

Effectiveness of Screening Modalities in Colorectal Cancer: A Network Meta-Analysis

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Abstract

The aim of the study was to evaluate on the effectiveness of screening modalities in the prevention of colorectal cancer (CRC) occurrence and deaths. General meta-analysis was performed to produce pooled estimates of the effect of CRC incidence and mortality using a search of PubMed, Web of Science, and the Cochrane Library for eligible studies from January 1992 to March 2016. A network meta-analysis was performed to synthetically compare the effectiveness of 5 frequently used screening modalities. A total of 44 studies with a focus on mortality from CRC using different screening methods were included. General meta-analysis showed that fecal immunohistochemical testing (FIT), flexible sigmoidoscopy (FS), colonoscopy, combination of fecal occult blood testing and FS screening respectively reduced CRC mortality by 59% (relative risk [RR], 0.41; 95% confidence interval [CI], 0.29-0.59), 33% (RR, 0.67; 95% CI, 0.58-0.78), 61% (RR, 0.39; 95% CI, 0.31-0.50), 38% (RR, 0.62; 95% CI, 0.42-0.91) compared with no screening, whereas guaiac fecal occult blood testing (gFOBT) reduced CRC-related mortality by 14% (RR, 0.86; 95% CI, 0.82-0.90). Subgroup analysis showed that summary estimates of reduction in distal CRC mortality and proximal CRC mortality were 26% (95% CI, 62%-89%) and 10% (95% CI, 83%-98%). A network meta-analysis revealed rank probability analysis in which the colonoscopy had a 94.6% probability of being the most effective examination to reduce CRC mortality. In addition, the network meta-analysis estimated odds ratio, which was a 79% reduction (95% CI, 0.09-0.60) in CRC mortality when screening with FIT was compared with annual or biennial gFOBT and colonoscopy was approximately 80% more effective than gFOBT for reducing CRC mortality (RR, 0.25; 95% CI, 0.13-0.54). Analysis of the effects of different screening methods showed that there was a significant reduction in the incidence of colon cancer, excluding gFOBT. This meta-analysis confirmed that gFOBT, FIT, FS, and colonoscopy were all effective in preventing CRC deaths and a major reduction in distal but not proximal CRC mortality was found. In addition, they were more effective in preventing CRC incidence in addition to gFOBT. The network meta-analysis suggests that colonoscopy is the most effective screening for preventing CRC deaths.

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Introduction

Colorectal cancer (CRC) is one of the most frequently diagnosed malignancies in the world, and an American study reported¹ the expected numbers of cancer deaths in 2016, in which it was estimated that 49,190 Americans will die from CRC this year, corresponding to approximately 130 deaths per day. Most relevant

studies have concluded that the best choice for decreasing the burden of CRC is therefore screening for early stage cancer and precancerous lesions, however, there is some controversy regarding the optimal modality of CRC screening, with current screening options including fecal occult blood testing (FOBT), computed tomography (CT) colonography, flexible sigmoidoscopy (FS), and colonoscopy.^{2,3}

The most commonly used and evaluated screening examination in average-risk populations is the FOBT, which has 2 types,⁴ including guaiac FOBT (gFOBT) and fecal immunohistochemical testing (FIT). A 16% reduction in CRC mortality was also reported in France in a population invited to screening matched with a nonscreened population.⁵ A US randomized trial in Minnesota, conducted among volunteers, also indicated the efficacy of gFOBT screening.⁶ Although the efficacy of FOBT at reducing CRC

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mortality has been proven in previous randomized trials and evidence,⁷ which has shown the advantages of FIT over gFOBT,⁸ organized service screening using FIT has been introduced in only a few countries, and its efficacy still needs to be further studied.⁹

Since 1992, several observational studies have suggested a major protective effect of lower gastrointestinal endoscopy against CRC via detection and removal of precancerous lesions.¹⁰⁻¹² As a result, use of sigmoidoscopy and colonoscopy supported by further improvements in technology for diagnostic and screening purposes has substantially increased in many countries.^{13,14} With regard to the use of FS for CRC screening, the sensitivity of FS for detecting CRC in the entire colon was 58% to 75% in the community setting in small studies.^{15,16} In addition, 5 large population-based randomized controlled trials (RCTs) have been published recently, which evaluated the effect of FS screening on CRC incidence and mortality.¹⁷⁻²¹ However, observational studies have raised doubts about the benefit of endoscopic screening in reducing mortality^{22,23} and the incidence^{24,25} of proximal CRC. Several case-control studies had indicated that colonoscopy was the most invasive and costly modality for CRC screening.^{22,26,27}

Although previous studies in CRC screening have done a few meta-analyses, most of the studies only analyzed and directly compared the screening group and nonintervention group and these meta-analysis studies were limited in that they were the study of a single colon cancer screening method; in addition, the research on the effectiveness of colon cancer screening method was not comprehensive. Therefore, we did further research, in which not only a simple comparison between the screening group and non-screening group was done, but also a synthetic comparison of different screening methods, and the review included several different screening methods to make a comprehensive evaluation. These general and network meta-analyses were used to evaluate the evidence from published RCTs and observational studies that investigated the effectiveness of screening tests on CRC incidence and mortality in the population at average risk and derived summative conclusions regarding the effectiveness of screening modalities to identify the most effective screening examination.

Materials and Methods

Data Searches

We searched PubMed, Web of Science, and the Cochrane Library for eligible studies from January 1992 to March 2016, including articles published ahead of print and without language restriction. We also performed a manual search of references cited in the primary articles. The combinations of keywords used were: “colonic neoplasm” or “colon neoplasms” or “colon cancer” or “colonic cancer” or “colorectal neoplasm” or “colorectal cancer” or “colonoscopy” or “sigmoidoscopy” or “endoscopy” or “FOBT” or “gFOBT” or “fecal immunohistochemical testing” or “stool DNA testing” and “screening” and “mortality.”

Study Selection

Studies were included in the meta-analysis if they met the following criteria:

- (1) published RCTs, observational studies, and cohort studies;
- (2) studies with ≥ 4 years of follow-up (for RCT and cohort studies);
- (3) the outcome of interest was mortality due to CRC;
- (4)

relative risk (RR), odds ratio (OR), or hazard ratio estimated with 95% confidence interval (CI; or sufficient data to calculate these) were reported; (5) studies in which the number of events and total number of participants in each study group were reported; (6) assessed the effects of colonoscopy, gFOBT, FIT, FS, CT colonography, or some combination versus no screening on CRC incidence or mortality, or both in the general population at average risk for CRC. We excluded studies published as abstracts only because we considered the information to be insufficient for our assessment.

Data Extraction

Three authors independently extracted relevant information from different studies to a standardized form. The following data were extracted from each study: the first author's last name, publication year, country where the study was performed, study population database, participant age and sex, screening modality or modalities evaluated, study methodology (RCT, cohort study, case-control study), follow-up duration, the number of events, and total number of participants in the intervention and control groups, RR along with 95% CIs according to site of CRC (any, proximal, distal), and outcome (incidence, mortality) as far as reported. Disagreements in data extraction were resolved by consensus.

Data Synthesis and Analysis

Death from CRC was the primary end point. A secondary end point was CRC incidence. From the original study data, we analyzed the outcome of incidence and mortality from CRC for patients (RR). OR, rate ratio, risk ratio, or hazard ratio yielded similar estimates of RR. Pairwise comparisons of each screening modality and incidence versus no active intervention were performed by using a random effects model (Stata 12.0; Stata Corp). The random effects model is more powerful than the fixed effects model and incorporates into the weighing scheme within study as well as between study variations.²⁸ We performed further subgroup analysis for mortality of distal and proximal CRC in the intervention and control groups. Statistical heterogeneity among trials was evaluated by using the Cochran *Q* statistic and quantified using *I*² statistics.²⁹ When heterogeneity was present, meta-influence analysis and publication bias³⁰ was assessed using funnel plots to identify responsible outlier studies.

We used the multiple treatment meta-analysis (MTM) method proposed by Salanti et al³¹ (a Bayesian method on the basis of the Markov Chain Monte Carlo simulation) to compare testing modalities for mortality from CRC. All MTMs were performed using Winbugs version 1.4.3 (Imperial College and Medical Research Council) using random effects models. The estimates obtained by generating 5 chains with 1000 initial iterations (burn in) and 10,000 iterations were used for the estimations. This form of meta-analysis generates estimates of effect sizes for all possible pairwise comparisons whether or not they have been evaluated in head to head trials. These comparisons form the basis for a rank probability analysis of competing modalities, which uses simulations to determine the probability of any particular intervention being most effective. We only combined studies in MTMs if we found that the studies were sufficiently similar to each other with regard to context, and method of implementation of the screening intervention.

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