Diagnostic precision of carcinoembryonic antigen in the detection of recurrence of colorectal cancer
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CRD summary
This review concluded that serum carcinoembryonic antigen has high specificity but insufficient sensitivity for detecting colorectal cancer recurrence in isolation. Given the limitations of the available evidence, and the lack of reporting of the review process, the results of the review should be treated with some caution.

Authors' objectives
To evaluate the diagnostic precision of serum carcinoembryonic antigen in the detection of local or distant recurrence following surgery for colorectal cancer.

Searching
PubMed, EMBASE, the Cochrane Library and Web of Science were searched without language restrictions to July 2007. Search terms were reported. Reference lists of identified articles were also scanned.

Study selection
Studies of carcinoembryonic antigen for the detection of the recurrence of colorectal cancer (local, distant and/or metachronous), compared to a combination of clinical examination and colonoscopy, were eligible for inclusion. Included studies had to report a cut-off level at which the carcinoembryonic antigen was considered positive for recurrent colorectal cancer and sufficient data for diagnostic outcomes to be extracted or calculated.

Most included studies recruited patients after curative resection and reported the use of colonoscopy as the reference standard. Some studies excluded patients with metastases. Where reported, carcinoembryonic antigen cut-offs ranged from 3 to 15 ng/mL and mean follow-up ranged from 12 to 80 months.

The authors did not state how studies were selected for the review, or how many reviewers performed the study selection.

Assessment of study quality
Study quality was assessed using the STARD (Standards for Reporting of Diagnostic Accuracy) statement and QUADAS (Quality Assessment of Diagnostic Accuracy Studies Assessment). High quality was associated with scores of 18 or more out of 25 for STARD and 11 or more out of 14 for QUADAS.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Sensitivity and specificity for recurrence (defined as locoregional, distant spread and/or metachronous) were either extracted or calculated from raw data. Diagnostic odds ratios calculated for each study and 95% confidence intervals (CI) were calculated for each outcome measure. Where there was overlap between studies, data were extracted from the most recent and better quality study.

Two reviewers extracted data. Disagreements were resolved by consensus.

Methods of synthesis
Pooled estimates of sensitivity, specificity and the diagnostic odds ratio, along with their corresponding 95% CI, were calculated using a random-effects model. Summary receiver operating characteristic curves using the Moses model were presented and the area under the curve was calculated. Heterogeneity was assessed using the χ² and I² statistics.
Sensitivity analyses were used to explore the impact of study quality, sample size, and date of publication. Meta-regression was used to determine the change in diagnostic odds ratios associated with differences in cut-off values for a positive carcinoembryonic antigen result. Bubble plots of sensitivity and specificity against carcinoembryonic antigen were presented.

**Results of the review**

Twenty studies met the inclusion criteria (n=4,285 patients, range 44 to 1,017). Three studies were retrospective in design. STARD (Standards for Reporting of Diagnostic Accuracy) scores ranged from 12 to 20, with seven studies scoring 18 or over. QUADAS (Quality Assessment of Diagnostic Accuracy Studies Assessment) scores ranged from 5 to 12, with seven studies scoring 11 or over. Eighteen studies reported avoiding verification bias.

Diagnostic sensitivity for carcinoembryonic antigen in the detection of colorectal cancer recurrence ranged from 33% (95% confidence interval (CI): 11.8 to 61.6) to 84% (95% CI: 75.5 to 91.0). Diagnostic specificity ranged from 77% (95% CI: 65.6 to 86.3) to 100% (95% CI: 84.6 to 100). Diagnostic odds ratio for carcinoembryonic antigen in the detection of colorectal cancer recurrence ranged from 3.0 (95% CI: 0.48 to 18.93) to 480.5 (95% CI: 27.0 to 8539.2). Pooled estimates were 62% for sensitivity (95% CI: 59 to 66) and 88% for specificity (95% CI: 87 to 90). Both analyses were subject to significant heterogeneity (p<0.001, sensitivity I²=71%, specificity I²=83%). Sensitivity analyses did not alter the results of the main analyses. The area under the Summary receiver operating characteristic curve was 0.79 (standard error 0.054).

The threshold of carcinoembryonic antigen diagnostic sensitivity and specificity was also investigated. The results from an analysis of studies reporting a specific cut-off of 5 ng/mL were similar to those of the main analysis, but in an analysis of studies with a specific cut-off of 3 ng/mL, sensitivity increased to 73% (95% CI: 69.3 to 77.0) and specificity decreased to 68% (95% CI: 65.1 to 71.8). Bubble plots showed the ideal balance of sensitivity and specificity at a threshold of 2.2 ng/mL.

**Authors’ conclusions**

Serum carcinoembryonic antigen had high specificity but insufficient sensitivity for detecting colorectal cancer recurrence in isolation.

**CRD commentary**

The authors addressed a clear research question, supported by appropriate inclusion criteria. Several sources were searched and attempts to avoid language bias were implemented. There was no specific search for unpublished data, so publication bias can not be ruled out. This was not investigated. Data extraction was conducted in duplicate, but it was unclear whether similar methods to reduce error and bias were employed during study selection.

Study quality was assessed using appropriate criteria and a composite score given for each study. The reporting of the composite scores precluded an assessment of the individual limitations of each study. Most of the studies were not considered to be of high quality. The studies demonstrated highly statistically significant heterogeneity and clinical heterogeneity was apparent from the tables of study details. Therefore, the reliability of the pooled estimates derived from traditional meta-analytical techniques is uncertain, particularly given the threshold effect identified. There seemed to be some discrepancies between the results presented in the forest plots and the text of the review. The authors did investigate some potential sources of heterogeneity. Given the limitations of the available evidence, and the potential for selection bias, the results of the review should be treated with some caution.

**Implications of the review for practice and research**

**Practice:** The authors stated that carcinoembryonic antigen may be useful as a first-line surveillance investigation in patients during surgical follow-up, based on serial carcinoembryonic antigen measurements using temporal trends in conjunction with clinical, radiological and/or histological data. A cut-off of 2.2 ng/mL was stated as potentially providing the ideal balance of sensitivity and specificity.

**Research:** The authors did not state implications for research.
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