RESEARCH COMMUNICATION

Repeat Colonoscopy Every 10 Years or Single Colonoscopy for Colorectal Neoplasm Screening in Average-risk Chinese: A Cost-effectiveness Analysis

Zhen-Hua Wang, Qin-Yan Gao, Jing-Yuan Fang*

Abstract

Background: The appropriate interval between negative colonoscopy screenings is uncertain, but the numbers of advanced neoplasms 10 years after a negative result are generally low. We aimed to evaluate the cost-effectiveness of colorectal neoplasm screening and management based on repeat screening colonoscopy every 10 years or single colonoscopy, compared with no screening in the general population. Methods and materials: A state-transition Markov model simulated 100,000 individuals aged 50–80 years accepting repeat screening colonoscopy every 10 years or single colonoscopy, offered to every subject. Colorectal adenomas found during colonoscopy were removed by polypectomy, and the subjects were followed with surveillance every three years. For subjects with a normal result, colonoscopy was resumed within ten years in the repeat screening strategy. In single screening strategy, screening process was terminated. Direct costs such as screening tests, cancer treatment and costs of complications were included. Indirect costs were excluded from the model. The incremental cost-effectiveness ratio was used to evaluate the cost-effectiveness of the different screening strategies. Results: Assuming a first-time compliance rate of 90%, repeat screening colonoscopy and single colonoscopy can reduce the incidence of colorectal cancer by 65.8% and 67.2% respectively. The incremental cost-effectiveness ratio for single colonoscopy (49 Renminbi Yuan [RMB]) was much lower than that for repeat screening colonoscopy (474 RMB). Single colonoscopy was a more cost-effective strategy, which was not sensitive to the compliance rate of colonoscopy and the cost of advanced colorectal cancer. Conclusion: Single colonoscopy is suggested to be the more cost-effective strategy for screening and management of colorectal neoplasms and may be recommended in China clinical practice.

Keywords: Cost-efficacy - colonoscopy - colorectal neoplasm - screening

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Introduction

Colorectal cancer (CRC) is a major public health concern in China (Lu et al., 2003; Yang et al., 2004). Several prospective randomized tests have confirmed that reduction in death rate is associated with early detection of invasive disease as well as removal of colorectal adenoma (CRA) (Hardcastle et al., 1996; Kronborg et al., 1996; Mandel et al., 2000). In the most updated guideline from Asia pacific consensus (Sung et al., 2008) and the US Multisociety Task Force on Colorectal Cancer and the American Cancer Society (Levin et al., 2008), colonoscopy (CSPY) every 10 years is recommended for colorectal neoplasm screening. 10-year interval after a negative CSPY is based on the rate at which advanced neoplasm develops (Winawer et al., 1993; Noshirwani et al., 2000). However, these data were from symptomatic patients who may not be representative of the average-risk screening population. Until 2010 year, a study (Brenner et al., 2010) from Germany found there was a very low risk of advanced colorectal neoplasm in asymptomatic participants more than 10 years after a negative colonoscopy, which suggested that single CSPY screening or extension of screening intervals could be more preferable and cost-effective. There are several limitations for CSPY screening in China. (1) endoscopic capacity insufficiency and population preference for noninvasive test; (2) serious complication as post polypectomy bleeding and perforation (Hui et al., 2004; Wu et al., 2006); (3) relatively high expenditure. Therefore, we aim to evaluate the cost-effectiveness of repeat screening colonoscopy every 10 years or single colonoscopy for colorectal neoplasm screening based on in the general population compared with no screening.

Materials and Methods

We set up a state-transition Markov model to evaluate repeat-screening CSPY versus single CSPY for the cost-effectiveness of screening for colorectal neoplasm. The

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Table 1. Clinical Transition Rate Applied in the Model for the Colorectal Neoplasm Screening and Management

Rate (annually)	Baseline value (range)%	Reference
Compliance rate of first time CSPY	90 (70–100)	Hou, et al, 2004; Yang, et al, 2006; Li, et al, 2003
Compliance rate of repeat CSPY after positive result	100	Clinical assumed
Compliance rate of repeat CSPY after negative result	38.87 (34.46–43.41) 95% CI	Pariente, et al, 2006
Prevalence of non-advanced CRA above age 50	15.35 (14.45–16.29) 95% CI	Liu, et al, 2005
Prevalence of advanced CRA above age 50	3.3 (2.89– 3.82) 95% CI	Liu, et al, 2005
Prevalence of early CRC above age 50	1.6	Li, et al, 2003
Prevalence of advanced CRC above age 50	1	Lieberman, et al, 2000
Normal to non-advanced CRA without screening	0.22 (0.14-0.3) 95% CI	Lieberman
Non-advanced CRA to advanced CRA without screening	5.7 (0.55-11) 95% CI	Chen, et al, 2003
Advanced CRA to early CRC without screening	6.3 (2.9-15) 95% CI	Chen, et al, 2003
Early CRC to advanced CRC without screening	30	Hankey, et al, 2000
Mortality rate from early CRC without screening	18	Xu, et al, 2007
Mortality rate from diagnosed early CRC	4	Xu, et al, 2007
Mortality rate from advanced CRC without screening	46	Xu, et al, 2007
Mortality rate from diagnosed advanced CRC	13	Xu, et al, 2007
Early CRC recurrence rate after curative resection	11.37 (6.50– 18.05) 95% CI	Rodríguez-Moranta, et al, 2006
Advanced CRC recurrence rate after curative resection	14.39 (8.89– 21.56) 95% CI	Rodríguez-Moranta, et al, 2006
Non-advanced CRA recurrence rate after non-advanced CRA post-polypectomy	25 (18.34– 32.66) 95% CI	Huang, et al, 2010
Advanced CRA recurrence rate after non-advanced CRA post-polypectomy	3.95 (1.46– 8.39) 95% CI	Huang, et al, 2010
Early CRC incidence rate after non-advanced CRA post-polypectomy	1.3(0.5–2.2)95% CI	Martínez, et al, 2009
Advanced CRC incidence rate after non-advanced CRA post-polypectomy	0.8(0.4–1.2)95% CI	Martínez, et al, 2009
Non-advanced CRA recurrence rate after advanced CRA post-polypectomy	45(37.14–53.05)95% CI	Huang, et al, 2010
Advanced CRA recurrence rate after advanced CRA post-polypectomy	13.12(8.31–19.36)95% CI	Huang, et al, 2010
Early CRC incidence rate after advanced CRA post-polypectomy	1.3(0.5–2.2)95% CI	Martínez, et al, 2009
Advanced CRC incidence rate after advanced CRA post-polypectomy	0.8(0.4–1.2)95% CI	Martínez, et al, 2009
Prevalence of non-advanced CRA following a negative CSPY for a 10-year interval	19.66 (12.89—28.02) 95% CI	Brenner, et al, 2010
Prevalence of advanced CRA following a negative CSPY for a 10-year interval	4.27 (1.40--- 9.69) 95% CI	Brenner, et al, 2010
Prevalence of early CRC following a negative CSPY for a 10-year interval	0	Brenner, et al, 2010
Prevalence of advanced CRC following a negative CSPY for a 10-year interval	0	Brenner, et al, 2010
CSPY examination bleeding rate	0.15	Hui, et al, 2004;
CSPY examination perforation rate	0.2	Wu, et al, 2006
CSPY polypectomy bleeding rate	2	Hui, et al, 2004;
CSPY polypectomy perforation rate	0.38	Wu, et al, 2006
Mortality due to perforation	10	Wu, et al, 2006

Markov model simulated disease progression through several specified health states of a population of 100,000 Chinese individuals aged from 50 to 80 year invited to participate in a screening and management program. Nine health states were modeled: normal, non-advanced CRA, non-advanced CRA post-polypectomy, advanced CRA, advanced CRA post-polypectomy, early CRC (Duke A and Duke B stages), early CRC post-curative resection, advanced CRC (Duke C and Duke D stages), CRC-related death, which represented a natural course on normal--non-advanced CRA--advanced -early CRC--advanced CRC--death pathway. In our study, advanced CRA was defined as polyps 10 mm or histologically having high-grade dysplasia or significant villous components. At each new cycle of one year, subjects could move from one state of health to another through predefined probability transitions, and the model estimated how many subjects were in each state. Thus, at the end of the study period, the model was able to estimate the cumulative number of CRC-related deaths, the cumulative number of life-years saved by screening and management strategies and the cumulative cost of the strategies.

Screening strategies in Markov model

The entire population underwent two different screening strategies, based on repeat screening CSPY and single CSPY.

Strategy 1: CSPY was used in the primary stage of screening. CSPY was offered to every subject. CRA found during CSPY were removed by polypectomy, and

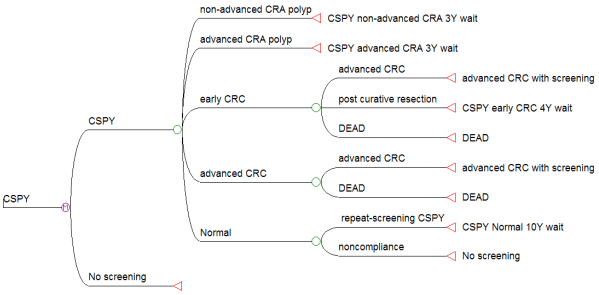

Figure 1. Markov Process on Repeat Screening CSPY Based Strategy

the subject was followed with surveillance CSPY every three years until no additional CRA were observed. The subjects diagnosed with early CRC were underwent curative resection and followed up with surveillance CSPY after four years. Those confirmed advanced CRC accepted enlarged radical resection and FOLFOX based chemotherapy. For subjects with a normal CSPY, CSPY was resumed within ten years (Figure 1).

Strategy 2: CSPY was used in the primary stage of screening. CSPY was offered to every subject. Screening process was terminated for those examined without abnormal findings. The remaining part is as same to the strategy 1 (Figure 2).

Clinical Data

We obtained the key parameter used to describe the screening and management progression of the disease in our model from publications or clinical assumption (Table1). If no screening, the annual age-specific

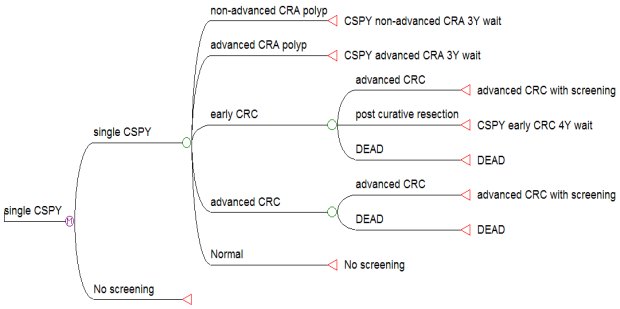

Figure 2. Markov Process on Single Screening CSPY Based Strategy

incidence rates of non-advanced CRA, advanced CRA, early CRC and advanced CRC from the population were 15.35%, 3.3%, 1.6% and 1.0% respectively. The compliance CSPY for first time was 90%, which drop to 38.87% for repeat examination after negative result. The overall prognosis was improved by earlier diagnosis of CRC. No matter which stage of CRC was detected, the mortality of diagnosed CRC was much lower than that of CRC without screening. CRA detected during CSPY were removed by polypectomy, and the subject was followed with surveillance CSPY every three years. The relapse rate of CRA in advanced CRA subjects was higher than that in non-advanced CRA individuals, but the incidence rate of CRC in the former was as same to that in the latter. Patients diagnosed with early CRC accepted curative resection. The recurrence rate of early CRC and advanced CRC after a median follow-up of 48 months were 11.37% and 14.39%. In strategy 1, for subjects with a normal CSPY, CSPY was resumed within ten years. The incidence of colorectal neoplasm was from a Germany statewide cohort study with the primary aim of monitoring long-term reduction in CRC incidence and mortality among participants of screening CSPY. Among participants aged 55 or older with a prior negative colonoscopy over the past 10 years, prevalence of non-advanced CRA, advanced CRA, early CRC and advanced CRC was 19.66%, 4.27%, 0% and 0% respectively. As a routine medical procedure, PET scan was wildly used for the pre-operative staging of advanced CRC. Then adjuvant chemotherapy after enlarged radical resection was offered to late CRC patients. FOLFOX for 6 months was regarded as the first-line adjuvant chemotherapeutic agent in China.

Cost

All cost data were shown in year 2010 Renminbi Yuan (RMB). Direct costs of screening tests, CRC stage evaluation (including CT and PET scan), CRA polypectomy, CRC treatment (including surgery and chemotherapy), and hospitalization were included in the Markov model (Table 2). Costs of hospitalization for complication (bleeding or perforation) after CSPY and/or polypectomy were also included in the model. Indirect costs, such as transportation costs and productivity lost were excluded from the model due to the lack of the corresponding statistics. Labor costs for daily hospital care and disposable instruments were included in hospitalization costs, which did not include the costs of CT, surgical procedures, and consultation. All cost data were obtained from Shanghai medical health care services and prices assembly (2010) Shanghai municipal health bureau. The average hospital stay period for patients who underwent CRC surgery was estimated to be 9 days. All future costs related CRC screening or care and all future life-years saved through screening are discounted at an annual rate of 3% (Drummond et al., 2006).

Table 2. Baseline Values and Ranges of Economic Parameters Used in the Model for the Colorectal Neoplasm Screening and Management

Cost item	Baseline value (RMB)
Colonoscopy	300
Polypectomy	450
Bleeding	5267
Perforation	15840
Treatment for the early CRC	
CT scan	200
Colorectal radical resection	2200
Hospital charges (9 days)	2250
Treatment for the late CRC	
CT scan	200
Colorectal enlarged radical resection	3000
PET scan	7500
Metastatic disease on liver	1500
Hospital charges 9 days (up to 30 days)	2250-7500
Chemotherapy: FOLFOX for 6 months_ Shanghai	12300

Cost-effectiveness analysis

Effectiveness of screening and management was measured from life-years saved by CRC prevention due to the diagnosis of CRA and earlier CRC. The number of life-years saved because of screening corresponded to the difference in life-years lost from cancer related deaths between a Markov model with and one without screening. The cost-effectiveness analysis was based on the determination of an incremental cost-effectiveness ratio (ICER). It was calculated by dividing the incremental costs by the incremental life-years saved. Life-years saved gained and costs were discounted at an annual rate of 3%.

Sensitivity analysis

Initial compliance influences the overall number of cancers prevented and the total costs of the screening and management program in a linear fashion due to determining how many subjects participate the program. Any decrease in the repeat compliance rate reduces the overall number of cancers prevented and the number of life years saved. The cost of health varies in China different areas. Sensitivity analyses on ICER were conducted in different stages of key parameters. One way sensitivity analyses based on the ICER were calculated between different screening and management over the possible range of model variables including initial, repeat screening compliance rates and cost of CSPY and advanced CRC therapy. While the results were not robust, they represented threshold values. All calculations were carried out using TreeAge Pro 2009 (TreeAge Software, Inc., Williamstown, MA).

Table 3. Outcome of A Cohort of 100000 Average-Risk Chinese Individuals Aged 50–80 Years with Two Strategies for Colorectal Neoplasm Screening and Management

Variable\screening strategy	No screening	Single CSPY	Repeat CSPY
Total number of non advanced CRA cases	15,175	22,261	35,529
Total number of advanced CRA cases	12,139	7,024	9,286
Total number of early CRC cases	12,952	4,463	4,087
Total number of advanced CRC cases	8,472	2,557	3,239
Cases of CRC prevented	0	14,404	14,098
Proportion of CRC case prevented (%)	0	67.23	65.8
Total number of early CRC-related dead cases	4,831	1,017	786
Total number of advanced CRC-related dead cases	8,472	2,525	3,138
Total loss of CRC-related life years	198,507	59,095	64,912
effect (life year)	2,801,493	2,940,905	2,935,088
Life-years saved	0	139,412	133,595
Number of procedures			
CSPY	0	113,760	177,213
bleeding	0	2,153	3,444
perforation	0	312	504
Therapeutic with polypectomy	0	22,322	39,311
Costs (RMB)			
CSPY(including complications)	0	34,850,193	57,949,151
polypectomy (including complications)	0	12,826,685	18,021,489
early CRC	67,628,355	19,661,173	17,798,375
advanced CRC	300,636,286	307,724,326	337,884,791
Total costs	368,264,641	375,062,377	431,653,806
increment costs		6,797,737	63,389,165
C/E	131	128	147
ICER	0	49	474

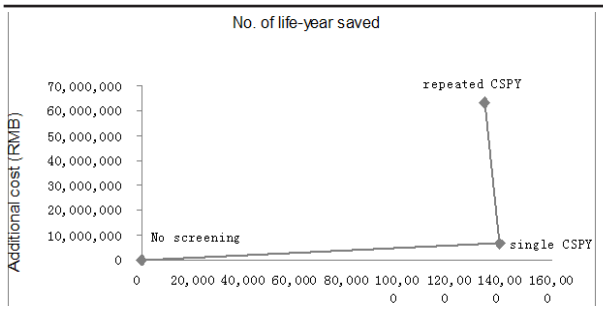

Figure 3. Cost-effectiveness Analyses for the Screening and Management Strategies. The line drawn represents the cost-effectiveness frontier. The increment costs for a life-year saved (ICER) of repeat CSPY based strategy and single CSPY based strategy are 49 RMB and 474 RMB, respectively

Results

Baseline analysis

The health and economic outcomes of two strategies compared with no screening for 100,000 Chinese individuals were shown in Table 3. The models projected that 21424 per 100000 live individuals would be diagnosed with CRC and would lose 198507 CRC-related life-years without screening. Assuming 90% adherence to first time screening test and 38.87% adherence to repeat screening after a negative result, the repeat CSPY based strategy and the single CSPY based strategy would prevent 65.80% and 67.23% of CRC cases, respectively. Total life-years saved of the repeat CSPY based strategy and the single CSPY based strategy would be 133,595 years and 139,412 years, respectively. The number of CSPY procedures in the repeat CSPY based strategy and the single CSPY based strategy was 177,213 and 113,760, respectively. The number of therapeutic with polypectomy in the former strategy and in the latter strategy was 39,311 and 22,322. The total costs for screening and managing colorectal neoplasm increased by 375 million RMB for the single CSPY based strategy and by 431 million RMB for the repeat CSPY based strategy. The single CSPY based strategy resulted in more life-years saved than repeat CSPY based strategy at a lower cost. Compared with a no screening strategy, the incremental costs of repeat CSPY based strategy and single CSPY based strategy were 63.4 million RMB and 6.8 million RMB (Figure 3); the ICERs of the repeat CSPY based strategy and the single CSPY based strategy were 474 RMB and 49 RMB. Therefore, the single CSPY based strategy was more cost-effective than the repeat CSPY based strategy.

Sensitivity analysis

The ICER for the single CSPY based strategy remained lower when the first-time CSPY compliances varied from 70% to 100%. In the same way, the ICER for the single CSPY based strategy was still lower than that of the repeat CSPY based strategy regardless of the repeat CSPY compliance varying from 20% to 80%. The overall costs of both strategies were lower than the simulation of advanced CRC therapy without screening. In order to equalize the cost of each of the strategies to that of no screening, it was necessary to raise the cost of the cost of CSPY to 500 RMB. The costs of CSPY had little influence on the fact that the single CSPY based strategy was the preferred strategy for colorectal neoplasm screening and management. Meanwhile, a higher treatment cost for advanced CRC would increase the ICER of both the single CSPY based strategy and the repeat CSPY based strategy, but the influence was greater on the latter, with greater cost-effectiveness advantages for the single CSPY based strategy.

Discussion

Among the various screening methods, CSPY has gained widespread acceptance and even some preference as the primary screening method for the detection of colorectal neoplasm (Pignone et al., 2002; Winawer et al., 2006) because it allows for a full structural examination of the colon and rectum in a single session and for the detection of colorectal neoplasm accompanied by biopsy or polypectomy. Although a repeat CSPY at a 10-year interval after a normal CSPY is recommended by the US Multisociety Task Force on Colorectal Cancer and the American Cancer Society (Levin et al., 2008), the appropriate interval between negative CSPY screening exams is uncertain because no direct data with which to assess the validity of this recommendation. Evidence supporting the 10-year interval is based on case control studies (Atkin et al., 1992; Winawe et al., 1993; VanStolk et al., 1998; Noshirwani et al., 2000) with possible recall and selection bias. There have been several large-scale prospective cohort studies (Imperiale et al., 2008; Leung et al., 2009; Brenner et al., 2010) to be shown that the rate of advanced neoplasm from 5 to 10 years after a negative screening colonoscopy in the asymptomatic population was considerably low. There are several disadvantages in CSPY examination. Effective performance of the procedure requires bowel preparation, which is an unpleasant experience for those who have undergone the test. Dependence on operator skill is another significant limitation for CSPY examination, especially in China. CSPY can result in significant harm, such as bleeding and perforation, most often associated with polypectomy. Therefore, we performed the cost-effectiveness analysis of repeat screening CSPY every 10 years or single CSPY for colorectal neoplasm screening in average-risk Chinese based on above mentioned considerations.

In our cost-effectiveness analysis, the single CSPY based strategy was more cost-effective than the repeat CSPY based strategy. The result was consistent with a previous cost-effectiveness study (Sonnenberg et al., 2002). However, there was much difference between two studies. In the study conducted by Sonnenberg, et al, the effect of the repeat CSPY based strategy was better than that of the single CSPY based strategy. Screening by the former prevented 75% of all CRCs, compared with 23% prevented by screening with the latter. The higher fraction of cancers prevented through screening with repeat versus single CSPY also results in more life years saved. But the effects such as the proportion of CRC case prevented by screening and life years saved in two strategies from our study were almost the same. There are two factors accounted for the difference. Firstly, the transition probabilities built into the model from two studies was different. In the study conducted by Sonnenberg, et al, the incidence rates of CRC was from adenoma retrospective cohort in the National Polyp Study (Winawer et al., 1993), the incidence of CRC after adenoma polypectomy was reduced by 76% to 90% compared with three non concurrent reference symptomatic populations. Related date in our analysis was from a prospective cohort study (Brenner et al., 2010) initiated in 2005 in Germany, with the primary aim of monitoring long-term reduction in CRC incidence and mortality among participants of screening CSPY. No CRC and 25 participants with advanced CRA were detected in 553 participants with previous negative colonoscopies. The long-time lower risk of CRC after a negative colonoscopy was not from a preventive effect by CSPY because no polyps were removed. Secondly, the more procedures of CSPY in the repeat CSPY based strategy translated into more complications. The mortality due to perforation in China is relatively high, which would offset the effect in our analysis.

We used the key clinical transition data from a Germany study in China cost-effectiveness analysis base on the following considerations. (1) To our knowledge, the study is a unique large scale prospective cohort study observing long-term reduction in CRC incidence and mortality among subjects more than 10 years after negative CSPY. (2) There was no significant ethnic difference in the incidence of advanced neoplasm after negative CSPY at 10 years interval. In German Caucasians (Brenner et al., 2010), the risk of advanced colorectal neoplasms was about 4% equally low within 1-5 and 6-10 years after a negative colonoscopy. In the HongKong study (Leung et al., 2009), for the 370 subjects with no baseline polyp, only five (1.4 %) subjects were found to have advanced neoplasm on rescreening CSPY after 5 years, which suggested that the chances of finding advanced neoplasm in average risk Chinese may be even lower than in the Caucasians screening population. Therefore, the data of incidence form German study would not take more advantage for the single CSPY based strategy.

This study has limitations. The primary shortcoming is no sensitivity analysis for age in our study due to lack of age distribution in Chinese population. Because the incidence rate of CRC shows an age-dependent increase, the number of cancers prevented per single CSPY is higher in the older than in the younger. Screening by a single colonoscopy is far more likely to lose its preventive power if scheduled too early. Secondly, although our clinical data were based on data mainly from China, some data from Europe and the USA had been used because of the data unavailable in China. Thirdly, indirect costs were not included.

Finally, the single CSPY based strategy was suggested to be the more cost-effective strategy for screening and management of colorectal neoplasm and may be recommended in China clinical practice.

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