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 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...
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               | 1.0                      | 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 | Rodriguez-Moranta, et al, 2006 |
| Advanced CRC recurrence rate after curative resection | 14.39 (8.89–21.56) 95% CI | Rodriguez-Moranta, et al, 2006 |
| Non-advanced CRA recurrence rate after non-advanced CRA post-polypectomy | 25.18 (13.64–36.66) 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 | Martinez, et al, 2009 |
| Advanced CRC incidence rate after non-advanced CRA post-polypectomy | 0.8 (0.4–1.2) 95% CI | Martinez, 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 (6.31–19.36) 95% CI | Huang, et al, 2010 |
| Early CRC incidence rate after advanced CRA post-polypectomy | 1.3 (0.5–2.2) 95% CI | Martinez, et al, 2009 |
| Advanced CRC incidence rate after advanced CRA post-polypectomy | 0.8 (0.4–1.2) 95% CI | Martinez, 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 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).

Figure 1. Markov Process on Repeat Screening CSPY Based Strategy

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 (Table 1). If no screening, the annual age-specific...
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 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 widely 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 or polypectomy were also included in the model. Indirect complication (bleeding or perforation) after CSPY and CRC treatment (including surgery and chemotherapy), and hospitalization were included in the model. 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 cost-effectiveness of Repeat or Single Colonoscopy for CRC in China was calculated by dividing the incremental costs by the incremental life-years saved. The cost of health varies in China over the possible range of model variables including initial, repeat screening compliance rates and cost of CSPY and 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 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                        | 12300                    |
| Shanghai                                                 |                          |

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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 100,000 live individuals would be diagnosed with CRC and would lose 198,507 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 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.

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 | 6,389,165 |
| C/E | 131 | 128 | 147 |
| ICER | 0 | 49 | 474 |
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; Winawer 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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