Systematic review: the Trousseau syndrome revisited - should we screen extensively for cancer in patients with venous thromboembolism?

Carrier M, Le Gal G, Wells P S, Fergusson D, Ramsay T, Rodger M A

CRD summary
The authors concluded that use of an extensive screening strategy, particularly where this includes computed tomography of the abdomen and pelvis, detected more malignant conditions than a limited screening strategy. These findings should be regarded with caution and further research is required.

Authors' objectives
To summarise the point prevalence of previously undiagnosed cancer within 1 month, after 6 months and after 12 months of venous thromboembolism (VTE) diagnosis, and to quantify the added value of extensive cancer screening strategies over more limited screening. (This abstract does not report the prevalence results but focuses on the comparison of screening strategies.)

Searching
The following databases were searched (terms and strategy reported): MEDLINE (1950 to November 2007), EMBASE (1980 to November 2007), Cochrane Central Register of Controlled Trials (2007) and EBM Reviews (2007). Relevant journals and proceedings of the International Society on Thrombosis and Haemostasis (2005 to 2007) were handsearched. References of included studies and narrative reviews were checked for additional papers. The searches placed no restrictions on language, publication date or type of publication. Only articles in English, French and Spanish were considered for inclusion.

Study selection
Eligible study designs included randomised controlled trials (RCTs) and observational studies which reported on adult patients with newly diagnosed VTE (deep venous thrombosis or pulmonary embolism). The interventions of interest were limited cancer screening (medical history, physical examination, routine blood tests and chest radiography) and extensive cancer screening (as limited screening plus one of the following: ultrasonography (US) of abdomen or pelvis; computed tomography (CT) of the abdomen or pelvis; tumour markers). Included studies conformed to these criteria. The primary outcome measure was detection of previously undiagnosed cancer. Secondary outcomes were any screening complications.

Studies were assessed by two independent reviewers and a third reviewer adjudicated any discrepancies.

Assessment of study quality
All included studies were quality assessed according to the Newcastle-Ottawa Quality Assessment Scale. This quality score was designed to assess non-RCT study quality, including items on selecting study groups, comparing groups and ascertaining the outcome of interest or exposure. Additional quality criteria used in this review were explicit inclusion criteria, length of follow-up and objective assessment of outcomes. The RCT was assessed using these same criteria, and allocation concealment was noted. No RCT specific tool was used because the treatment arms were used as cohorts within this review.

Studies were assessed by two independent reviewers and a third reviewer adjudicated any discrepancies.

Data extraction
Data were extracted by two independent reviewers onto a standardised abstraction form and a third reviewer adjudicated any discrepancies.

Methods of synthesis
A cross-sectional design was used to assess the additional benefits of an extensive screening program versus limited
screening in terms of cancer detection rates. Detection rates were derived using a denominator based on the total number of cancer cases detected at the end of follow-up. The authors estimated the pooled probability of identifying a previously undetected cancer according to screening type, further sub-divided by type of diagnostic test (US, CT) and tumour markers which were treated separately. The 95% confidence intervals (CI) were calculated based on averaged, inverse variance-weighted estimates for each study.

**Results of the review**

A total of 15 studies (n=4378) were included in this review comparing screening strategies for cancer detection. Thirteen studies were cohort designs (4 retrospective, 9 prospective), one study prospectively compared exposed and non-exposed cohorts and the final study was an RCT, although the data had been extracted and used as additional cohorts.

CT of abdomen/pelvis: analysis of five studies found that this technique significantly increased the proportion of undiagnosed cancer detected following extensive screening to 66.1% (95% CI: 59.0, 73.2) compared to limited screening which detected only 47.6% of cases (95% CI: 40.0, 55.1) in all patients with VTE. In the subgroup of patients with unprovoked VTE there was a significant increase in the proportion of detected cancer, from 49.4% (95% CI: 40.2, 58.5) in the limited screening groups, to 69.7% (95% CI: 61.1, 77.8) in the extensive screening groups.

US of abdomen/pelvis: analysis of eight studies did not find a significant difference in the proportion of undiagnosed cases of cancer detected between screening types.

Four studies compared the rate of cancer detection in early-stage, previously undiagnosed cancer between limited and extensive screening programs. Pooled data across diagnostic tests suggested that extensive screening increased the number of cases detected from 13.5% (95% CI: 8.8, 21.0) under limited screening to 22.0% (95% CI: 15.6, 30.1).

One study reported rate of cancer-related mortality by screening strategy: an absolute difference of 1.9% cancer-related mortality (95% CI: -5.5, 10.9) in favour of extensive screening was detected.

US of the abdomen/pelvis and screening for carcinoembryonic antigen (CEA) and prostate-specific antigen (PSA) tumour factors did not significantly increase the frequency of cancer detection over and above limited screening alone.

No studies reported screening complications.

**Authors' conclusions**

Use of an extensive screening strategy, particularly where this includes computed tomography of the abdomen and pelvis, detects more malignant conditions than a limited screening strategy. It is not clear if this could translate to an increase in the detection rate of early-stage cancer or a decrease in cancer-related mortality or morbidity.

**CRD commentary**

This review addressed a clear clinical question with detailed searches and robust use of systematic review methodology including checked study selection, data extraction and quality assessment. The authors acknowledge the limitations placed on this review by the available data, particularly the inability to calculate sensitivity and specificity values, and the potential inflation of the effect estimates as a result of pooling retrospective and prospective studies. Although quality assessment was carried out, this does not appear to have been taken into account within the subsequent analyses and no attempt was made to assess comparability between the cohorts/trial arms. It is therefore difficult to judge whether pooling was appropriate for this data set. The analysis was not reported in sufficient detail to comment on. The conclusions should be considered with caution since they are based on a small number of studies which may have displayed baseline heterogeneity. Further research is required to confirm the findings.

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

Practice: the authors stated that, although cancer is more likely to be detected by an extensive screening strategy, many cases of previously undiagnosed cancer remain undetected following screening. Clinicians should monitor their patients closely for any signs of malignant conditions.

Research: the authors stated that further research is needed to explore the impact of detection on morbidity, quality of
life, survival rates and the cost-effectiveness of such screening strategies.

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