
Article:
Bradley, SH orcid.org/0000-0002-2038-2056, Abraham, S, Callister, MEJ et al. (5 more authors) (2019) Sensitivity of chest X-ray for detecting lung cancer in people presenting with symptoms: a systematic review. British Journal of General Practice, 69 (689). e827-e835. ISSN 0960-1643

https://doi.org/10.3399/bjgp19X706853

How this fits in

Chest x-ray remains the first line investigation for suspected lung cancer in the UK. Outcomes for lung cancer are relatively poor compared to the healthcare systems of many other advanced economies, which make more extensive use of other imaging modalities such as CT. This systematic review found that there is limited high quality evidence published on the diagnostic accuracy of chest x-ray. The few high quality studies identified suggest that chest x-ray misses (at least initially) lung cancer in over 20% of people. As earlier diagnosis is closely associated with improved survival, it is therefore possible that the use of chest x-ray in UK practice may delay the diagnosis of lung cancer in some patients. These findings support calls to increase open-access CT for GPs, but given resource restrictions and the potential to cause harm through over-diagnosis, further research is required to help identify which patients who have had a non-diagnostic chest x-ray should be referred for additional investigation.

Abstract

Background: Despite increasing use of CT, chest x-ray remains the first-line investigation for suspected lung cancer from primary care in the UK. No systematic review evidence exists as to the sensitivity of chest x-ray for detecting lung cancer in people presenting with symptoms.

Aim: To estimate the sensitivity of chest x-ray for lung cancer in symptomatic people.

Design and Setting: Systematic review of the sensitivity of chest x-ray for the detection of lung cancer.

Method: Databases including MEDLINE, EMBASE and the Cochrane Library were searched and a grey literature search performed.

Results: 21 studies met the eligibility criteria. Almost all were of poor quality. Only one study had the diagnostic accuracy of chest x-ray as its primary objective. Most papers were case studies with a high

risk of bias. Several were drawn from non-representative groups e.g. specific presentations, histological subtypes, or co-morbidities. Only three studies had a low risk of bias. Two primary care studies reported sensitivities of 76.8% (95% CI: 64.5-84.2%) and 79.3% (95% CI: 67.6-91.0%). One secondary care study reported a sensitivity of 79.8% (95% CI: 72.7 to 86.8%).

Conclusion: Although there is a paucity of evidence, the highest quality studies suggest that the sensitivity of chest x-ray for symptomatic lung cancer is only 77-79%. In high risk patients who have had a negative chest x-ray GPs should consider if further investigation is necessary.

Introduction

Lung cancer is the single largest cause of cancer mortality both worldwide (1) and in the UK (2). Compared to many other cancers, improvements in lung cancer survival over recent decades have been modest. The age standardised 5-year survival has only increased from approximately 5% to 10% (2) since 1971, compared to improvements from 53% to 87% in 5-year survival for breast cancer in the same period (3).

Diagnosis of lung cancer at earlier stages of disease is associated with improved survival. Optimising early detection is therefore considered an important strategy in improving outcomes (4). Chest x-ray is comparatively cheap, accessible (5), and has a low radiation dose (6). It remains the first-line investigation for lung cancer in primary care and the most common radiological route to diagnosis (7). This is reflected in current NICE lung cancer guidelines which recommend chest x-ray for initial evaluation in all patients, aside from those aged over 40 who have unexplained haemoptysis(8).

Despite its predominance in guidelines and clinical practice, no systematic review has determined the sensitivity of chest x-ray alone for lung cancer in patients presenting with symptoms.

Methods

A systematic review was conducted in June 2017 and updated in December 2018.

The sensitivity of chest x-ray for lung cancer was estimated by identifying studies that:

- reported the numbers of patients who were investigated with chest x-ray due to symptoms in the year before their diagnosis of lung cancer, and
- reported the contemporaneous results of the chest x-rays.

Screening studies were not included. The authors registered the study protocol with PROSPERO (9). An amendment to the protocol was subsequently made to correct an error. In addition, papers were screened based on their title and abstract, rather than on the basis of title only, as reported in the protocol.

Search strategy

In July, 2017 we searched CINAHL, Cochrane CDSR, CENTRAL, DARE, HTA, NHS EED, Embase, Medline, Medline In Process and Medline Epub Ahead of Print, PubMed and Science Citation Index (SCI). These resources were searched with no language restrictions from 1999 using a search strategy with subject headings and free text words for the concepts 'chest x-ray' and 'lung cancer'. In order to ensure that evidence reflected contemporary radiological technology and practice, only studies published after 1999 were included. The searches were peer reviewed, and updated in December 2018 in all the databases. The full search strategies can be found in supplementary material. The reference lists of included papers were screened. The websites of several organisations (10-24) were manually searched to identify any potentially eligible reports, guidelines and audits.

Inclusion & Exclusion criteria

We considered any study which reported the number of adult patients who had a chest x-ray following a symptomatic presentation to a clinician in the year before diagnosis with lung cancer. The period of one year was selected with reference to estimates of detectable, pre-clinical phase of lung cancer

(mean sojourn time) (25), estimated to be between 5.5 months (26) and 2.2 years (27). Studies where it was unclear if the duration between chest x-ray and diagnosis was less than one year existed were excluded. Studies based on screening populations were excluded. Studies of patients aged under 18 years, other intrathoracic malignancies such as mesothelioma and lymphoma, metastatic lung disease from a non-lung cancer primary tumour and imaging undertaken for staging or diagnostic surveillance for recurrent lung cancer were also excluded. In order to evaluate the diagnostic accuracy of chest x-ray in clinical practice, we excluded studies which examined the proportion of chest x-rays where lesions were 'missed' but identified in retrospect.

Chest x-rays were considered positive if any abnormality considered suspicious for lung cancer was noted at the time of reporting and were considered negative if no features suspicious of lung cancer were noted at the time of reporting. Where the findings of chest x-ray were not reported in a way which could be classified as positive or negative according to this definition, we reported the presence or absence of abnormalities on the chest x-rays.

We did not exclude any studies based on the reference standard used.

Study selection

Title and abstracts of all studies were screened by SB with reference to the inclusion and exclusion criteria. A random 20% of all titles and abstracts were independently screened by AG. As it was anticipated that relevant data in some cases be would reported incidentally, rather than as a primary finding of studies, the reviewers maintained a low threshold for selecting citations for full text review. In the case of disagreements or uncertainty, a third reviewer (RN) was consulted. A full text review of all selected texts was undertaken by SB to determine final eligibility.

Data extraction

Data from included studies was extracted using a form by SB including demographics and presenting symptoms of participants, sensitivity of chest x-ray, sample size, setting (e.g. primary or secondary care) and the reference standard implemented to determine true disease status.

Analysis

The outcome was the sensitivity of chest x-ray for the detection of lung cancer. This was determined by evaluating the stated numbers of patients in each study who presented with symptoms, who had chest x-ray in the year before diagnosis with lung cancer and for whom their chest x-ray had yielded a positive result. 95% confidence intervals for each within-study sensitivity estimate were also calculated. It was intended to undertake meta-analysis if possible. In the event of high between-study heterogeneity or a low quality of eligible studies, we planned to proceed with a descriptive synthesis the studies only. A modified version of the QUADAS-2 tool (28) for diagnostic accuracy studies was used for quality assessment.

Results

The selection of the 21 studies (29-50) included in this review is presented in the PRISMA diagram in Figure 1. Although 987 citations were selected for full text review, 187 citations could not be obtained despite attempts to contact authors by email. The majority of the citations which were not obtained were in non-English publications (n=119, 64.6%), while a substantial proportion (n=90, 48.1%) of these citations reported no clinical data at all in their abstracts, but were selected for full text review due to the comprehensive approach taken by the reviewers.

The most common reason for exclusion (n=739) was that the study did not contain research or data that was pertinent to the study question. This included a large number (n=117) of general texts, such as reviews, correspondence, and educational articles which did not address the study question.
Some citations (n=59) were excluded because the interpretation of the imaging was undertaken retrospectively, when the diagnosis of lung cancer was already known. Seventeen studies were not eligible because patients had been chosen for inclusion on the basis of a chest x-ray that was known to be positive or negative for lung cancer. Four studies were ineligible because they evaluated individual performance at interpreting chest x-rays using films, where the presence or absence of lesions was already known to the study investigators. Other studies were excluded because: the cancers considered were not a primary lung cancer (n=44), they were case reports of a single patient (n=53), the duration between chest x-ray and diagnosis was greater than 1 year or unclear (n=28), they were drawn from screening data (n=22), or patients were under 18 years old (n=2).
Given the high heterogeneity between studies included and their low quality, meta-analysis was not appropriate.

<u>Summary of eligible studies</u>

Twenty-one studies met the inclusion criteria (see Table 1). The number of patients in each study varied notably (range 2-208). Study estimates of sensitivity ranged from 0 to 100%. Most of the studies

were case series. Estimating the diagnostic accuracy of chest x-ray for lung cancer was the primary objective of only one study (42).

Many of the studies only included particular sub-groups of the relevant patient population, such as atypical tumour histology, or specific co-morbidities and symptom presentations. Of those with representative patient populations, only four (40, 42, 43, 49) had a sample size greater than 10.

A population-based observational case series (40) identified all patients in the Danish county of Aarhus who had a diagnosis of lung cancer during a six month period in 2003. The purpose of the study was to explore reasons for diagnostic delay in lung cancer. Of 58 patients who had a chest x-ray arranged from general practice, 46 (79.3%) of these patients had chest x-rays which suggested the possibility of lung cancer including two cases in which infection was identified with a recommendation for repeat imaging after an appropriate interval. The remaining 12 (20.7%) chest x-rays were reported as 'raised no suspicion of lung cancer'.

An English retrospective cohort study (42) examined chest x-ray results of 164 patients from general practices in a Primary Care Trust diagnosed with lung cancer between January 1998 and September 2002 (aged 40 or over). In over three-quarters (n=126, 76.8%), the chest x-ray indicated the possibility of lung cancer, while 38 (23.17%) patients had a 'negative' chest x-ray. Of the 38 'negative' chest x-rays, 21 (12.8%) were categorised as abnormal but not suspicious of malignancy while 17 (10.4%) were reported as 'normal'.

A retrospective case note review of all patients diagnosed with lung cancer in a Spanish centre from January 2001 to September 2006 included 102 patients who had a chest x-ray before diagnosis (43). An 'abnormality' was present on 97 (95.1%) of the patients' chest x-rays; however this could not be considered synonymous with 'sensitivity' as the authors did not indicate which of the abnormalities

were considered to be suspicious for lung cancer when they were reported. The abnormalities were nodules or masses in 53 cases (52.0%), pleural effusions in 16 (15.7%), an enlarged hilum in 16 (15.7%), multiple pulmonary metastasis in 6 (5.9%), a widened mediastinum 4 (3.9%), and an interstitial infiltration in 2 (2.0%).

Finally, a conference abstract reported a retrospective review of chest x-ray reports in a secondary care setting in the Republic of Ireland (49). Of 158 patients, 126 (79.8%) were identified as likely to have a lung malignancy and/or advised to have repeat imaging. A further 23 patients had a chest x-ray in which the authors refer to as 'lesion not identified' (14.6%) and 9 in which an abnormality was identified but no follow up recommended (5.7%).

Quality Assessment

Assessment of quality was undertaken by SB and AG using a modified version of the QUADAS-2 tool (29) with disagreements between reviewers resolved through discussion. Three studies (40, 42, 49) were deemed to have a low risk of bias. A further study (43) was deemed to have a low risk of bias in the selection of patients, however the reporting of chest x-ray result as normal or abnormal, rather than suspicious or not suspicious for lung cancer resulted in limited applicability for this review. The majority of studies (17, 81.0%) were deemed to be have a high risk of bias. In particular, many (14, 66.7%) included particular sub-groups of the relevant patient population, such as atypical tumour histology, or specific co-morbidities and symptom presentations. .

Discussion

Summary

This systematic review identified three studies which reported sensitivity of chest x-ray and which had a low risk of bias.. The sensitivity estimates for these studies were: 79.3% (95% CI: 67.6-91.0%) (41), 76.8% (95% CI: 64.5-84.2%) (43) and 79.8% (95% CI: 72.7-86.8%). (50).

These results suggest that chest x-ray fails to identify lung cancer (at least initially) in over 20% of people who are subsequently diagnosed with lung cancer. All three of these studies were conducted in countries with broadly similar primary care systems (Denmark, England, Republic of Ireland). Two of these studies (40, 42) were derived from primary care settings and, although the remaining study (49) was from a secondary care radiology department, it is likely that many of the chest x-rays performed resulted from primary care referrals.

Strengths and limitations

This review featured a sensitive and comprehensive search of bibliographic databases and grey literature in order to identify published and unpublished sources. This study is highly relevant both to national cancer policy and everyday clinical practice. With approximately 46,700 new diagnoses of lung cancer in the UK per year (2), of which approximately 56% are diagnosed following referral for chest x-ray (7), our findings suggest that false-negative chest x-rays could contribute to a delayed diagnosis for several thousand patients each year.

Diagnostic accuracy was the stated primary outcome of only one study; in most included studies an estimate of sensitivity was estimated from the data reported. These studies were therefore at high risk of bias. Indeed, none conformed to the conventional standards of diagnostic accuracy studies (51). While the best available evidence was selected for analysis, many other eligible studies were of poor quality making meta-analysis inappropriate. In order to identify all relevant evidence, the review included studies from different settings. The different disease prevalence in primary and secondary

care is known to impact on test performance (52) which could not be accounted for in this review. However, the consistency in the sensitivity estimates from the higher quality studies is striking. Due to the large number of citations, selection was peer reviewed in only 20% of cases and data extraction was conducted by one researcher. 187 citations could not be obtained, reflecting the broad search strategy used and the low threshold used for selection for full text review. Only about half of those papers (n=97, 51.2%) contained any study data in their abstracts.

Comparisons with Existing Literature

Several studies have evaluated the performance of chest x-ray by re-examining radiographs in the light of a known lung cancer diagnosis. While such studies were not eligible for this review, that literature provides an important context. Notably, a Dutch retrospective review of radiographs of non-small cell lung cancer cases (n=495) reported that 19% had a nodular lesion which had been 'missed' (53).

It is possible that lung cancers may not have been present when imaging occurred ('interval cancers'). A large screening trial concluded that of those cancers which were not detected on screening chest x-ray but subsequently diagnosed within one year, the lung cancer was not visible, even in retrospect, in 65% of cases (54).

A separate literature has explored the role of 'observer error' in failing to recognise cancers which were evident in retrospect. Inexperience, poor technique in visual scanning of the image, failures in recognising abnormalities and of decision making along with lapses of concentration have all been identified as factors contributing to 'missed' lung cancers on chest x-ray (55, 56).

Other studies have considered the characteristics of lesions which may make them less identifiable. Smaller tumours are identified much less frequently; lesions measuring less than 1cm in diameter are particularly likely to be missed on chest x-ray compared to other modalities such as CT (53).

Location is also important, with missed lung cancers frequently located in the upper lobes (53, 57-60) or obscured by overlying anatomy such as ribs, lung vasculature and heart. Many missed cancers are located in the hilar regions, where the confluence of complex anatomy makes diagnosis particularly challenging (55). The technical quality of the radiograph itself and the positioning of the patient are additional factors that can influence the likelihood of successful detection of lung cancer on chest x-ray (61).

Implications for research and practice

Chest x-ray retains a predominant role in the UK clinical practice and guidance for the diagnosis of lung cancer (62). Most lung cancers are diagnosed following suspicious findings on chest x-ray (7) and increasing the use of chest x-ray in primary care has been associated with diagnosis at an earlier stage and reduced mortality (63). However, this review suggests that chest x-ray may have a false-negative rate of at least 20%. GPs should take limited reassurance from a non-diagnostic chest x-ray and consider additional imaging or referral of those at high risk, or re-imaging in the face of continuing symptoms. If chest x-ray were a novel technology, it is debatable whether the available evidence would be deemed sufficient to support its implementation as a diagnostic test for lung cancer. In order to improve the UK's lung cancer outcomes, diagnostic strategies may necessitate widening access to more definitive modalities, such as CT. While this study has demonstrated a significant false negative rate for chest x-ray it is important to recognise that the benefits of increased rates of CT investigation must be balanced against known harms including over-diagnosis and 'false positives' (64), Future work is required to determine which patients can be reasonably followed up by safety netting following an unremarkable chest x-ray and which patients require further investigation.

Acknowledgements

The authors are extremely grateful to Monica Koo, Marie Bourne, Nazia Ahmed, Sibel Saya and Dorota Karasek for their assistance in translation of non-English studies. Advice regarding the systematic review received from Judy Wright and Natalie King. Tracey Farragher provided additional advice regarding the design of the study. The authors would also like to thank the many authors whom kindly provided additional information in order to determine eligibility of their studies for this review.

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