Original Article

Cost-effectiveness of Screening Colonoscopy in Iranian High Risk Population

Hamideh Javadinasab MSc[1,2], Rajabali Daroudi PhD[3], Hamideh Salimzadeh PhD[4], Alireza Delavari MD•[4], Payam Vezvaie MD[4], Reza Malekzadeh MD[4]

Abstract

Background: Colorectal cancer (CRC) is the fourth most common cancer among men and the second among women in Iran. First-Degree Relatives (FDRs) of patients with CRC are known to be at higher risk of CRC. The aim of this study was to identify the most cost-effective strategy for CRC screening in Iranian high risk individuals.

Methods: A Markov model was developed to assess the cost-effectiveness of six colonoscopy screening strategies for individuals at increased risk of CRC because of positive history of the disease in at least one first-degree relative in their family. Our strategies included five-yearly or ten-yearly colonoscopy starting from the age of 40 or 50 and colonoscopy once at 50 or 55 years. Data were extracted from the published literature, Globocan 2012 database, and national cancer registry reports. The Markov model contained 11 mutually exclusive health states. Time horizon of model was life time and cycle duration was 1 year. Outcomes included life year gains, Quality Adjusted Life Years (QALYs) and costs. The TreeAge Pro software was used for data modeling.

Results: All six screening strategies increased the life expectancy and QALY and were costlier than no screening. The incremental cost per QALY gained for CRC screening varied from $489 for one colonoscopy screening per lifetime at 55 years to $3,135 for colonoscopy screening every five years starting at the age of 40, compared with no screening. When strategies were compared with the next best strategy, dominated strategies were removed from analysis, one colonoscopy screening per lifetime at 55 years old; or every ten years starting at the age 40; or every five years starting at age 40 remained with incremental cost effective ratios of $489, $2,505, and $26,080 per QALY gained, respectively.

Conclusions: CRC colonoscopy screening in high-risk individuals is cost-effective in Iran. Colonoscopy screening every 10 years starting at the age of 40 was the most cost-effective strategy.

Keywords: Colonoscopy, colorectal cancer, cost-effectiveness, first degree relative, screening

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Introduction

Annually, 1.3 million new diagnosed cases of colorectal cancer (CRC) are reported worldwide, of which more than 60% lead to death. In 2012, CRC was the third most common diagnosed cancer and the fourth most common leading cause of cancer death in the world.[1,2]

If detected early, CRC is both preventable and treatable. It has been shown that screening and diagnosis of CRC in early stages, the curable stage, are effective in decreasing the CRC mortality rates, so that early detection can increase the five-years survival.[3] First-Degree Relatives (FDRs) of patients with CRC are known to be at higher risk of CRC, leading to recommendations for earlier CRC screening in them.[4–6] According to the current US guidelines, screening colonoscopy should begin at the age of 40 in individuals at higher risk for CRC (i.e. FDRs of patients with CRC).[7] There are several strategies for CRC screening and choosing the most cost-effective strategy depends on the circumstances of each country and individual's risk. However, colonoscopy is considered the gold standard for CRC screening.[8]

The cost-effectiveness of CRC screening has been well confirmed in high-income countries.[9,10] Although there are limited studies about the cost-effectiveness of CRC screening in Low and Middle-Income Countries (LMICs), the available evidence indicates that CRC screening could be cost-effective in these countries, too.[11,12] Since most LMICs, including Iran, face limited resources, there are financial barriers in organizing mass CRC screening programs in these countries. However, screening high-risk groups such as FDRs can be regarded as an appropriate alternative approach.[13,14]

To date, a large body of literature has investigated the cost-effectiveness of different modalities/strategies for CRC screening among individuals with moderate risk of CRC.[3,8,10,15,16] However, few studies have been conducted with this purpose among individuals at higher risk of CRC. Recent studies on cost-effectiveness of screening colonoscopy in Spain and Australia underscore a five-year interval for regular colonoscopy as the most efficient and cost-effective strategy for CRC screening

Authors' affiliations: [1]Department of Health Services Management, Science and Research Branch, Islamic Azad University, Tehran, Iran, [2]High Council of Health and Food Security, Ministry of Health and Medical Education, Tehran, Iran, [3]Department of Health Economics and Management, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran, [4]Digestive Oncology Research Center, Digestive Disease Research Institute, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.

•Corresponding author and reprints: Alireza Delavari MD, Gastroenterologist Digestive Diseases Research Center, Tehran University of Medical Sciences, Shariati Hospital, North Kargar Avenue, 14666, Tehran. Iran. Tel: +98-21-82415785, E-mail: delavariar@yahoo.com.

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among high risk individuals.[7,17]

Iran, like all developing countries, is experiencing an epidemiological transition and will face the additional burden of CRC in the near future.[18] According to recent statistics, CRC is the fourth most common cancer among men and the second among women in Iran.[2,19] In 2012, the economic burden of CRC was estimated to be about 300 million US$, inflicting catastrophic costs on Iranian CRC patients and society as a whole.[20] Yet, mass screening of CRC is not organized in Iran. Considering the limitation of resources and high economic burden of the disease on the Iranian health-care system, CRC screening, especially in high-risk individuals, will be a desirable approach to reduce the economic burden of this type of cancer. Furthermore, based on recent local data, FDRs in Iran have nearly a 4-fold risk of developing CRC compared to the general population.[21] These issues highlight the necessity of developing strategic plans for early detection of CRC in order to decrease the treatment costs and mortality rates, especially in high risk individuals (i.e., FDRs of CRC patients).[20] Therefore, we aimed to investigate the cost-effectiveness of screening colonoscopy in Iranian high-risk individuals and to recognize the most cost-effective strategy for CRC screening in this population.

Methods

A Markov model developed by Telford, et al.[22] was applied to simulate the natural history of CRC and to estimate the cost-effectiveness of six strategies for screening and no screening, among FDRs aged 40 years and above. The Markov model contained 11 mutually exclusive health states as follows: normal mucosa, low-risk polyp, advanced adenoma, three preclinical (undiagnosed) cancer states, three diagnosed cancer states, surveillance and death due to CRC or other causes. An individual can remain in the same health state (curved arrows) or move to different Markov health states (straight arrows) (Figure 1). The model time horizon was life time and the cycle duration was 1 year. Outcomes were Life Year Gains (LYG), Quality Adjusted Life Years (QALYs), and costs. All future costs and effects were discounted using five percent annual rate. Half-cycle correction was used for both costs and effects which assumed that both costs and effects occur half way through a model cycle. The TreeAge pro software (TreeAge pro Software, Inc., Williamston, MA) was used for data modeling.

Parameters

Table 1 shows the parameters of the model. The annual transition probabilities from normal to low-risk polyp in moderate risk individuals were estimated by calibration based on age-specific incidence rates of CRC in Iran, obtained from national cancer registry reports and Globocan 2012 database.[2,19] The annual transition probabilities from low-risk polyp to advanced adenoma and from advanced adenoma to CRC were obtained from previous studies.[22–26] The annual probability of diagnosis of a pre-clinical cancer was estimated from the stage distribution of preclinical cancer based on the distribution of CRC stages at diagnosis in Iran.[4,27,28] The annual probability of mortality due to CRC by stage was extracted from previous studies in Iran and Globocan 2012 database.[2,19,29–33]

The age-specific all-cause mortality rates for the Iranian population were obtained from the Iranian life tables.[34] In order to

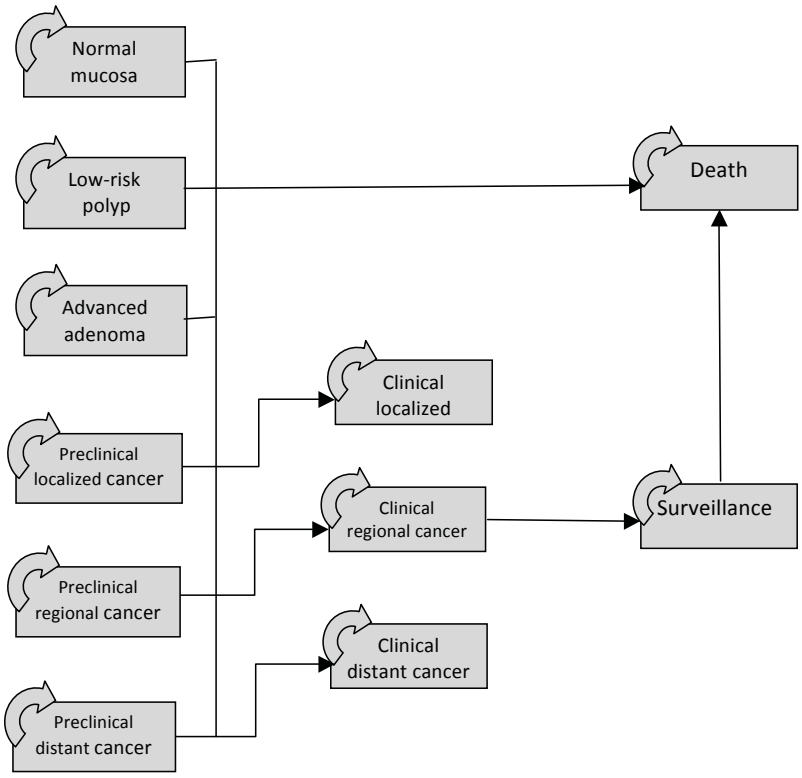

Figure 1. Markov states for the natural history of colorectal cancer.

Table 1. Base-case estimates and ranges used in sensitivity analysis

Variable	Input Parameter estimate	Standard deviation	Reference
Prevalence of low risk polyp at 40 years	0.051	0.0051	21,46
Prevalence of advanced adenoma at 40 years	0.014	0.0014	46
Prevalence of pre-clinical cancer at 40 years	0.002	0.0002	2,19,30,46
Annual transition probabilities			
Normal to low risk polyp	Age-dependent	+ 10% input parameter	Calibration
Low-risk polyp to advanced adenoma	0.036	0.011	22–26
Advanced adenoma to localized cancer	0.042	0.013	22–26
Localized cancer to regional cancer	0.36	0.072	2,4,19,27,28
Regional cancer to distant cancer	0.15	0.03	2,4,19,27,28
Diagnosed from pre-clinical localized cancer	0.04	0.008	2,4,19,27,28
Diagnosed from pre-clinical regional cancer	0.31	0.062	2,4,19,27,28
Diagnosed from pre-clinical distant cancer	1	0.2	2,4,19,27,28
Mortality from localized cancer	0.13	0.026	2,29–33
Mortality from regional cancer	0.225	0.045	2,29–33
Mortality from distant cancer	0.51	0.102	2,29–33
Screening test performance			
Sensitivity to detect a low risk polyp	0.85	0.083	4,6,22,47
Sensitivity to detect an advanced adenoma	0.9	0.046	4,6,22,47
Sensitivity to detect cancer	0.95	0.031	4,6,22,47
Specificity	1	- - -	7,15,17,22
Serious complication	0.0008	0.0002	22
Compliance	1	- - -	Assumption
Relapse (annual)			
Stage I	0.01	0.007	22
Stage II/III	0.04	0.028	22
Medical costs (2012 US dollars)		0	
Colonoscopy	204	61	20,48
Polypectomy	163	49	20,48
Complication	5,078	1,524	20,48
Cost of colorectal cancer			
Localized cancer			
Year 1	5,199	1,560	20
Year 2–5 (annual)	182	55	20
Regional cancer			
Year 1	19,115	5,734	20
Year 2–5 (annual)	360	108	20
Distant cancer			
Year 1	20,904	6,271	20
Year 2–5 (annual)	360	108	20
Utilities			
No colorectal cancer	1		Assumption
Stage I colorectal cancer	0.74	0.15	22
Stage II colorectal cancer	0.69	0.15	22
Stage III colorectal cancer	0.64	0.15	22
Stage IV colorectal cancer	0.25	0.055	22
Death	0	0	Assumption

reflect a cohort of persons with a family history of CRC in Iran, the average-risk population transition probabilities from normal to low-risk polyp, as well as the age-specific prevalence of adenoma and CRC at age 40 years, the age of entry into the simulation, were multiplied by a conversion factor, like previous studies.[7,17] A conversion factor of four was used in the base case model and 2 and 6 in sensitivity analysis. Colonoscopy performance characteristics including sensitivity, specificity and serious complication as well as health-related quality of life in individuals with CRC were extracted from previous data on economic evaluation.[7,15,17,22] The utility of individuals without CRC was assumed equal to 1.

Costs

In this study, in order to calculate costs, a health-care system perspective was employed and only direct costs were included. CRC diagnosis and treatment cost were extracted by stage and time

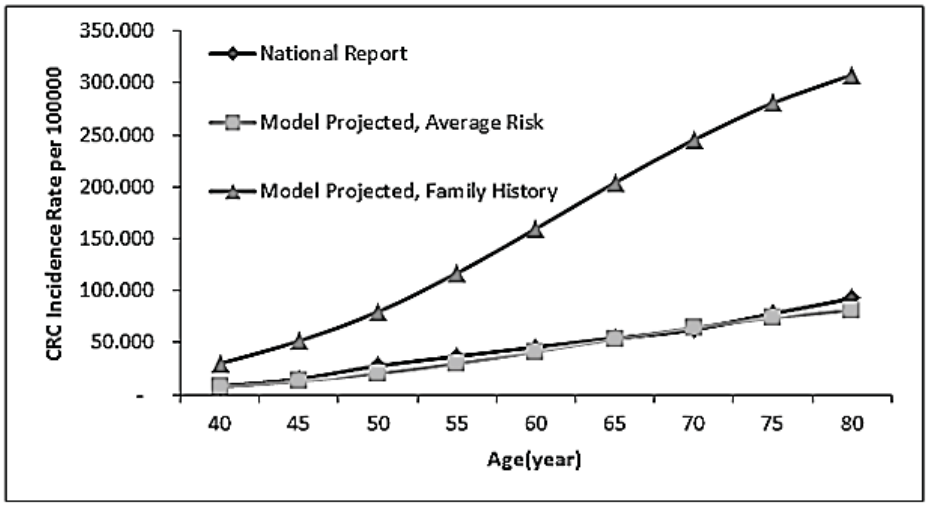

Figure 2. Model calibration for colorectal cancer incidence in I. R. of Iran

period (initial and continuing period) from a study that calculated the economic burden of CRC in Iran in 2012.[20] Using the Iranian medical tariff system, the costs of colonoscopy screening test, polypectomy, and treatment of colonoscopy complications (i.e. bleeding and perforation) were calculated.[2] In Iran, the exchange rate is not fixed; thus, all costs were converted to US dollars using average annual exchange rate, which was 1 US$ = 12,260 rials in 2012.[35]

Screening strategies

The following six alternative CRC screening strategies were compared:

1) Colonoscopy screening every five years starting at age 40 years (COLO40_5).

2) Colonoscopy screening every ten years starting at age 40 years (COLO40_10).

3) Colonoscopy screening every five years starting at age 50 years (COLO50_5).

4) Colonoscopy screening every ten years starting at age 50 years (COLO50_10).

5) Colonoscopy screening once per lifetime at 50 years (COLO50).

6) Colonoscopy screening once per lifetime at 55 years (COLO55).

All individuals at 40 years of age were entered into the simulated cohort model. Screening was performed from age 40 through age 75 years. The participants' initial state was distributed as normal, low-risk polyp, advanced adenomas or CRC according to their respective prevalence rates at 40 years of age. Adenomas detected by colonoscopy will be removed by polypectomy and patients with low-risk polyps and advanced adenomas, respectively, will receive a surveillance colonoscopy after five years and three years. Patients with normal results at their surveillance colonoscopy will return to the normal state in the natural history and will be screened according to the standard screening strategies.[36] In case screened individuals are diagnosed with CRC, they enter a treatment state according to their CRC stage, and will be followed for 5 years. During the 5 years of follow-up, there is a yearly probability of dying of other causes, dying of CRC, or sustaining a relapse. Patients surviving CRC treatment after 5 years enter surveillance.

The model assumed that all CRCs developed from advanced adenomas, which developed from low-risk polyp, which arose from normal bowel.

Analysis

To assess the comparative performance of various screening strategies, Incremental Cost-Effectiveness Ratios (ICERs) were calculated, in which the additional cost of each strategy divided by the additional savings in life expectancy or QALY were compared with no screening strategy. However, according to the opportunity cost principle, in economic evaluation studies in order to choose the most cost effective strategy, each strategy must be compared with the next best strategy.[37] Therefore, to calculate the ICER of each screening strategy compared with the next best strategy, absolutely dominant and extended dominant strategies were removed, and then the ICER of remaining strategies were calculated. A strategy was considered as absolutely dominated if it was more expensive but less effective than one of the competing strategies. Also, a strategy was considered as extended dominated if it was less effective and had a higher ICER.[38] In the next step, the ICERs of dominant strategies were compared with a cost-effectiveness threshold. Since there is no official cost-effectiveness threshold in Iran, based on the World Health Organization (WHO) recommendations, the national annual Gross Domestic Product (GDP) per capita was used as a cost-effectiveness threshold in Iran.

Using a hypothetical cohort of 10000 individual aged 40 to 90 years, the incidence and mortality of CRC for different screening strategy as well as no screening strategy were determined. To assess the impact of changes in parameters over plausible ranges, deterministic sensitivity analysis was conducted (Table 1).

Results

Model validation

We compared the incidence of CRC in the natural history model with the CRC incidence in the national cancer registry report. Figure 2 demonstrates that the results from our natural history model were similar to the national cancer registry report.

Table 2. Number of expected clinical events for each screening strategy in the 50-year follow up model

Variable	No Screening	COLO 40_5	COLO 40_10	COLO 50_5	COLO 50_10	COLO 50	COLO 55
CRC cases occurring per 10,000 persons from age 40 to 90 years, n	707	20	60	100	133	304	318
Reduction in CRC incidence compared with No Screening, %	- - -	97	91	86	81	57	55
Deaths attributable to CRC, n	399	29	50	82	99	179	184
Reduction in CRC mortality compared with No Screening, %	- - -	93	87	79	75	55	54

Table 3. Incremental cost-effectiveness ratios for alternative CRC screening strategies

Strategy	Mean cost, US $	Mean QALY	Life expectancy (years)	ICER (US $/QALY)		ICER (US $/LYG)	
				compared with no screening	compared with the next best strategy ‡	compared with no screening	compared with the next best strategy ‡
No Screening	382	16.263	16.316	- - -	- - -	- - -	- - -
COLO50	421	16.343	16.370	489	489	725	725
COLO55	426	16.325	16.355	709	Dominated*	1,115	Dominated*
COLO50-10	479	16.360	16.379	1,010	Dominated†	1,540	Dominated†
COLO40-10	583	16.408	16.416	1,386	2,505	1,995	3,482
COLO50-5	619	16.366	16.383	2,310	Dominated*	3,508	Dominated*
COLO40-5	871	16.419	16.425	3,135	26,080	4,489	35,014

*Absolutely Dominated: A strategy that is more expensive but less effective; †Extended Dominated: A strategy is considered to be extended dominated if another strategy is more effective and has a lower ICER; ‡Dominated strategies are removed from the analysis and the ICER of remaining strategies calculated.

Base-case scenario

Table 2 shows CRC incidence and mortality in hypothetical cohorts of 10,000 high-risk individuals entering each strategy at 40 years of age. In the cohort, when not undergoing screening, the number of CRC incidence and mortality were 707 and 399, respectively. Compared to no screening, the CRC incidence and mortality declined in all screening strategies. The model predicted a reduction in CRC incidence ranging from 97% for COLO40_5 strategy to 55% for COLO55 strategy, respectively. Furthermore, the decline in CRC mortality ranged from 93% to 54%, applying COLO40_5 and COLO55 strategies, respectively (Table 2).

As shown in Table 3, all six screening strategies resulted in greater QALY and LYG and were costlier than no screening. The mean number of discounted QALY ranged from 16.29 for no screening to 16.42 for COLO40-5 strategy. Also, the mean discounted cost ranged from $382 for no screening to $871 for colonoscopy every 5 years starting at the age of 40. The mean number of discounted LYG ranged from 16.32 for no screening to 16.43 for COLO40-5 strategy.

Strategies of COLO55 and COLO50-5 were absolutely dominated with lower effectiveness and higher costs. Furthermore, strategy of COLO50-10 was extended dominated by COLO40-10 strategy, because it was less effective than COLO40-10, and had higher ICER. However, COLO40-5 strategy was both the most effective and the costliest strategy (Figure 3).

The ICER per QALY gained for CRC screening varied from $489 for COLO50 strategy to $3,135 for COLO40-5 strategy, compared with no screening. Also, the variation of ICER per LYG for the two above strategies was from $725 to $4,489, respectively, compared with no screening. When each strategy was compared with the next best strategy and dominated strategies were removed from the analysis, the COLO50, COLO40-10, and COLO40-5 strategies remained with ICERs of $489, $2,505, and $26,080 per QALY gained, respectively (Table 3).

Sensitivity analysis

Based on one-way sensitivity analysis, variables that can significantly influence the model's results included transition from low-risk polyps to advanced adenomas and from advanced adenomas to CRC, sensitivity of colonoscopy to detect low-risk polyps and advanced adenomas, cost of colonoscopy, and cost of CRC care. The cost of screening colonoscopy had the greatest impact on the results; a 30% decline in colonoscopy costs compared to the base case, the no screening strategy would be absolutely dominated by COLO50 strategy. Under this scenario, colonoscopy screening once at the age of 50 was found to be much more cost-effective compared with no screening and the ICER of COLO40_5 compared to COLO50 was $3,516 per QALY. In contrast, an increase of 30% in colonoscopy cost compared to base case, respectively, would lead to 39%, 66%, and 46% increases in the ICER of COLO50, COLO40_10, and COLO40_5 strategies vs. no screening. However, variation on other aforementioned variables did not change the dominant strategies and their order compared to base case, but their ICER value changed. Clinical and cost-effectiveness results for the model with individuals at two and six times higher risk of CRC compared to average-risk population, are presented in Appendix Tables: 1 to 4.

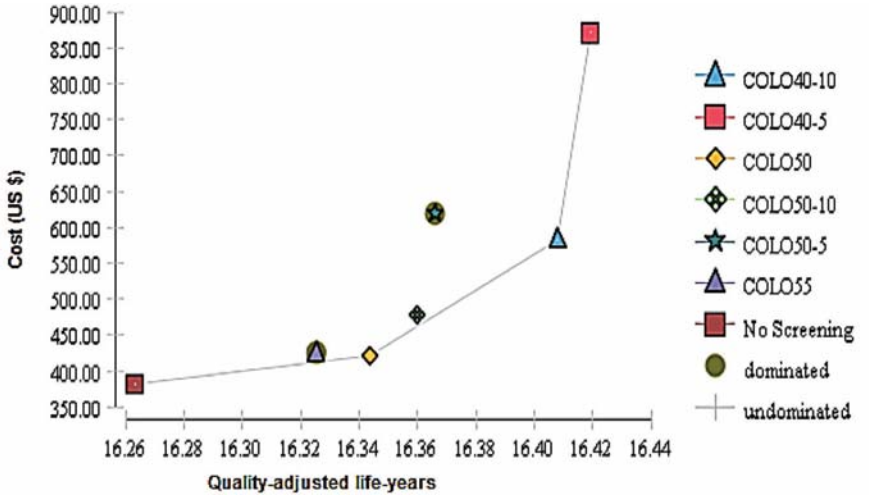

Figure 3. Cost-effectiveness of the screening strategies included in the model.

Discussion

We compared six colonoscopy screening strategies for CRC at high-risk people in Iran. Our results show that compared to no screening, the CRC incidence and mortality declined in all screening strategies. The incremental cost per QALY and LYG for CRC screening varied from $489 and $725 for COLO50 strategy to $3,135 and $4,489 for COLO40-5 strategy respectively, compared with no screening. When strategies were compared with each other and dominated strategies were removed from the analysis, the COLO50, COLO40-10, and COLO40-5 strategies remained with ICERs of $489, $2,505, and $26,080 per QALY gained, respectively.

According to the World Health Organization (WHO) recommendations, an intervention is considered cost-effective if its ICER is less than three times of national annual Gross Domestic Product (GDP) per capita and highly cost–effective if its ICER is less than once the national annual GDP per capita.[39] In 2014, the GDP per capita of Iran was 5442$.[40] Moreover, our study results show that when screening strategies were compared with no screening strategy, for all strategies, the ICER was less than GDP per capita of Iran. However, when each strategy was compared with the next best strategy and dominated strategies were removed, only the ICER of COLO50 and COLO40-10 strategies were below the threshold of cost-effectiveness in Iran. Although the COLO50 strategy had the least ICER, the ICER of COLO40-10 strategy was below the cost-effective threshold in Iran too. Implementation of this strategy would result in more reduction in CRC incidence and mortality than the COLO50 strategy. Compared to no screening strategy, implementation of the COLO40-10 strategy would reduce the incidence and death rates of CRC in high risk individuals by 87% and 91%, respectively, while with the COLO50 strategy, these rates would be reduced by 57% and 55%, respectively. Therefore, colonoscopy screening every ten years from the age of 40 years appears to be the most cost-effective strategy.

The results of previous studies conducted in high income countries show that colonoscopy screening of CRC in high risk individuals is cost-effective. In most of these studies, CRC colonoscopy screening every five years starting at the age of 40 years was the most cost-effective strategy.[7,17,41,42] Although in our study the COLO40-5 strategy had the highest benefit, compared with the COLO40-10 strategy, the ICER of this strategy was $26,080 which is above the cost-effectiveness threshold of Iran. Since the CRC incidence rate in high income countries is higher than Iran, CRC screening in these countries would yield greater benefit than Iran. On the other hand, the cost-effectiveness threshold in Iran is lower than high income countries.

Due to population aging and changing lifestyles, the CRC incidence is increasing in Iran where, according to the Globocan 2012 prediction, the CRC incidence will almost double by 2030.[2] Therefore, the CRC colonoscopy screening with five-year interval may be cost-effective in the high risk group in future years in Iran.

To the best of our knowledge, this study is the first study that investigated the cost-effectiveness of CRC screening in high-risk individuals in Iran as a low and middle-income country. Our study has some limitations. First, we assumed that all cancers arose from polyps, given that the natural history of CRC is based on assumptions regarding the progression from normal to low-risk polyps. Nevertheless, some studies have suggested that a small percentage of cancers arise from lesions other than polyps.[22] Second, we assumed that 100% of the target populations would participate in the CRC screening, which may not be true due to some barriers including: lack of access to healthcare facilities, limited knowledge or awareness, low perceived risk of CRC and fear of colonoscopy.[43] Providing detailed information about the benefit of colonoscopy to patient and performing colonoscopy by experienced physicians would increase colonoscopy screening compliance rate.[44] Third, the model was developed from the perspective of health system and was limited to direct costs only. Fourth, we did not address the controversial aspects of screening colonoscopy whether it should only be used to the right side of colon, or for left segments of colon.[45]

In conclusion, our study showed that CRC colonoscopy screening in high-risk individuals would decrease the incidence and mortality rates of this disease and is cost-effective in Iran. Colonoscopy screening every ten years starting at the age of 40 years was the most cost-effective strategy. The results of this study could help the policy makers in Iran and other LMICs to introduce a targeted screening test for high-risk individuals.

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Appendix Table 1. Clinical results for model with individuals at two times higher risk of CRC

Variable	No Screening	COLO 40_5	COLO 40_10	COLO 50_5	COLO 50_10	COLO 50	COLO 55
CRC cases occurring per 10,000 persons from age 40 to 90 years, n	367	10	31	51	68	157	166
Reduction in CRC incidence compared with No Screening, %	- - -	97	92	86	81	57	55
Deaths attributable to CRC, n	206	15	26	41	50	93	94
Reduction in CRC mortality compared with No Screening, %	- - -	93	88	80	76	55	54

Appendix Table 2. Incremental cost-effectiveness ratios for alternative CRC screening strategies for individuals at two times higher risk of CRC

Strategy	Mean cost, US $	Mean QALY	Life expectancy (years)	ICER (US $/QALY)		ICER (US $/LYG)	
				compared with no screening	compared with the next best strategy ‡	compared with no screening	compared with the next best strategy ‡
No Screening	195	16.359	16.386	- - -	- - -	- - -	- - -
COLO50	275	16.401	16.414	1,949	1,949	2,890	2,890
COLO55	263	16.391	16.407	2,112	Dominate†	3,325	Dominated†
COLO50-10	358	16.409	16.419	3,268	Dominate†	4,989	Dominated†
COLO40-10	508	16.433	16.438	4,226	7,088	6,094	9,881
COLO50-5	513	16.412	16.421	5,995	Dominated*	9,116	Dominated*
COLO40-5	818	16.439	16.442	7,811	54,376	11,206	73,024

*Absolutely Dominated: A strategy that is more expensive but less effective; †Extended Dominated: A strategy is considered to be extended dominated if another strategy is more effective and has a lower ICER; ‡Dominated strategies are removed from the analysis and the ICER of remaining strategies calculated.

Appendix Table 3. Clinical results for model with individuals at six times higher risk of CRC

	No Screening	COLO 40_5	COLO 40_10	COLO 50_5	COLO 50_10	COLO 50	COLO 55
CRC cases occurring per 10,000 persons from age 40 to 90 years, n	854	25	67	140	176	372	366
Reduction in CRC incidence compared with No Screening, %	- - -	97	92	84	79	56	57
Deaths attributable to CRC, n	581	44	74	122	147	261	269
Reduction in CRC mortality compared with No Screening, %	- - -	92	87	79	75	55	54

Appendix Table 4. Incremental cost-effectiveness ratios for alternative CRC screening strategies for individuals at six times higher risk of CRC

Strategy	Mean cost, US $	Mean QALY	Life expectancy (years)	ICER (US $/QALY)		ICER (US $/LYG)	
				compared with no screening	compared with the next best strategy ‡	compared with no screening	compared with the next best strategy ‡
No Screening	561	16.170	16.247	---	---	---	---
COLO50	562	16.288	16.327	9	9	14	14
COLO55	584	16.260	16.305	258	Dominate*	405	Dominated*
COLO50-10	599	16.311	16.340	269	Dominated†	410	Dominated†
COLO40-10	656	16.383	16.395	446	986	640	1,367
COLO50-5	724	16.320	16.346	1,094	Dominate*	1,659	Dominated*
COLO40-5	923	16.399	16.407	1,582	16,648	2,262	22,345

*Absolutely Dominated: A strategy that is more expensive but less effective; †Extended Dominated: A strategy is considered to be extended dominated if another strategy is more effective and has a lower ICER; ‡Dominated strategies are removed from the analysis and the ICER of remaining strategies calculated.