

Comparing the effectiveness of competing tests for reducing colorectal cancer mortality: a network meta-analysis

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Background: Comparative effectiveness data pertaining to competing colorectal cancer (CRC) screening tests do not exist but are necessary to guide clinical decision making and policy.

Objective: To perform a comparative synthesis of clinical outcomes studies evaluating the effects of competing tests on CRC-related mortality.

Design: Traditional and network meta-analyses. Two reviewers identified studies evaluating the effect of guaiac-based fecal occult blood testing (gFOBT), flexible sigmoidoscopy (FS), or colonoscopy on CRC-related mortality.

Interventions: gFOBT, FS, colonoscopy.

Main Outcome Measurements: Traditional meta-analysis was performed to produce pooled estimates of the effect of each modality on CRC mortality. Bayesian network meta-analysis (NMA) was performed to indirectly compare the effectiveness of screening modalities. Multiple sensitivity analyses were performed.

Results: Traditional meta-analysis revealed that, compared with no intervention, colonoscopy reduced CRC-related mortality by 57% (relative risk [RR] 0.43; 95% confidence interval [CI], 0.33-0.58), whereas FS reduced CRC-related mortality by 40% (RR 0.60; 95% CI, 0.45-0.78), and gFOBT reduced CRC-related mortality by 18% (RR 0.82; 95% CI, 0.76-0.88). NMA demonstrated nonsignificant trends favoring colonoscopy over FS (RR 0.71; 95% CI, 0.45-1.11) and FS over gFOBT (RR 0.74; 95% CI, 0.51-1.09) for reducing CRC-related deaths. NMA-based simulations, however, revealed that colonoscopy has a 94% probability of being the most effective test for reducing CRC mortality and a 99% probability of being most effective when the analysis is restricted to screening studies.

Limitations: Randomized trials and observational studies were combined within the same analysis.

Conclusion: Clinical outcomes studies demonstrate that gFOBT, FS, and colonoscopy are all effective in reducing CRC-related mortality. Network meta-analysis suggests that colonoscopy is the most effective test. (*Gastrointest Endosc* 2015;81:700-9.)

Abbreviations: CRC, colorectal cancer; EBGSG, Evidence-Based Gastroenterology Steering Group; FOBT, fecal occult blood testing; FS, flexible sigmoidoscopy; gFOBT, guaiac-based FOBT; NMA, network meta-analysis.

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Colorectal cancer (CRC) is a leading, worldwide cause of cancer-related deaths.^{1,2} Although screening for CRC reduces the incidence and mortality of this malignancy,^{3,4} clinical outcomes studies directly comparing the effectiveness of competing screening tests are not available to guide clinical decision making or policy.

Two randomized trials comparing colonoscopy with fecal immunohistochemical testing are ongoing; however, results may not be available for another decade or longer.^{5,6} There are currently no ongoing registered clinical outcomes trials comparing colonoscopy with flexible sigmoidoscopy (FS), CT colonography, or stool DNA testing. As a result, the optimal test remains uncertain, and national screening strategies vary. Fecal occult blood testing (FOBT) is used in most European countries,⁷ Canada,⁸ and Japan.⁹ In contrast, colonoscopy—the most invasive and costly modality—is preferred in Germany, Poland, and the United States,^{7,10,11} despite the absence of comparative effectiveness data demonstrating its superiority.

Colonoscopy may indeed be the most effective screening modality because it provides structural evaluation of the entire colon, detects both precancerous lesions and early prevalent cancers, and allows real-time polyp removal (thereby eliminating the risk of missing the lesion at follow-up examination). However, evidence of the comparative advantage of colonoscopy is necessary to justify its continued growth in this era of increasing screening acceptance¹² but limited endoscopic capacity¹³ and rising health care expenditures.¹⁴

Because substantial clinical outcomes data are available for each test, and validated methodologies exist to indirectly compare the effectiveness of modalities, we used traditional and network meta-analysis to perform a comprehensive comparative appraisal of the effects of competing screening tests on CRC-related mortality. The results of this analysis may inform additional research in this field and supplement previously published decision analyses^{15,16} in guiding clinical decision making and screening policy.

METHODS

Data sources and search

The study was conducted in accordance with the PRISMA and MOOSE statements.^{17,18} A research librarian designed and conducted a computer-assisted search by using the National Library of Medicine's interface to PubMed/MEDLINE and Embase to identify potentially relevant articles. A search of human studies in these databases from inception through April 20, 2014 was performed by using controlled vocabulary descriptors (medical subject headings and Emtree) and keywords to represent the concepts of colorectal cancer, colon or rectal cancer, screening, and mortality. Results from this base search were combined with descriptors and keywords for various diagnostic procedures or screening methods including colonoscopy, colonography,

sigmoidoscopy, endoscopy, FOBT, fecal immunohistochemical testing, and stool DNA testing.

The search was augmented by manual searches of reference lists from potentially relevant articles to identify any additional studies that may have been missed by using the computer-assisted strategy. Additionally, all available guidelines, systematic reviews, and meta-analyses pertaining to CRC screening or individual screening modalities published after 2007 were identified through a manual search of the [PubMed.gov](http://pubmed.gov) database. These documents and their reference lists were reviewed for additional potentially relevant studies. The search was not limited by language.

Study selection

Two investigators (B.J.E., A.K.W.) independently reviewed the titles of all identified citations to generate a list of potentially relevant articles. Abstract and brief manuscript review of articles with potentially relevant titles was then independently performed to select studies appropriate for our analysis. These studies were then reviewed in depth and the following eligibility criteria applied: (1) published manuscripts that examine the effect of colonoscopy, flexible sigmoidoscopy, stool-based CRC screening tests, CT colonography, or some combination thereof on the mortality of colorectal cancer; (2) studies that evaluate clinical outcomes in humans (not test performance characteristics); (3) studies in which data or patients are not duplicated in another manuscript—for randomized controlled trials (RCTs) and cohort studies that were longitudinally updated, only the most recent report was included; (4) studies with ≥ 5 years (mean) of follow-up (for trials and cohort studies); and (5) studies in which the number of events and total number of participants in each study group were reported. Articles reporting the effects of rigid sigmoidoscopy and barium enema were excluded because these are no longer accepted screening modalities.

Data extraction

The following data were abstracted from each study in duplicate (B.J.E., A.G.S.) and independent fashion: first author, year of publication, country in which the study was conducted, screening modality or modalities evaluated, study methodology (trial, cohort study, case-control study, prospective vs retrospective), whether or not the study focused primarily on screening, follow-up duration, the number of events and total number of participants in the intervention and control groups (by using the intention-to-treat principle for trials), and the reported (adjusted) summary estimate (with confidence limits) of the intervention's effect on overall CRC mortality or deaths related to CRC in the proximal or distal colon. Discrepancies in data extraction were resolved by consensus.

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