How useful is it clinically to analyse the K-ras mutational status for the diagnosis of exocrine pancreatic cancer? A systematic review and meta-analysis

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CRD summary
This review concluded that the utility of analysing K-ras mutations for the diagnosis of exocrine pancreatic cancer remains unknown due to the numerous methodological limitations of the available studies. The authors’ cautious conclusions reflect the poor quality of the data presented and are likely to be reliable but some relevant studies may have been missed.

Authors' objectives
To assess the utility of analysing K-ras mutational status for the diagnosis of exocrine pancreatic cancer.

Searching
PubMed and EMBASE were searched to July 2010 and search terms were reported (such as methodological terms for test accuracy studies). The bibliographies of key articles were screened for additional studies.

Study selection
Studies that assessed the diagnostic accuracy of detecting K-ras mutations for diagnosis of exocrine pancreatic cancer in at least 50 patients were eligible for inclusion. Studies that assessed K-ras determination in combination with other diagnostic procedures were included. Studies could use any type of sample (such as tissue, blood, pancreatic juice) for DNA extraction.

The prevalence of exocrine pancreatic cancer in the included studies varied widely (9.3% to 81.8%). Approximately one third of the included studies reported the tumour stage of participants; a mean of 43.5% were stage IV. All but three of the included studies detected K-ras mutations in codon 12, and just over half used restriction fragment length polymorphism polymerase chain reaction. The method for obtaining the sample for K-ras analysis was considered to be highly invasive in eight studies, moderately invasive in nine studies, minimally invasive in ten and non-invasive in seven.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
The methodological quality of included studies was assessed with a 14-item adaptation of the QUADAS tool. The item on indeterminate test results was omitted and items specific to exocrine pancreatic cancer (reporting of socio-demographic and relevant clinical details of participants) were added.

Two reviewers independently assessed study quality and disagreements were resolved by consensus.

Data extraction
Data were extracted to calculate the sensitivity and specificity, with 95% confidence intervals (CIs) of K-ras determination for the diagnosis of exocrine pancreatic cancer. Data were extracted separately for different sample types and/or patient populations and for combinations of K-ras with other tests.

Two reviewers independently extracted data and disagreements were resolved by consensus.

Methods of synthesis
Pooled estimates of sensitivity and specificity were calculated using a bivariate model. Meta-regression analysis was used to explore the impact of methodological characteristics and clinical sub-groups on sensitivity and specificity.

Results of the review
Thirty studies that reported results for 34 independent patient series were included in the review; sample size ranged...
from 51 to 532. Most studies used a diagnostic case-control design. Other quality criteria which were poorly rated (met by 10 or less studies) were histological confirmation of all exocrine pancreatic cancer cases, blinded interpretation of K-ras results, and explanation for exclusion of participants from K-ras analysis.

The pooled sensitivity estimates for K-ras determination were poor in serum or plasma samples (37.6%; 95% CI 17.5 to 63.1%; four studies), stool samples (65.7%; 95% CI 38.2 to 85.5%; three studies) and pancreatic juice (60.0%; 95% CI 43.6 to 74.5%; nine studies). The pooled sensitivity estimates for K-ras determination in tissue samples were 76.5% (95% CI 66.7 to 84.2%) and specificity estimates were 91.8% (95% CI 87.6 to 94.7%); 17 studies.

Sensitivity was significantly higher in studies that used a case-control design than in those that used more clinically relevant patient groups (82.7% compared with 68.4%, P = 0.039). Studies that determined K-ras in all patients reported higher sensitivity than studies that excluded some patients (83.8% compared with 66.3%, P = 0.004). For the five studies that reported data by tumour stage, sensitivity in stage IV tumours was greater than in stages I to III; the pooled estimate was 30.5% (95% CI 19.5 to 44.0%) for tumours in stages I to III and 71.6% (95% CI 61.6 to 79.8%) for stage IV tumours.

Eight studies reported data for the combination of K-ras mutations with cytopathology; sensitivities ranged from 53.3% (95% CI 27.4 to 77.7%) to 97.0% (95% CI 82.5 to 99.8%) and specificities ranged from 61.5% (95% CI 32.3 to 84.9%) to 100% (95% CI 82.8 to 100%)

**Authors' conclusions**
Because of the numerous methodological limitations of studies, the utility of analysing K-ras mutations for the diagnosis of exocrine pancreatic cancer remains unknown.

**CRD commentary**
The review stated a clear research objective and defined appropriate inclusion criteria. Only two bibliographic databases were searched for relevant studies and searches included methodological terms for test accuracy studies, which were known to reduce the sensitivity of searches so relevant studies may have been omitted. Data extraction and quality assessment processes incorporated measures to minimise error and/or bias, but it was not clear whether similar measures were applied to study selection.

The methodological quality of included studies was assessed; the results of this were reported in full and used in the meta-analyses to investigate the impact of elements of study design upon estimates of test performance. The meta-analytic methods used were generally appropriate, but the number of explanatory variables that appear to have been included in the meta-regression analysis would indicate that it was likely to have been “underpowered”.

The authors' cautious conclusions reflect the poor quality of the data presented and were likely to be reliable but some relevant studies may have been missed.

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

**Practice:** The authors stated that practical difficulties in obtaining appropriate samples may limit the clinical utility of K-ras mutation status as a test. In addition, sensitivities were poor in patients with suspected exocrine pancreatic cancer (the most clinically relevant population); this could result in significant numbers of cases being missed if the diagnosis were based on K-ras status alone. K-ras in cytopathological samples may be a useful part of future diagnostic strategies.

**Research:** The authors stated that further robust studies were needed to discover clinically meaningful tumour markers.

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**Bibliographic details**
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.