

RESEARCH ARTICLE

Markov's Modeling for Screening Strategies for Colorectal Cancer

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Abstract

Economic decision models are being increasingly used to assess medical interventions. Advances in this field are mainly due to enhanced processing capacity of computers, availability of specific software to perform the necessary tasks, and refined mathematical techniques. We here estimated the incremental cost-effectiveness of ten strategies for colon cancer screening, as well as no screening, incorporating quality of life, noncompliance and data on the costs and profit of chemotherapy in Iran. We used a Markov model to measure the costs and quality-adjusted life expectancy of a 50-year-old average-risk Iranian without screening and with screening by each test. In this paper, we tested the model with data from the Ministry of Health and published literature. We considered costs from the perspective of a health insurance organization, with inflation to 2011, the Iranian Rial being converted into US dollars. We focused on three tests for the 10 strategies considered currently being used for population screening in some Iranians provinces (Kerman, Golestan Mazandaran, Ardabil, and Tehran): low-sensitivity guaiac fecal occult blood test, performed annually; fecal immunochemical test, performed annually; and colonoscopy, performed every 10 years. These strategies reduced the incidence of colorectal cancer by 39%, 60% and 76%, and mortality by 50%, 69% and 78%, respectively, compared with no screening. These approaches generated ICER (incremental cost-effectiveness ratios) of \$9067, \$654 and \$8700 per QALY (quality-adjusted life year), respectively. Sensitivity analyses were conducted to assess the influence of various scales on the economic evaluation of screening. The results were sensitive to probabilistic sensitivity analysis. Colonoscopy every ten years yielded the greatest net health value. Screening for colon cancer is economical and cost-effective over conventional levels of WTP8.

Keywords: Markov model - colorectal cancer screening - ICER

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Introduction

More than 1 million people worldwide are recently diagnosed with colon cancer each year. Around half of these patients expire of the disease, making colon cancer the fourth leading reason of cancer death in the world (Lijmer et al., 2005). Screening can stop many of these deaths by detecting colorectal cancer in an early, more treatable stage and by detecting and removing its nonmalignant precursor lesion, the adenoma, thereby preventing colon cancer incidence. Screening is not only an efficient tool for reducing colon cancer mortality but also has been estimated to do so at acceptable costs (Leddin et al., 2004).

Iran, which is located in southwest Asia, is in an epidemiologic transition and faces the double burden of diseases (2). The demographic and epidemiological transition that is ongoing will have a significant effect on the pattern of morbidity and mortality in the near and

distant future, particularly as it affects the emergence of chronic non-communicable diseases, medical problems of an aging population and road traffic injuries (Goya, 2007). In addition, cancer is a main public health problem in Iran. Based on recent reports from the Ministry of Health and Medical Education (MOHME); it is the third cause of death in Iran after coronary heart disease and Accidents. Unfortunately, few national programs according to the World Health Organization (WHO) guidelines for cancer screening and prevention are active in Iran, such as those for colon and gastric cancer (Naghavi et al., 2009). In 1984, the Iranian Parliament passed a bill mandating that physicians and pathology centers report all cancer cases according to the International Classification of Diseases-Oncology (ICD-O) to the Ministry of Health. In practice, the principal sources of cancer registries are hospital records and records from diagnostic departments, in particular histopathology. When possible, death certificates in which cancer is included as a main

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or contributory cause of death are also used. In Iran, the National Cancer Registry (NCR) which is only a pathology report band as well as population based cancer registry reports from five provinces (Kerman, Golestan, Mazandaran, Ardabil, Tehran) are the most important sources of Collecting information. In Iran, most northern and north western areas are at high risk for gastric cancer, whereas the central and western provinces are at medium risk and the southern regions are at a low risk (Willingness to Pay). Ardabil, a north western province, has the highest incidence of gastric cancer in Iran with an ASR of 49.1 and 25.4 in men and women, respectively (Willingness to Pay). The provinces of Semnan, Golestan, and East Azerbaijan as well as the Tehran metropolitan area also have high rates of gastric cancer in both men and women. In contrast to the northern areas, Kerman, a province in the south, shows a lower incidence rate of gastric cancer with an ASR of 10.2 and 5.1 in men and women. It is important to know that the higher incidence rate of gastric cancer in Ardabil is due to higher rates of gastric cardia rather than non-cardia cancer, with an incidence of 26.4 and 8.6 in men and women, respectively (Zauber et al., 2009). Although, cancer is the third cause of death in Iran, it's mortality are on the rise during recent decades. An effective population-based screening program is likely to decrease mortality associated with colorectal cancer. through earlier detection and to decrease incidence by allowing removal of precursor colorectal adenomas. Professional societies and government-sponsored committees have released guidelines for screening of average-risk individuals for colorectal cancer by means of several testing options (Winawer et al., 2006). These tests vary in sensitivity, specificity, risk, costs and availability. With no published studies designed to directly compare screening strategies, decision analysis is a useful technique for examining the relative cost-effectiveness of these strategies. Previous papers have shown that screening for colorectal cancer is cost-effective at conventional levels of willingness to pay, but no single strategy has emerged as clinically superior or economically dominant. The interpretations of cost-effectiveness in this area have been restricted because investigators have not simultaneously accounted for the positive effects of screening on quality of life, the effect of noncompliance with screening schedules, and the greater efficacy and cost of more modern chemotherapy regimens for coloncancer (Rex et al., 2008).

Our aim was to estimate the incremental cost-effectiveness of strategies for colorectal cancer screening, as well as the absence of a screening program. The current study is more complete than earlier studies because we included information on quality of life, noncompliance with screening and the efficacy observed in recent randomized trials of colorectal cancer treatments. This paper focuses on the comparison of no screening and three screening strategies: 1 low-sensitivity guaiac fecal occult blood test, 2 performed annually; fecal immunochemical test, 3 performed annually; and colonoscopy, performed every 10 years. These three tests are currently being not used in Iranian provinces, we get some patients in some provinces (that above mentioned) for this studies.

Materials and Methods

Description

In this article we used Markov model for economic decision in colon cancer. Markov Chains present support for problems involving decision on uncertainties through a continuous period of time. The greater accessibility and access to processing power through computers allow that these models can be used more often to represent clinical structures. Markov models consider the patients in a discrete state of health, and the events represent the transition from one state to another stage. The possibility of modeling repetitive events and time dependence of probabilities and utilities associated permits a more accurate representation of the evaluated clinical structure. These templates can be used for economic evaluation in medical care taking into account the evaluation of costs and clinical outcomes, especially for evaluation of chronic diseases. The first stage in the construction of a Markov model is defining the different states of the disease. These states must represent the important clinical and economic effects of the disease, and said effects should be included in the model. One key consideration is that these stages of disease are mutually exclusive, because the patient cannot be in more than one state of the disease at the same time. Cost-effective decision models have been progressively more used to assess medical interventions (National Cancer Institute, 2008). Advances in this field are mainly due to enhanced processing capability of computers, accessibility of specific software to perform these tasks, and SMT (sophisticated mathematical techniques), which have become more popular (Regula et al., 2007). Due to the reasons pointed out above, more investigators adopted the Markov models, which traditionally had previously been used in epidemiological and clinical evaluations (10). In health and medical economics, the strong point of Markov models is that they take into consideration the use of resources and the outcomes (Lieberman et al., 2009).

With the growth of chronic diseases in developing countries Markov models became essential tools for planning medical and health care programs.

Markov model in this study

We used a Markov model using TreeAge DATA Pro (TreeAge Software Inc., Williamstown, Mass.) to measure the CE of 10 strategies for screening, as well as no screening, in 50-year-old individuals at average risk for colon cancer that shown in Table 1. Screening and surveillance continued until 75 years of age, and the analysis continued through the lifetime of the cohort. The length of the model cycle (or, equivalently, the duration over which an individual remained in the same health state before having the opportunity to transition to another health state) was one year. We calculated costs from the perspective of a health insurance organization such as a provincial ministry of health and inflated these costs to 2011 US dollars. The model output was QALY. We discounted costs and effects at 5% annually and used a half-cycle correction to account for these discounts (Imperiale et al., 2010).

Results

We simulated the natural history of colorectal cancer. We calibrated the input parameters of incidence and progression of adenoma to colorectal cancer to generate the known age-specific prevalence of adenomas and colorectal cancer. We obtained probabilities of transition between health states, utilities and costs from the published literature by searching in internet; reviewing the reference lists of the papers identified in the internet search; and searching the Surveillance, Epidemiology, and End Results database. We searched publicly available data for costs and other model inputs (including Iranian life tables, Ministry of health, and iranain statistical office).

The natural history of colorectal cancer was simulated from normal epithelium to a low risk polyp to an advanced adenoma (size >9 mm and/or villous histology and/or high grade dysplasia) to cancer. Cancer stages were modeled as localized, regional and distant and could be either pre-clinical (undiagnosed) or diagnosed through investigation of patient symptoms. Superimposed on the natural history of colorectal cancer were ten screening strategies to detect polyps and pre-clinical colorectal cancer. All patients with a polyp detected on the screening test (other than colonoscopy) underwent colonoscopy with polypectomy. If the colonoscopy was negative, then the patient would return to the original screening strategy in the tenth year following the negative colonoscopy.

Following polypectomy, these patients underwent a surveillance colonoscopy in five years or in three years if an advanced adenoma was excised (Schoenfeld et al., 2009). Following a diagnosis of colorectal cancer, patients

entered a stage-specific colorectal cancer health state for the next five years during which time they had a yearly probability of dying of other causes, dying of colorectal cancer, or sustaining a relapse. If a patient survived five years without relapse, they were assumed to be disease-free and underwent surveillance colonoscopy every five years (Strul et al., 2006). In summary, in above figure that shown Markov states for the natural history of colorectal cancer. Individuals transitioned to different Markov health states (straight arrows) or remained in their current health state. Transitions occurred yearly from age 50 years to death. The Markov model contained three Precancer states, three preclinical (undiagnosed) cancer states, three diagnosed cancer states and the absorbing health state of death (Rex et al., 2008). After treatment of colorectal cancer, individuals entered a surveillance health state with the opportunity for development of further adenomas and cancer. The 10 screening strategies were superimposed on the natural history model (Lieberman et al., 2009).

We estimated ICER for each strategy. The numerators were the differences in costs for each strategy relative to the preceding strategy (ranked in order of effectiveness), and the denominators were the differences in QALY in hypothetical cohorts of 100,000 individuals undergoing screening. We used deterministic and probabilistic sensitivity analyses to assess uncertainty associated with the input parameters. We also calculated net health benefits, which are presented in cost-effectiveness acceptability curves.

Finding

In the base case the mean number of life-years ranged from 26.02 for no screening to 26.42 for colonoscopy every 10 years. After adjustment for the utility and discount on future life-years, the mean number of discounted, quality-adjusted life-years ranged from 10.15 for no screening to 10.27 for colonoscopy every 10 years, with the mean discounted cost of screening for and treating colorectal cancer ranging from \$683 for no screening to \$1429 for colonoscopy every 10 years. All 10 screening strategies for colorectal cancer increased the number of quality-adjusted life years and were more costly than not screening.

Table 1. Strategies to Screen for Colorectal Cancer in this Paper

List of strategies for colorectal cancer
Colonoscopy every 10 years
Low-sensitivity guaiac fecal occult blood test plus sigmoidoscopy every 5 years
Sigmoidoscopy every 5 years
Computed tomography colonography every 5 years
Double-contrast barium enema every 5 years
Fecal DNA every 3 years
Fecal immunochemical test every 1 years
High- sensitivity guaiac fecal occult blood test every 1 years
Low-sensitivity guaiac fecal occult blood test every 1 years
Low-sensitivity guaiac fecal occult blood test every 2 years

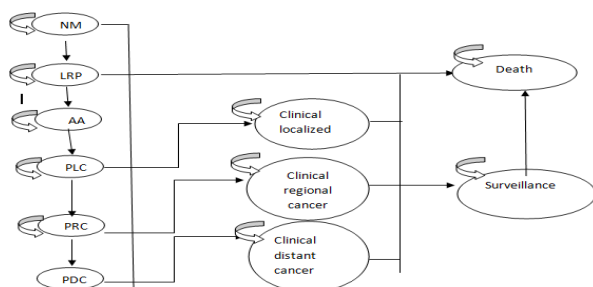


Figure 1. Markov States for the Natural History of Colorectal Cancer. *NM denoted to normal mucosa, LRP=Low risk polyp, AA=advance adenoma, PLC=Preclinical localized cancer, PRC=Preclinical cancer, PDC=preclinical distant cancer

Table 2. Results from the Base-Case Analysis

ICER	Incremental QALY	Incremental cost	Mean QALY	Mean cost 2011 US dollar	Strategy
Not applicable	Not applicable	Not applicable	10.15	683	No screening
9067	0.059	535	10.21	1315	S1
654	0.026	17	10.25	1337	S2
8700	0.01	87	10.27	1429	S3

*S1: Low-sensitivity guaiac fecal occult blood test, performed annually, S2: Fecal immunochemical test, performed annually, S3: Colonoscopy, performed every 10 years

Table 3. Cost and Effectiveness of Three Strategies

Decrease in incidence, %	Cases of cancer prevented	Decrease mortality rate, %	Deaths in prevented	QALYG	Cost	Strategy
39	2648	50	2013	6 814	63039/723	S1
60	3981	69	2734	10 391	65329/721	S2
76	4982	78	3057	11913	75994/657	S3

Of the three screening tests currently used in Iran, colonoscopy every 10 years was both the most effective and the most costly strategy. The cost of annual performance of the fecal immunochemical test was slightly more than the cost of annual performance of the low-sensitivity guaiac fecal occult blood test and yielded a higher quality-adjusted life expectancy. The incremental cost per quality-adjusted life-year gained for colorectal cancer screening ranged from \$654 with annual fecal immunochemical testing through \$8700 for colonoscopy every 10 years to \$9067 for annual low-sensitivity guaiac fecal occult blood testing.

Table 3 shows the decrease in incidence and mortality associated with colorectal cancer in hypothetical cohorts of 100 000 average-risk persons starting each strategy at age 50 years.

In cohorts undergoing screening, the decrease in mortality rate associated with colorectal cancer ranged from 50% for annual low-sensitivity guaiac fecal occult blood test to 78% for colonoscopy every 10 years, and the decrease in incidence of colorectal cancer ranged from 39% for annual low-sensitivity guaiac fecal occult blood test to 76% for colonoscopy every 10 years.

Sensitivity analysis

In this research, we used The one-way and probabilistic sensitivity analyses and net benefits investigation comparing all ten colon cancer screening strategies and no screening. In the one-way sensitivity analysis, the Markov model was sensitive to variations in sensitivity of the test to detect complex adenoma, cost of the test, compliance with screening and cost of colon cancer care.

In briefly, as the sensitivity of the test to detect advanced adenomas rose, the cost of the strategy decreased and its effectiveness increased. For instance, if the sensitivity for advanced adenomas was greater than 49% for the fecal immunochemical test or less than 12% for the low sensitivity guaiac fecal occult blood test, then the yearly fecal immunochemical test conquered. If the cost of the fecal immunochemical test rose beyond \$31, then this strategy was conquered by colonoscopy performed each 10 years. In contrast, colonoscopy costing less than \$355 conquered the other strategies. Under no circumstances was colonoscopy every 10 years dominated by one of the other strategies.

Decreased compliance with screening was connected with a reduce in the cost and effectiveness of a strategy. Also, the one-way sensitivity analysis of every screening test while the compliance of the other tests was held stable at 68% (the base-case value resulting from the text). When compliance with the fecal immunochemical test was less than 66% or compliance with the low-sensitivity guaiac fecal occult blood test was greater than 72%, the annual fecal immunochemical test was less costly than and conquered the annual low-sensitivity guaiac fecal occult blood test. Increasing the cost of cancer care increased the cost of each strategy. Because of the similar costs of the fecal tests, a relatively larger increase in the cost of annual low-sensitivity guaiac fecal occult blood test led to this strategy being dominated by annual fecal immunochemical test. More informatively, when the cost

of treating localized cancer was increased, the cost of strategies with a higher sensitivity for detecting advanced adenoma rose less, as a result of cancer being prevented. This effect was not seen when the cost of treating regional or distant colorectal cancer was varied.

The probabilistic sensitivity analysis did not change the ranking of strategies, and no strategy was dominant. The difference in incremental cost-effectiveness ratios from the base-case analysis was due to changes in the effectiveness of annual low-sensitivity guaiac fecal occult blood test, which reflected the large degree of uncertainty about test performance. At a willingness-to-pay of \$50 000 per quality-adjusted life-year gained, the likelihood of the strategies being cost-effective was 80% for colonoscopy every 10 years and 15% for annual fecal immunochemical test (Annual low-sensitivity guaiac fecal occult blood test contributed less than 1% over a range of willingness-to-pay up to \$100 000 per quality-adjusted life-year gained.

Discussion

The present analysis is reliable with earlier studies in representing that screening for colorectal cancer is cost-effective relative to not screening, according to the conventionally accepted scale of willingness-to-pay of \$50 000 per life-year gained. Additionally, the share of cancer cases prevented was comparable to that reported in earlier studies. In addition, the present model produced reductions in mortality and incidence of colorectal cancer similar to those reported from a microsimulation model of colorectal cancer used to inform the 2008 US Preventive Task Force recommendations for colorectal cancer screening. This study was subject to main limitations. Model-based economic evaluation depends on the data accessible in the medical text, which is continuously evolving. As new information becomes accessible, the consequences of the present analysis will have to be updated. The natural history of colon cancer is based on assumptions concerning the development from adenoma to carcinoma and the transition time from a low-risk polyp to a malignant neoplasm. We did not include the possibility of regression of polyps. We also did not model malignancies arising from lesions other than polyps, as quantitative estimates of this phenomenon have not been published, and some screening strategies may detect nonpolypoid dysplasia. Other boundaries were related to incorporating the following untested assumptions: characteristics of test performance would remain constant on repeat testing, incidence of adenoma would be impassive by screening and compliance with testing was random. The potential effect of these limitations on the results and interpretations is reported in Appendix 1. The model did not incorporate the costs of establishing the infrastructure to implement population-based screening for colorectal cancer. The model was developed from the perspective of a health insurance organization, such as a provincial ministry of health, the organization that decides on funding for a provincial screening program for colorectal cancer. For this reason, lost productivity costs, which are essential to determine the societal viewpoint, were not integrated.

Finally, some previous researches have focused on the

cost effectiveness (CE) of CRC screening in the general population, and some panels have recommended CRC screening for the general population. As the risk of CRC and life expectancy are quite different between cancer survivors and the general population, screening strategy for the general population could not be practical to the cancer survivors. On the other hand, until now, there have been few recommendations for CRC screening for cancer survivors. To propose a feasible economic strategy of second primary CRC screening for cancer survivors in Iran, we constructed a decision analytic model, and compared the CE consequences of cancer screening in cancer survivors and in the average-risk general population.

In conclusion, screening of individuals (average-risk) for colon cancer is a cost-effective measure, even with less-than-perfect compliance. Recognizing that decisions about screening for colorectal cancer depend on local resources and individual patient preferences, either an annual high-sensitivity fecal test, such as a fecal immunochemical test, or colonoscopy every 10 years offer good value for money in Iran. Finally, Annual high-sensitivity fecal occult blood testing, such as a fecal immunochemical test, or colonoscopy every 10 years offer the best value for the money in Iran.

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