

Cost-effectiveness of Colorectal Cancer Screening and Treatment Methods: Mapping of Systematic Reviews

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ABSTRACT

Objective: Due to extensive literature on colorectal cancer and their heterogeneous results, this study aimed to summarize the systematic reviews which review the cost-effectiveness studies on different aspects of colorectal cancer.

Methods: The required data were collected by searching the following key words according to MeSH: “colorectal cancer,” “colorectal oncology,” “colorectal carcinoma,” “colorectal neoplasm,” “colorectal tumors,” “cost-effectiveness,” “systematic review,” and “meta-analysis.” The following databases were searched: PubMed, Cochrane, Google Scholar, and Scopus. Two reviewers evaluated the articles according to the checklist of “assessment of multiple systematic reviews” (AMSTAR) tool. **Results:** Finally, eight systematic reviews were included in the study. The Drummond checklist was mostly used for assessing the quality of the articles. The main perspective was related to the payer and the least

was relevant to the social. The majority of the cases referred to sensitivity analysis (in 76% of the cases) and the lowest point also was allocated to discounting (in 37% of cases). The Markov model was used most widely in the studies. Treatment methods examined in the studies were not cost-effective in comparison with the studied units. Among the screening methods, computerized tomographic colonography and fecal DNA were cost-effective. The average score of the articles’ qualities was high (9.8 out of 11). **Conclusions:** The community perspective should be taken into consideration at large in the studies. It is necessary to pay more attention to discounting subject in studies. More frequent application of the Markov model is recommended.

Key words: Colorectal cancer, cost-effectiveness, screening, treatment, systematic review of systematic reviews

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Introduction

Colorectal cancer is a common, fatal, and yet preventable disease which has attracted health centers' attention across the world. It is accounted for the second leading cause of deaths resulted by cancers.^[1,2] Worldwide, colorectal cancer is the third most common type of cancers and accounts for 10% of all cancer cases. In 2012, the disease incidence was 1.4 million cases and it caused 694,000 deaths.^[3] The disease is more common in developed countries and 65% of cases are found in such countries. The prevalence of the disease in females is less than that of males.^[4-8]

Many colorectal cancers are caused by the factors related to lifestyle and aging, and few cases occur due to inherited genetic disorders. Risk factors include diet, obesity, smoking, and lack of enough physical activity.^[9-13] Colorectal cancer can be diagnosed by taking a sample of the colon through sigmoidoscopy or colonoscopy (COL).^[14,15] Screening is effective to reduce the chance of dying from colorectal cancer, and is recommended to start at the age of 50 and then on an ongoing basis until the age of 75.^[16-18] Polyps are removed during COL.^[19,20] Aspirin and other anti-inflammatory nonsteroidal drugs may reduce the disease risk. Of course, their general use is not recommended because of their side effects.^[21,22]

Therapies used for colorectal cancer may include a combination of surgery, radiation, chemotherapy, and targeted therapies. The cancers which are confined to the inside wall of the colon may be treated by surgery, but the spreading cancer throughout the body (metastasis) is not usually curable, and the process of controlling the disease usually focuses on improving the quality of life and disease symptoms.^[23-27]

Nowadays, regarding the high costs of screening, treatment, and care of cancer patients, health-care systems in the world are looking for the most cost-effective care and therapies. Thus, in many countries, including Britain, Australia, Canada, Sweden, and other countries, decisions in this area are made based on econometric studies. The cost-effectiveness study is an example of this type of studies that is greatly applied in planning and policymaking for service deliveries in health-care system of countries.^[28,29]

Fortunately, given the sensitivity and importance of colorectal cancer, a lot of cost-effectiveness studies have been conducted by different researchers, and good evidence has been produced in this area. Even in the recent years, due to the development of these studies in each of the expertise areas of cancer, systematic review studies have also been designed and carried out.^[30-34]

Although systematic review studies make the integrated and reliable information available to the users,^[35] conducting different systematic reviews in various areas with different

conclusions can confuse the users. Therefore, according to the expansion of these studies and the dispersed results, it is required to gather and report the results of this type of studies cohesively and collectively. Hence, the purpose of this study is to study the systematic review of systematic reviews that reviewed the cost-effectiveness studies on different areas related to colorectal cancer.

Methods

This review study was conducted in 2016, using the approach of systematic review which was adopted from the book entitled, "A Systematic Review to Support Evidence-Based Medicine,"^[36] and also it was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist.^[37-39]

Eligibility criteria

The following can be mentioned as the inclusion criteria for the study: systematic review and meta-analysis studies on the colorectal cancer patients, studies conducted on cost-effectiveness, articles published in English language, and articles published from January 2000 to March 1, 2016. Exclusion criteria of the study included the following: articles that reported other types of economic studies, articles conducted only in one country, conference presentations, case reports, and narrative reviews, as well as articles that had low scores based on the Assessment of Multiple Systematic Reviews (AMSTAR) checklist.

Information sources and search strategy

Required data were collected by searching the following key words selected from MeSH: "colorectal cancer," "colorectal oncology," "colorectal carcinoma," "colorectal neoplasm," "colorectal tumors," "cost-effectiveness," "systematic review," and "meta-analysis." The following databases were searched: PubMed, Cochrane Library electronic databases, Google Scholar, and Scopus. The complete search strategy is summarized in Table 1. The search strategy was adapted for each database as necessary. Some of the relevant journals and websites were searched manually. References lists of the selected articles also were checked. In the final stage of the literature review, we also searched the gray literature (European Association for Grey Literature Exploitation, Health Care Management Information Consortium) and made contact with the experts.

Review process

In the first phase of the review process, an extraction table was designed in which the following items were included: first author's name, publication year of the study, aim of the study, number of all publications included, meta-analysis,

Table 1: Completed search strategy for PubMed

Database	Concept	Search strategy
PubMed	Colorectal cancer	"Colorectal cancer" OR "colorectal oncology" OR "colorectal carcinoma" OR "colorectal neoplasm" OR "colorectal tumors"
	AND	
	Cost-effectiveness	"Cost-effectiveness"
	AND	
	Systematic review	"Systematic review," "meta-analysis"
	Completed search strategy: ("colorectal cancer"[Title/Abstract]) OR "colorectal oncology"[Title/Abstract] OR "colorectal carcinoma"[Title/Abstract] OR "colorectal neoplasm"[Title/Abstract] OR "colorectal tumors"[Title/Abstract] AND "cost-effectiveness"[Title/Abstract] AND "systematic review"[Title/Abstract] OR "meta-analysis"[Title/Abstract]	
Google Scholar	Colorectal cancer	"Colorectal cancer" OR "colorectal oncology" OR "colorectal carcinoma" OR "colorectal neoplasm" OR "colorectal tumors"
	AND	
	Cost-effectiveness	"Cost-effectiveness"
	AND	
	Systematic review	"Systematic review," "meta-analysis"
	All in title: "colorectal cancer" OR "colorectal oncology" OR "colorectal carcinoma" OR "colorectal neoplasm" OR "colorectal tumors" AND "cost-effectiveness" AND "Systematic review" OR "meta-analysis"	
Cochrane	Colorectal cancer	"Colorectal cancer" OR "colorectal oncology" OR "colorectal carcinoma" OR "colorectal neoplasm" OR "colorectal tumors"
	AND	
	Cost-effectiveness	"Cost-effectiveness"
	AND	
	Systematic review	"Systematic review," "meta-analysis"
	"Colorectal cancer:"ti, ab, kw or "colorectal oncology:"ti, ab, kw or "colorectal carcinoma:"ti, ab, kw or "colorectal neoplasm:"ti, ab, kw or "colorectal tumors:"ti, ab, kw (word variations have been searched) AND "cost-effectiveness:"ti, ab, kw (word variations have been searched) AND "Systematic review:"ti, ab, kw or "meta-analysis:"ti, ab, kw (word variations have been searched)	
Scopus	Colorectal cancer	"Colorectal cancer" OR "colorectal oncology" OR "colorectal carcinoma" OR "colorectal neoplasm" OR "colorectal tumors"
	AND	
	Cost-effectiveness	"Cost-effectiveness"
	AND	
	Systematic review	"Systematic review," "meta-analysis"
	"Colorectal cancer"(abs) OR "colorectal oncology"(abs) OR "colorectal carcinoma"(abs) OR "colorectal neoplasm"(abs) OR "colorectal tumors"(abs) AND "cost-effectiveness" (abs) AND "Systematic review"(abs) AND "meta-analysis"(abs)	

time horizon covered, quality assessment tool, screening or treatment, perspective, model type, discounting, sensitivity analysis, incremental analysis, and overall result. Validity of the data extraction table was confirmed by experts, and a pilot study was conducted for its further improvement. Two authors who had enough experience and knowledge were responsible for independent extraction of the data.

In the first phase of articles' selection, articles with nonrelevant titles were excluded. In the second phase, the abstract and the full text of articles were reviewed to include those articles matching the inclusion criteria. A reference management software (Endnote X5, Thomson Reuters, Philadelphia, PA 19130, USA) was used for organizing and assessing the titles and abstracts, as well as for identifying the duplicate entries.

Quality assessment

Two reviewers evaluated the articles according to the checklist of AMSTAR tool.^[40] This checklist has 11 items as follows: *a priori* design, duplicate study selection and

data extraction, a comprehensive literature search, the use of status of publication as an inclusion criterion, a list of included/excluded studies, characteristics of included studies, documented assessment of the scientific quality of included studies, appropriate use of the scientific quality in forming conclusions, the appropriate use of methods to combine findings of studies, assessment of the likelihood of publication bias, and documentation of conflict of interest. Responses of the AMSTAR tool are "Yes," "No," "Can't Answer," or "Not Applicable," by presuming "yes" as "1," and rating "no," "can't answer," or "not applicable" as "0." Based on this tool, the quality of reviews was rated as "low" from 1 to 4, "moderate" from 5 to 7 or "high" from 8 to 11. Articles with "low" quality were excluded. Controversy cases between reviewers were referred to a third author.

Data analysis

The retrieved data were briefed in the extraction table and finally, a manual content analysis was used for mapping and categorizing the result. This is a method for detecting

information from articles, reaching the conclusion and implementing a detailed study of information, creating preliminary themes/categories, inserting information in categories, obtaining assurance and consensus on the accuracy of the categories, reporting themes from the text, and also it is very useful in analyzing qualitative data.^[41-44]

Results

In this study, finally, 8 out of 336 articles were included in the analyses which were completely related to the study objective [Figure 1]. As shown in Figure 1, a total of 149 articles were excluded because of replication among databases, and 171 articles in the phase of reviewing the titles and abstracts, as well as 10 articles in the full-text reviews were excluded. Also, in the stage of quality assessment, five articles were excluded.

The results of extracted data from the entered articles are summarized in Table 2.

In eight systematic reviews investigated, the total information of 86 articles was studied. Meta-analysis method was used in none of the studies. Only in one study, the number of participants was calculable. Search time frame in the reviewed articles varied from the years 1999 to 2013. In the eight articles studied, six different tools were used to assess the quality of the articles and the Drummond checklist was mostly used for quality assessment of the articles (Drummond’s checklist that contains ten items is a tool for assessing the quality of economic evaluation studies [Appendix 1]). In four out of the eight articles, the authors focused on the cost-effectiveness of colorectal cancer treatments, as well as four articles targeted on cost-effectiveness of screening methods of colorectal cancer.

Specific information related to the cost-effectiveness (perspective, discounting, sensitivity analysis, incremental analysis, overall result, and model type) is summarized in Table 3.

In this study, the perspectives mentioned in the studies were categorized into four groups as follows: social, health, payer, and not report. The results of each of the four groups’ replication are depicted in Figure 2.

As shown in Figure 2, the most perspective was related to the payer (40 times) and the least belonged to social (15 cases), and in four studies, the perspective was not mentioned.

Among the eight investigated studies, in two studies, discounting and model type were not mentioned, and also in one study, sensitivity analysis and incremental analysis were not referred. The Markov model was used in five systematic reviews (including 35 studies). The frequency of mentioning to discounting, sensitivity analysis, and incremental analysis in 86 investigated studies in eight systematic reviews entered in the current study is depicted in Figure 3.

As shown in Figure 3, the highest cases refer to sensitivity analysis (in 76 cases from 86) and the least refers to discounting (in 37 cases from 86).

The most important cases which studied on the cost-effectiveness of treatment methods of colorectal cancer included monoclonal antibodies (MoAbs): monoclonal, pharmaceutical therapies, laparoscopic laparoscopically assisted (hereafter together described as laparoscopic surgery), hand-assisted laparoscopic surgery, bevacizumab, cetuximab, and panitumumab.

The results of the study by Lange *et al.* on cost-effectiveness of MoAbs showed that patients’ treatment with bevacizumab, cetuximab, and panitumumab was not cost-effective. However, patients’ treatment with the mutation Kirsten ras

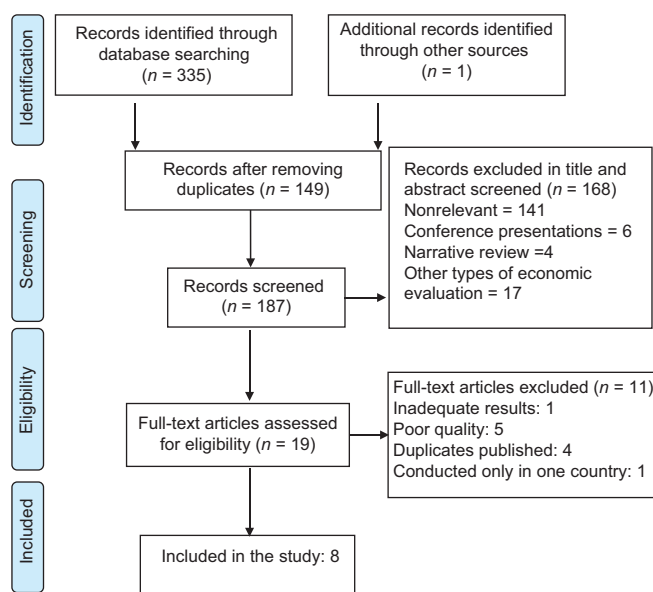


Figure 1: Searches and inclusion process

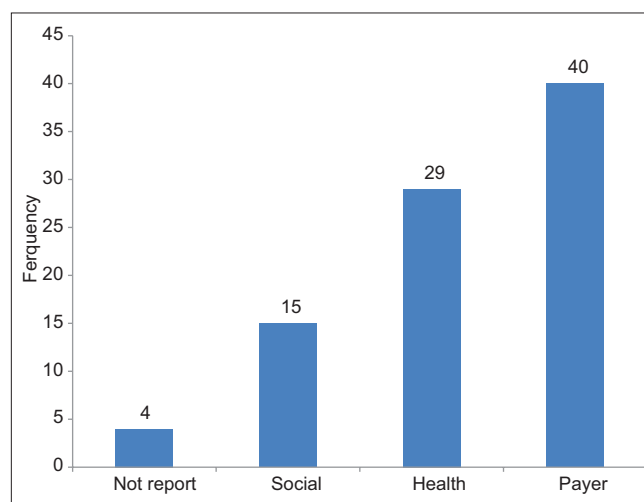


Figure 2: Frequency of perspectives mentioned in the studies (total number = 86)

Table 2: Characteristics of the studies included

Reference	Aim of study	Number of all publications included	Meta-analysis	Time horizon covered	Quality assessment tool	Screening or treatment	Number of participants
Lange <i>et al.</i> , 2014 ^[45]	To review and assess the economic evidence of MoAbs treatment in mCRC	15	NO	2000-2013	QHES	Treatment	NA
Kriza <i>et al.</i> , 2014 ^[46]	To examine cost-effectiveness of CTC versus optical COL for colorectal cancer screening	9	NO	2006-2012	CHEC-list, and the CRD's guidance for undertaking systematic reviews in health care	Screening	NA
Skally <i>et al.</i> , 2013 ^[47]	Cost-effectiveness of fDNA as a colorectal cancer screening tool (compared with no screening and other screening modalities)	7	NO	2000-2011	Amended checklist for economic evaluations	Screening	NA
Hanly <i>et al.</i> , 2012 ^[48]	Key factors influencing, cost-effectiveness of CTC screening	16	NO	1999-2010	Drummond 35-point checklist	Screening	NA
Leung <i>et al.</i> , 2013 ^[49]	CEAs of pharmaceutical therapies for mCRC	24	NO	1999-2009	Quality checklist created by the panel on cost-effectiveness in health and medicine	Treatment	23,427
Murray <i>et al.</i> , 2006 ^[50]	Cost-effectiveness of laparoscopic laparoscopically assisted (hereafter together described as laparoscopic surgery) and HALS in comparison with open surgery for the treatment of colorectal cancer	5	NO	2000-2005	NHS economic evaluation database guidelines for reviewers	Treatment	NA
Westwood <i>et al.</i> , 2014 ^[51]	Cost-effectiveness of the use of different KRAS mutation tests to decide between standard chemotherapy and cetuximab in combination with standard chemotherapy in adults with mCRC in whom metastases are confined to the liver and are unresectable	5	NO	2000-2013	Drummond checklist	Screening	NA
Hoyle <i>et al.</i> , 2013 ^[52]	The cost-effectiveness of bevacizumab, cetuximab, and panitumumab compared with relevant comparators within their licensed indications for the treatment of mCRC after first-line chemotherapy	5	NO	2005-2010	Drummond checklist	Treatment	NA

MoAbs: Monoclonal antibodies, mCRC: Metastatic colorectal cancer, CTC: Computerized tomographic colonography, COL: Colonoscopy, CEAs: Cost-effectiveness analyses, HALS: Hand-assisted laparoscopic surgery, QHES: Quality of Health Economic Studies, CHEC: Consensus on health economic criteria, CRD: Centre for Reviews and Dissemination, NHS: National Health Service, NA: Not applicable, KRAS: Kirsten ras oncogene, fDNA: Fecal DNA

Table 3: Characteristics of the studies included

Reference	Perspective	Model type (n)	Discounting	Sensitivity analysis	Incremental analysis	Overall result
Lange <i>et al.</i> , 2014 ^[45]	Social: 0 Health: 8 Payer: 7 Not report: 0	NS	11	12	15	The treatment with bevacizumab, cetuximab, and panitumumab is mainly considered not to be cost-effective in patients with mCRC. However, testing for KRAS oncogene mutation prior to the treatment with cetuximab or panitumumab is found to be clearly cost-effective compared to no testing
Kriza <i>et al.</i> , 2014 ^[46]	Social: 3 Health: 2 Payer: 4 Not report: 0	Markov: 7 Micro simulation: 2/9	9	9	9	CTC has the potential to be a cost-effective CRC screening strategy when compared to COL. The most important assumptions that influenced the cost-effectiveness of CTC and COL were related to CTC threshold-based reporting of polyps, CTC cost, CTC sensitivity for large polyps, natural history of adenoma transition to cancer, AAA parameters, and importantly adherence

Contd...

Table 3: Contd...

Reference	Perspective	Model type (n)	Discounting	Sensitivity analysis	Incremental analysis	Overall result
Skally <i>et al.</i> , 2013 ^[47]	Social: 1 Health: 0 Payer: 6 Not report: 0	Markov: 6 Micro simulation: 1/7	7	7	6	fDNA was cost-effective when compared with no screening in six studies. Compared with other screening modalities, fDNA was not considered cost-effective in any of the base-case analyses: in five studies, it was dominated by all alternatives considered. Sensitivity analyses identified cost, compliance, and test parameters as key influential parameters
Hanly <i>et al.</i> , 2012 ^[48]	Social: 5 Health: 0 Payer: 10 Not report: 1	Markov: 14 Micro simulation: 2/16	NS	16	16	Evidence on the cost-effectiveness of CTC screening is heterogeneous. CTC appears cost-effective compared with no screening and is cost-effective compared with fecal tests and FS in some studies. Cost-effectiveness compared with COL is uncertain. The heterogeneity is due largely to between-study differences in comparators and parameter values
Leung <i>et al.</i> , 2013 ^[49]	Social: 3* Health: 12 Payer: 8 Not report: 3	Retrospective population data from clinical trials: 7 0 decision-tree: 2 Markov: 3 Others: 12/24	5	22	17	This study has shown a wide variation in the methodology and quality of cost-effectiveness analysis for mCRC. Improving quality and harmonization of CEA for cancer treatment is needed
Murray <i>et al.</i> , 2006 ^[50]	Social: 3 Health: 2 Payer: 0 Not report: 0	Clinical trials: 5	1	5	5	Laparoscopic surgery was generally more costly than open surgery as the former seems to involve longer operation times and higher equipment costs, although the evidence is mixed
Westwood <i>et al.</i> , 2014 ^[51]	Social: 0 Health: 3 Payer: 2 Not report: 0	Markov: 5/5	4	5	5	In general, although KRAS testing is obviously more cost-effective option than administering cetuximab to all patients, there was no strong evidence that any one KRAS mutation test was more effective or cost-effective than any other tests
Hoyle <i>et al.</i> , 2013 ^[52]	Social: 0 Health: 2 Payer: 3 Not report: 0	NS	NS	NS	NS	The base-case ICER for KRAS wild-type patients for cetuximab compared with best supportive care is $\leq 98,000$ per QALY, for panitumumab compared with best supportive care is $\leq 150,000$ per QALY and for cetuximab plus irinotecan compared with best supportive care is $\leq 88,000$ per QALY

*In one study used from different perspectives.

Perspective: In any economic evaluation, it is important to specify the study perspective which essentially defines the basis of analysis and determines the relevant costs that need to be accounted for. An item may be a cost from one perspective but not another. For example, patient's travel costs are a cost from a patient's or society's perspective but not a cost from a health-care provider's perspective.

Social perspective: The perspective of society accounts for all costs incurred by the society in delivering health service and they include loss of productivity due to employees being away due to medical leaves.

Health perspective: From the perspective of health-care provider, costs of health service delivery including salaries of doctors, costs of medications and equipment involved must be accounted for in the evaluation study. This is different from the perspective of the patient which only accounts for costs incurred by the patient for receiving the health service.

Payer perspective: From payer's perspective, those costs related to health care should be considered in economic evaluations which are paid directly by the patients through out of pocket at the time of service delivery or those which have been undertaken by insurance companies based on their contract with health-care providers.

Sensitivity analysis: Sensitivity analysis is used to illustrate and assess the level of confidence that may be associated with the conclusion of an economic evaluation. It is performed by varying key assumptions made in the evaluation (individually or severally) and recording the impact on the result (output) of the evaluation. Sensitivity analysis may take a number of forms: "one-way" where input parameters are varied one by one, "multi-way" where more than one parameter is varied at the same time, "threshold" analysis where the model is used to assess the tipping point for an input parameter (at what value of this parameter would the decision based on the output of the evaluation be altered?) and probabilistic (a stochastic approach is taken to produce a distribution of outputs based on the distributions of input parameters).

Incremental analysis: An incremental analysis is a decision-making technique used in economic evaluation to determine the true cost and health outcome differences between alternatives. The ICER is a statistic used in cost-effectiveness analysis to summarize the cost-effectiveness of a health-care intervention. It is defined by the difference in cost between two possible interventions, divided by the difference in their effect. It represents the average incremental cost associated with 1 additional unit of the measure of effect.

Discounting: Discounting seeks to take into account the impact of time on how those costs and outcomes are valued. Any economic evaluation where costs and benefits occur over a number of years should consider discounting. Discounting adjusts for costs (and benefits) occurring at different points in time.

NS: Not specified clearly, CTC: Computerized tomographic colonography, CRC: Colorectal cancer, COL: Colonoscopy, CEA: Cost-effectiveness analysis, ICER: Incremental cost-effectiveness ratio, QALY: Quality-adjusted life-year, KRAS: Kirsten ras oncogene (KRAS), fDNA: Fecal DNA, AAA: Abdominal Aortic Aneurisms

oncogene (KRAS) testing compared with no testing was cost-effective.^[45] The study of Leung *et al.* that assessed the cost-effectiveness of pharmacotherapy did not achieve a clear result, and the reasons mentioned were high dispersion and current problems in the methodology of studies.^[49] The results of the study by Murray *et al.* did not indicate the cost-effectiveness of laparoscopic surgery compared

with open surgery.^[50] Results of a study by Hoyle *et al.* also failed to demonstrate considerable cost-effectiveness of bevacizumab, cetuximab, and panitumumab in comparison with the best supportive care.^[52]

Results of the study of Westwood *et al.* have also revealed the cost-effectiveness of KRAS testing compared with cetuximab.^[51] The results of Kriza *et al.*^[46] and

Hanly *et al.*^[48] indicated that computerized tomographic colonography (CTC) compared with optical COL and without screening is cost-effective. Besides, in the field of colorectal cancer screening, the results of a study by Skally *et al.* showed that fecal DNA (fDNA) screening method was cost-effective in comparison with no screening and other screening methods.^[47]

The results of articles' quality assessment are summarized in Table 4. All the eight articles which have entered into the current study had high quality, and in four articles, all quality points were considered (score 11). The average score of articles' quality was high (9.8 out of 11).

Discussion

Nowadays, health-care systems are facing with limited resources, while in the recent years, the demand for health care has been increase, especially in the field of chronic diseases.^[53-55] Cancer is one of the most important diseases which imposes heavy cost to health-care system, community, and patients.^[56-60] Among all cancers, colorectal cancer is one of the serious cancers in terms of the high cost and

burden of disease.^[61-63] Therefore, many researches have been executed on determining cost-effectiveness interventions and methods in screening and treatment of colorectal cancer.^[64-68] Due to the high number of cost-effectiveness studies which have been conducted in the recent years, some researchers have attempted to carry out systematic reviews on these studies.^[31,32,69-73] Due to the fact that the studies considered specific aspects of cost-effectiveness of colorectal cancer screening and treatment methods, it was required to collect the results of these studies systematically and provide valid and usable information for decision-makers and economists to better policy-making and planing. In fact, by systematic review of the systematic review studies, it can be argued that the results of all conducted studies in the subject area will be studied, and useful summaries will be collected in one place. Therefore, this study aimed to systematically review the studies conducted as systematic reviews on cost-effectiveness of different methods of screening and treatment of colorectal cancer. The results of this study showed that, in eight systematic reviews, 86 articles were studied. In none of the studies reviewed, the meta-analysis technique was not used. The Drummond checklist tool was mostly used in assessing the quality of the articles. The highest perspective was related to payer (40 times), and the lowest one was related to social (15 times). In four articles, the study perspective was not mentioned. Most of the cases refer to sensitivity analysis (in 76% cases) and the lowest point is also discounting (in 37% of cases). In only five out of the eight articles studied, the Markov model was mentioned. The results revealed that treatment methods which were studied, in comparison with the units, did not have any special cost-effectiveness. Among the screening methods, CTC and fDNA methods were cost-effective. The average of articles' quality scores was evaluated to be so high (9.8 out of 11).

The results showed that quantitative analysis methods (meta-analysis) of the results have been used in none of the systematic reviews. Although systematic review

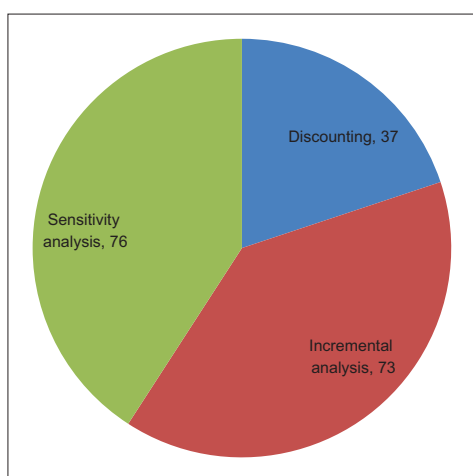


Figure 3: Frequency of cases referred to discounting, sensitivity analysis, and incremental analysis in eight systematic reviews including 86 study articles

Table 4: Assessment of multiple systematic reviews checklist												
Reference	1	2	3	4	5	6	7	8	9	10	11	Score out of 11
Lange <i>et al.</i> , 2014 ^[45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Kriza <i>et al.</i> , 2014 ^[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Skally <i>et al.</i> , 2013 ^[47]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	9
Hanly <i>et al.</i> , 2012 ^[48]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	8
Leung <i>et al.</i> , 2013 ^[49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	8
Murray <i>et al.</i> , 2006 ^[50]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Westwood <i>et al.</i> , 2014 ^[51]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Hoyle <i>et al.</i> , 2013 ^[52]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11

1: Was an "a priori" design provided?, 2: Was there duplicate study selection and data extraction?, 3: Was a comprehensive literature search performed?, 4: Was the status of publication (i.e., gray literature) used as an inclusion criterion?, 5: Was a list of studies (included and excluded) provided?, 6: Were the characteristics of the included studies provided?, 7: Was the scientific quality of the included studies assessed and documented?, 8: Was the scientific quality of the included studies used appropriately in formulating conclusions?, 9: Were the methods used to combine the findings of studies appropriate?, 10: Was the likelihood of publication bias assessed?, 11: Was the conflict of interest included?

studies hold their own value, when a systematic review is accompanied by meta-analysis methods, of course, the value will be multiplied.^[74-76] Two probable reasons for not using meta-analysis in the articles are discussed. First, the researchers do not know how to do it, that in this case, providing the necessary training on how to perform meta-analysis will be necessary. Second, the existence of data and methodological problems in the studies does not allow a meta-analysis to be done. In this case, the use of severe standards for article publication as well as training researchers to carry out studies can have brilliant results.

According to the study results, among various evaluation tools, the Drummond checklist was mostly used in assessing the quality of articles. This checklist contains 35 questions in three main sections: study design (7 questions), data collection (14 questions), and analysis and interpretation of results (14 questions).^[77] Due to the comprehensiveness and application of this tool in assessing the quality of economic studies,^[78] localization of this tool and its use in different countries is recommended.

Based on the study results, among the existing perspectives, community perspective was in the lowest points. In addition to the fact that cancer imposes a huge cost to the health-care system and third-party payer, it causes enormous direct and indirect financial and psychological costs to the society. Thus, putting the society on the topic of economic evaluations seems important. It is also recommended by Drummond *et al.*^[79,80] that one of the possible reasons for researchers to pay little attention to the community perspective refers to difficulties in calculating costs in this method. Moreover, the possible cause of these problems can be due to unavailability of data and the difficulties in collecting these data, compared with the perspectives of health-care systems and third-party payers.^[81-83]

Among the concepts of economic evaluations such as discounting, sensitivity analysis, and incremental analysis, discounting was the least referred to (in 43% of cases). Given the importance of this topic in economic evaluations, the neglect of this issue could have distorted the results of economic evaluations and reduced the usability of the results.^[84-89] Of course, it is possible that either the researcher neglected from reporting them or those researchers who conducted the systematic reviews on the studies' results have made mistake in data extraction.

Markov model was mostly used in the studies compared with the other models. The optimal capabilities and capacity of this model in econometric studies and its focus on the costs and outcomes along with other unique features of this model have made it as the best model in econometric studies.^[81,90] Despite the good capabilities and features of the Markov model, the results showed that, only in five systematic review

articles, the Markov model was mentioned. These five systematic reviews contain 35 studies used Markov model (in total, 35 out of 86 articles), which these numbers seem insufficient. Therefore, it is recommended that the Markov model should be used more often in econometric studies.

The results showed that investigated treatments in studies are not cost-effective compared to the other subjects. The information provided in this area did not have the transparency needed for decision-making, and despite doing relative research in the field, yet there is no strong evidence to support the cost-effectiveness of a particular treatment. The reasons include the extent and high complexity of treatment of colorectal cancer or defects in the econometric studies. Unlike studies on cost-effectiveness of treatments, in cost-effectiveness studies of screening methods, the presented data were transparent and provided the decision-makers with strong evidences.

Among the screening methods, CTC techniques were cost-effective compared with optical COL and no screening; also fDNA screening methods in comparison with no screening. In regard to the treatments and screening, it should be noted that the cost-effectiveness of these methods is affected by many factors that may be neglected in studies. Therefore, the results of these studies should be used more cautiously.

One of the main limitation of this study was limited of included articles to English language studies, because this matter is also possible for other systematic review of studies which have been published in other languages and were not included in this study. As well as other systematic review studies, possible errors might have occurred in the extraction and analysis of results, though the authors have tried to apply the highest accuracy possible in this study.

Conclusion

Along with the increasing costs of chronic diseases, especially colorectal cancer, in the recent years, many cost-effectiveness studies have been performed on the selection of appropriate methods for screening and treating this type of cancer. Due to the high number of cost-effectiveness studies conducted in the recent years, some researchers have attempted to review the studies systematically. The results of the current systematic review showed that taking advantage of meta-analysis techniques is required in this field. Localization of the Drummond checklist is recommended to use it in the other different countries. In cost-effectiveness studies, community perspective should be highly taken into consideration. Paying more attention to discounting topic is necessary; also more use of the Markov model is highly suggested. Providing clear information and reliable evidence for

decision-makers in the field of cost-effectiveness in the treatment of colorectal cancer is essential.

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Conflicts of interest

There are no conflicts of interest.

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APPENDIX

Appendix 1: Drummond's checklist

1. Was a well-defined question posed in answerable form?
2. Was a comprehensive description of the competing alternatives given (i.e., can you tell who did what to whom, where, and how often)?
3. Was the effectiveness of the program or services established?
4. Were all the important and relevant costs and consequences for each alternative identified?
5. Were costs and consequences measured accurately in appropriate physical units?
6. Were the cost and consequences valued credibly?
7. Were costs and consequences adjusted for differential timing?
8. Was an incremental analysis of costs and consequences of alternatives performed?
9. Was allowance made for uncertainty in the estimates of costs and consequences?
10. Did the presentation and discussion of study results include all issues of concern to users?