rate after advanced CRA post-polypectomy | 45 (37.14-53.05) | [6] |
| Advanced CRA recurrence rate after advanced CRA post-polypectomy | 13.12 (8.31-19.36) | [6] |
| Early CRC incidence rate after advanced CRA post-polypectomy | 1.3 (0.5-2.2) | [12] |
| Advanced CRC incidence rate after advanced CRA post-polypectomy | 0.8 (0.4-1.2) | [12] |
| Prevalence of non-advanced CRA following a negative CSPY over a 10-year period | 19.66 (12.89-28.02) | [1] |
| Prevalence of advanced CRA following a negative CSPY over a 10-year period | 4.27 (1.40-9.69) | [1] |
| Prevalence of early CRC following a negative CSPY over a 10-year period | 0 | [1] |
| Prevalence of advanced CRC following a negative CSPY over a 10-year period | 0 | [1] |
| CSPY examination bleeding rate | 0.15 | [7] |
| CSPY examination perforation rate | 0.2 | [16] |
| CSPY polypectomy bleeding rate | 2 | [7] |
| CSPY polypectomy perforation rate | 0.38 | [16] |
| Mortality from perforation | 10 | [16] |

CSPY, colonoscopy; CRA, colorectal adenoma; NACRA, non-advanced colorectal adenoma; ACRA, advanced colorectal adenoma; ECRC, early colorectal cancer; ACRC, advanced colorectal cancer.

Earlier diagnosis of CRC improved overall prognosis. Regardless of the stage at which CRC was detected, mortality was much lower than CRC mortality in individuals that had not undergone screening. CRA relapse rate was higher in ACRA subjects than in NACRA subjects, but both groups had similar CRC incidence rates. Subjects diagnosed with early CRC underwent curative resection. After a median follow up of 48 months, recurrence rates of early CRC and advanced CRC were 11.37% and 14.39%, respectively. Incidence of colorectal neoplasm was derived from a German statewide cohort study aimed at monitoring long-term reductions in CRC incidence and mortality in participants that underwent a CSPY [1]. Among 553 participants aged 55 or older with a prior negative CSPY, prevalence of NACRA, ACRA, ECRC, and ACRC was 19.66%, 4.27%, 0%, and 0%, respectively. PET scans were routinely used in pre-operative staging of ACRC, followed by six months of FOLFOX chemotherapy after enlarged radical resection.

*Cost*

All cost data are presented in 2014 Renminbi Yuan (RMB). The model includes direct costs of screening tests, CRC stage evaluation (including CT and PET scans), CRA polypectomy,

**Table 2.** Baseline values and ranges of economic parameters used in the model for colorectal neoplasm screening and management

| Cost item | Baseline value (RMB) |
|---|---|
| Colonoscopy | 300 |
| Polypectomy | 450 |
| Bleeding | 5,267 |
| Perforation | 15,840 |
| Treatment for early CRC | |
| CT scan | 200 |
| Colorectal radical resection | 2,200 |
| Hospital charges (up to 9 days) | 2,250 |
| Treatment for late CRC | |
| CT scan | 200 |
| Colorectal enlarged radical resection | 3,000 |
| PET scan | 7,500 |
| Metastatic liver disease | 1,500 |
| Hospital charges (10-30 days) | 2,250-7,500 |
| Chemotherapy: FOLFOX for 6 months_ | 12,300 |

CRC, colorectal cancer; RMB, Renminbi Yuan.

CRC treatment (including surgery and chemotherapy), and hospitalization for complications (bleeding or perforation) after CSPY and/or polypectomies (**Table 2**). This study excluded indirect costs such as transportation and lost productivity costs because of a lack of data. Labor costs for daily hospital care and disposable instruments were included in hospitalisation costs, but the costs of CT, surgical procedures, and consultation were not. All cost data were obtained from 2014 Shanghai Medical Health Care Services and price lists were provided by the Shanghai Municipal Health Bureau. Subjects that underwent CRC surgery were hospitalized an average of 9 days. All future costs related to CRC screening or care and all future life-years saved through screening were discounted at an annual rate of 3% [3].

*Cost-benefit analysis*

This study measured the effectiveness of screening and management in terms of life-years saved by CRC prevention following early diagnosis of CRA and early-stage CRC. To derive the number of life-years saved by screening, the difference in life-years lost to cancer-related deaths was compared between a Markov model that included screening and one that did not. Cost-benefit analysis was based on the determination of an incremental cost-effectiveness ratio (ICER), calculated by dividing the incremental costs by incremental life-years saved. Life-years gained and costs were discounted at an annual rate of 3%.

*Sensitivity analysis*

As the cost of healthcare varies regionally in China, sensitivity analyses of the ICER were conducted to assess its robustness across different intervals of key parameters. One-way sensitivity analyses were computed of the ICER between different screening strategies over the possible range of CSPY costs and advanced CRC therapy. Compliance rates for initial, repeated, and follow up screening were assumed to be the same. When results were not robust, threshold values for the change in conclusion are presented. All calculations were simulated using TreeAge Pro 2009 (TreeAge Software, Inc., Williamstown, MA, USA).

## Results

*Opportunistic screening*

Five hundred and seventy-six patients met screening criteria during the study period at the Gastroenterology Outpatient Department of Shanghai Dachang Hospital and were screened. They consisted of 264 male and 312 female patients, aged 50-80 (median age: 61 years). Among the 576 patients, 324 cases were classified as high-risk (positive rate: 56.3%), according to the colorectal neoplasm questionnaire, while the other 252 cases (negative rate: 43.7%) were classified as the low-risk group. High-risk individuals underwent a CSPY. CSPY yielded the following results: Normal, 200 cases (61.7%); NACRA, 32 cases (9.9%); ACRA, 56 cases (17.3%); ECRC, 16 cases (4.9%); ACRC, 20 cases (6.2%). FOBT was performed in low-risk individuals. There were 224 FOBT-positive cases (positive rate: 88.9%) in the low-risk group. CSPY was performed in the 224 FOBT-positive individuals and yielded the following results: Normal, 168 cases (73.6%); NACRA, 24 cases (11.3%); ACRA, 28 cases (13.2%); ECRC, 4 cases (1.9%); ACRC, 0 cases (0.0%).

*Mass screening*

This study mass-screened 10,589 asymptomatic individuals aged 50-80 during the study period at 17 community hospitals in the Bao-

**Table 3.** Outcomes of a cohort of 100,000 average-risk Chinese individuals aged 50-80 years with two strategies for colorectal neoplasm screening and management

| Variable/screening strategy | No screening | Mass screening | Opportunistic screening |
|---|---|---|---|
| Total number of non-advanced CRA cases | 15,266 | 19,727 | 14,435 |
| Total number of advanced CRA cases | 12,313 | 6,396 | 3,958 |
| Total number of early CRC cases | 13,032 | 4,511 | 2,082 |
| Total number of advanced CRC cases | 8,579 | 3,223 | 1,815 |
| Number of CRC cases prevented | 0 | 5,789 | 2,213 |
| Proportion of CRC cases prevented (%) | 0 | 74.85 | 56.79 |
| Total number of early CRC-related deaths | 13,032 | 3,548 | 1266 |
| Total number of advanced CRC-related deaths | 8,579 | 3,109 | 1,757 |
| CRC-related life-years lost | 200,663 | 65,409 | 33,478 |
| Effect (life-years) | 2,799,337 | 2,934,591 | 2,966,522 |
| Life-years saved | 0 | 135,254 | 167,185 |
| Number of procedures | | | |
| Colonoscopy | 0 | 114,473 | 114,130 |
| Bleeding | 0 | 2,059 | 2,000 |
| Perforation | 0 | 294 | 283 |
| Polypectomy | 0 | 17,089 | 14,385 |
| Costs (RMB) | | | |
| Colonoscopy (including complications) | 0 | 41,009,007 | 41,861,489 |
| Polypectomy (including complications) | 0 | 8,084,290 | 6,774,248 |
| Early CRC | 67,904,807 | 21,194,736 | 8,282,163 |
| Advanced CRC | 306,584,341 | 220,289,951 | 193,739,802 |
| Total costs | 374,489,148 | 294,172,583 | 252,409,702 |
| Incremental costs | 0 | -80,316,564 | -122,079,446 |
| Cost-effectiveness | 66057302.27 | 34687063.48 | 27152868.34 |
| ICER | 0 | -593.8202499 | -730.2057357 |

CRA, colorectal adenoma; CRC, colorectal cancer; ICER, incremental cost-effectiveness ratio; RMB, Renminbi Yuan.

shan District of Shanghai. FOBT-positive cases numbered 2,842 (positive rate: 26.8%). Among these cases, 465 subjects underwent CSPY, which yielded these numbers: Normal, 373 cases (80.2%); NACRA, 78 cases (16.8%); ACRA, 9 cases (1.9%); ECRC, 2 cases (0.4%); ACRC, 3 cases (0.6%).

*Cost-benefit analysis*

Cost-benefit analysis outcomes of the two strategies for 100,000 Chinese individuals are presented in **Table 3**. The models projected that 21,611 per 100,000 live individuals would be diagnosed with CRC and would lose 200,633 CRC-related life-years without screening. OS-based and MS-based strategies would prevent 56.79% and 74.85% of CRC cases, respectively. Total life-years saved by OS and MS strategies would be 167,185 years and 135,254 years, respectively. The number of CSPY procedures conducted under OS and MS strategies would be 114,130 and 114,473, respectively. Number of interventions involving polypectomy would be 14,385 and 17,089, respectively. Screening and management costs would increase by 252 million RMB (OS strategy) and by 294 million RMB (MS strategy). OS-based strategy resulted in more life-years saved than the MS-based strategy, at a lower cost. Compared with a no-screening strategy, incremental costs of OS and MS were -122 million RMB and -80 million RMB, respectively (**Figure 1**). The ICERs of the OS strategy and MS strategy were -730 RMB and -594 RMB, respectively. Based on this model, it was therefore concluded that OS would be more cost-effective than MS.

*Sensitivity analysis*

Overall costs of both strategies were lower than the cost of simulated ACRC therapy without screening. To equalize the cost of each strategy to that of no screening, it was necessary to

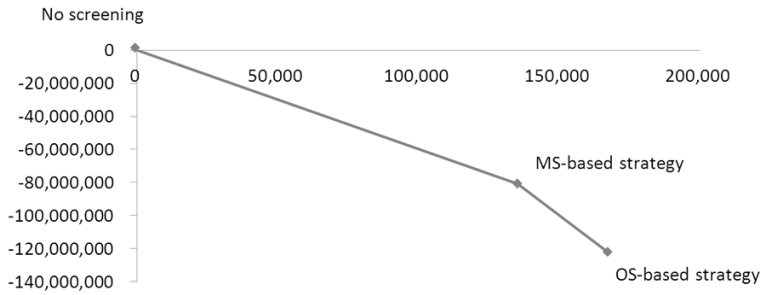


**Figure 1.** Cost-benefit analyses for opportunistic screening (OS) and mass screening (MS) and management strategies. The line represents the cost-effectiveness frontier. Incremental costs for a life-year saved (ICER) were -730 RMB for OS and -594 RMB for MS.

raise the cost of CSPY and ACRC treatment to 800 and 500,000 RMB, respectively. CSPY costs had little influence on the finding that OS-based strategy was the medically preferred strategy for colorectal neoplasm screening and management. Costs of CSPY ranged from 250 to 800 RMB. The ICER for MS varied from -590 to -185 million RMB while the ICER for OS varied from -749 to -415 million RMB. See also the supplementary spreadsheet (sensitivity analysis CSPY.xsl).

Higher ACRC treatment costs would increase the ICER for both OS and MS strategies, but the influence was greater on the latter. Costs of ACRC treatment ranged from 10,000 to 50,000 RMB. The ICER for MS varied from -285 to -1,183 million RMB; the ICER for OS varied from -163 to -968 million RMB. See also the supplementary spreadsheet (sensitivity analysis ACRA.xsl). Overall, the OS strategy offered greater cost-benefit advantages.

## Discussion

While incidence of CRC has risen dramatically, patient survival remains unsatisfactory, mainly due to diagnosis in the late stages. CRAs, and especially ACRAs, are CRC precursors and their removal is central to reducing incidence and mortality rates [15]. Treatment strategies for CRA removal rely on detection by screening and surveillance follow up.

Colorectal neoplasm screening mainly consists of two strategies: MS and OS. The former is rapid screening based on the population (community or units) meeting screening criteria determined by relevant entities using a standardized method. The purpose of MS is to detect precancerous disease and reduce cancer incidence with appropriate preventive measures [3]. OS is clinic-based screening that can be performed in community clinics or town hospitals. Screening methods are selected based on individual patients, including healthy individuals undergoing physical examinations, patients treated for other diseases who exhibit high-risk factors for CRC, and asymptomatic outpatients.

Because of China's large population, the annual national expenditure would be approximately 18.081 billion RMB for the lowest-cost FOBT and CRC screenings among people aged over 60. According to Guidelines for the Screening and Early Diagnosis and Treatment of Major Cancers in China [4], all individuals over 40 should be screened for CRC. This cost would not be feasible. In addition, national MS would require a large full-time specialized staff. This would not be feasible either. OS, as a clinic-based screening, can be conducted in town hospitals, community clinics, and regional medical centers. Special funding and additional staff would not be required, but patient compliance is essential. Although OS is cost-effective and recommended, there has not been enough economic evidence to date to support it. This study performed cost-benefit analysis based on the abovementioned considerations.

In this analysis, prevalence of CRA and CRC in OS high-risk individuals was 27.2% and 11.1%, respectively. This finding is consistent with findings from a Romanian population [8]. That study reported an adenoma detection rate of 32.1%, but with an almost identical advanced neoplasia detection rate of 9.2% (2433 CSPYs over a 5-year period, 2008-2013). These numbers are similar to those reported by Lieberman et al. for a US cohort of military veterans [10], although with a lower CRA rate. In the present model, OS screening would prevent 56.79% of all CRCs, compared with 74.85% prevented by MS screening. However, in the model, the lower fraction of cancers prevented through OS screening resulted in more life-years saved. The higher number of CSPYs in the MS-based screening strategy translated into more complications. Mortality from perforation is rela-

tively high in China [12], possibly offsetting the effects in the present analysis.

This study used key clinical transition data from a German study [14] in China-based cost-benefit analysis for the following reasons: (1) The German study was a unique large-scale prospective cohort study tracking prognoses among individuals more than 10 years after a negative CSPY; and (2) No significant ethnic differences were observed in incidence of advanced neoplasm 10 years after a negative CSPY. In German Caucasians, incidence of advanced colorectal neoplasms was approximately 4% and equally low 1-5 years and 6-10 years after a negative CSPY. In a Hong Kong-based study [9], only five (1.4%) out of 370 subjects with no baseline polyp were found to have advanced neoplasms upon a 5-year rescreening CSPY. This suggests that the odds of finding advanced neoplasms in average-risk Chinese subjects may be even lower than in Caucasians.

This study has several limitations. The primary shortcoming was the absence of sensitivity analysis by age due to a lack of information on age distribution in the screening population. Because CRC incidence rates displays an age-dependent increase, the number of cancers prevented was higher in older subjects than in younger subjects. Second, although clinical data were based on key parameters derived mainly from Chinese sources, some data from Europe and the US were used when Chinese information was unavailable. Third, indirect costs were excluded from the model.

## Conclusions

The present model suggests that OS is a cost-effective strategy for detecting and managing colorectal neoplasms in China and may be recommended in clinical practice.

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## Disclosure of conflict of interest

None.

## Abbreviations

RMB, Renminbi Yuan; CRC, colorectal cancer; CRA, colorectal adenoma; ACRA, advanced colorectal adenoma; OS, opportunistic screening; MS, mass screening; NACRA, non-advanced CRA; ACRA, advanced CRA; ECRC, early CRC; ACRC, advanced CRC; CSPY, colonoscopy; FOBT, faecal occult blood test; ICER, incremental cost-effectiveness ratio.

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