The role of imaging in the diagnosis of lung cancer in primary care

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The candidate confirms that the work submitted is his own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Jointly authored publications arising from this thesis with contributions made by co-authors

Chapter	Paper	Role of Stephen Bradley	Co-Authors Roles
1: Introduction	Recognising Lung Cancer in Primary Care, Stephen H Bradley, Martyn P T Kennedy, Richard D Neal, Advances in Therapy 36, 19-30 (2019) 10.1007/s12325-018-0843-5	Conceived and authored paper/chapter	Contributed Revisions
2: Diagnostic accuracy of low dose CT versus chest x-ray and sensitivity of chest x-ray for lung cancer in symptomatic people: systematic review	Sensitivity of chest X-ray for detecting lung cancer in people presenting with symptoms: a systematic review, Stephen H Bradley, Sarah Abraham, Matthew EJ Callister, Adam Grice, William T Hamilton, Rocio Rodriguez Lopez, Bethany Shinkins & Richard D Neal, British Journal of General Practice 2019; 69 (689) doi.org/10.3399/bjgp19X70685	Designed and authored protocol, designed search strategy, maintained EndNote library of papers, screened papers, authored first draft of paper, assessment of bias of included papers	Adam Grice-Second screen on proportion of papers and second check on assessment of bias of included papers Sarah Abraham-Undertook grey literature search under supervision of SB Rocio Rodriguez Lopez- Ran literature search All-contributed revisions to paper
Chapter 3: What is the sensitivity of primary care chest x-ray for lung cancer and what are the differences in time to diagnosis and outcomes between patients who have a true positive and those who have a false negative chest x-ray?	Chest X-ray sensitivity and lung cancer outcomes: a retrospective observational study, Stephen H Bradley, Bobby SK Bhartia, Matthew EJ Callister, William T Hamilton, Nathaniel Luke Fielding Hatton, Martyn PT Kennedy, Luke TA Mounce, Bethany Shinkins, Pete Wheatstone & Richard D Neal. British Journal of General Practice 26 July 2021; BJGP.2020.1099 doi.org/10.3399/BJGP.2020.1099	Designed and authored protocol and analysis plan with advice of collaborators. Obtained ethical permissions. Coded all chest x-rays. Undertook statistical analysis. Authored first draft of paper.	Bethany Shinkins, Luke TA Mounce-advice on statistical aspects Matthew EJ Callister-adjudicated on chest x-ray coding when ambiguous. All- contributed revisions to draft of paper
Chapter 4: What is the risk of lung cancer in people who have symptoms but who have who have had a negative chest x-ray result?	Stephen H Bradley, Nathaniel Luke Fielding Hatton, Rehima Aslam, Bobby Bhartia, Matthew EJ Callister, Martyn PT Kennedy, Luke TA Mounce, Bethany Shinkins, William T Hamilton & Richard D Neal. British Journal of General Practice 2021; 71 (705): e280-e286 https://doi.org/10.3399/bjgp20X713993	Authored protocol and analysis plan with advice from co-authors. Supervision of research assistant Luke Hatton, including directing how to undertake statistical analysis on SPSS. Authored first draft of paper.	Luke Hatton- Chest x-ray coding under supervision of Stephen Bradley. Executed statistical analysis under supervision of Stephen Bradley and with advice from Luke Mounce. Luke Mounce – Advice on how to undertake statistical analysis

			Bethany Shinkins- Advice on statistical analysis and interpretation Rehima Aslam- Transcribed SRCXR service forms into database All – contributed revisions
Chapter 5: What are the associations between general practice characteristics and chest x-ray rate?	Associations between general practice characteristics and chest x-ray rate?, Stephen H Bradley, Matthew Barclay, Benjamin Cornwell, Gary A Abel, Matthew EJ Callister, Mayam Gomez-Cano, Thomas Round, Bethany Shinkins, Richard D. Neal. British Journal of General Practice 2021; https://doi.org/10.3399/BJGP.2021.0232	Protocol and analysis plan written by Stephen Bradley with advice from co-authors. Data extraction. Database management and statistical analysis. Authored first draft of paper.	Benjamin Cornwell-Contributed to data extraction Mayam Gomez-Cano – Contributed data on GP survey Matthew Barclay, Gary Abel and Bethany Shinkins-Advice on statistical analysis and interpretation All- contributed revisions

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Abstract

Background

Lung cancer is the leading cause of cancer death worldwide. The UK relies more heavily upon chest x-ray than many other high income countries. Little is known about the performance of the test, the risk of cancer following negative test, consequences of 'false negative' results and the factors that affect how frequently chest x-ray is used.

Aims

1. Determine sensitivity and specificity of chest x-ray.
2. Determine if there are differences in outcomes between patients with 'true positive' versus 'false negative' chest x-rays.
3. Determine the risk of lung cancer following a negative chest x-ray with respect to symptoms.
4. Quantify the volume of chest x-rays undertaken by English general practices and understand the extent to which variations in chest x-ray frequency are due to differences in patient populations and the practices themselves.

Methods

1. Systematic review on sensitivity of chest x-ray
2. Observational study to determine sensitivity and compare stage and survival between those with 'true positive' versus 'false negative' results.
3. Cohort study to determine chest x-ray specificity and lung cancer risk following negative chest x-ray.
4. Retrospective study to quantify general practices' chest x-rays with respect to characteristics of their patient populations and the practices.

Results

1. Sensitivity was 77-80% (systematic review) and 82% (observational study). Specificity was 90%.
2. 'False negative' chest x-rays were not associated with adverse outcomes, although given the retrospective methodology this cannot be excluded.
3. Lung cancer risk following negative chest x-ray was <1% for all symptoms except haemoptysis (3%).
4. There was substantial variation in chest x-ray utilisation (median 34/1000 patients, IQR 26-43), with 18% of variance accounted for by recorded characteristics.

Conclusions

Chest x-ray does not identify ~20% of lung cancers but it continues to have a useful role. The substantial variation in rates of investigation suggest that it may be underutilised in many practices.

Contents

List of tables

List of Illustrations

Abbreviations

CI	Confidence Interval
CXR	Chest X-Ray
DID	Diagnostic Imaging Dataset
EU	European Union
FBC	Full Blood Count
GP	General Practitioner
GPMS	General Practice Medical Services
ICD	International Classification of Diseases
ICBP	International Cancer Benchmarking Partnership
IMD	Index of Multiple Deprivation
IQR	Interquartile Range
LTHT	Leeds Teaching Hospitals NHS Trust
MIRR	Median Incidence Rate Ratio
mSv	Milisevert
NELSON	Nederlands–Leuvens Longkanker Screenings Onderzoek
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NLST	National Lung Cancer Screening Trial
NPV	Negative Predictive Value
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QOF	Quality Outcomes Framework
SD	Standard Deviation
SRCXR	Self Request Chest X-Ray
UK	United Kingdom
USC	Urgent Suspected Cancer
TWW	Two Week Wait

1. Introduction

1.1 Overview

- Lung cancer epidemiology and policy
- Symptoms and signs
- Investigation of suspected lung cancer
- Screening
- Methodological challenges
- Outstanding questions and rationale for thesis
- Thesis objectives
- Thesis overview

1.2 Lung cancer epidemiology and policy

Excluding non-melanoma skin cancers, lung cancer is the both the commonest type of cancer world-wide and the single largest cause of cancer mortality.(1) In England, lung cancer accounts for 13% of all cancers, following only breast and prostate cancer in terms of incidence,(2) but is the leading cause of cancer deaths.(3) Lung cancer is the leading cause of cancer deaths in those aged under 75 (premature mortality) in England.(4) Due to the higher prevalence of smoking in more deprived populations, respiratory cancers rank second only to cardiovascular disease in causes of premature mortality attributable to socioeconomic inequality.(5)

Improvements in early diagnosis and treatment have led to improved outcomes for many cancers. Between 1971 and 2011, age standardised five year survival from breast cancer, prostate cancer and colorectal cancer in the England and Wales have increased from 53% to 87%,(6) 37% to 85%,(7) and 24% to 59% respectively.(8) In contrast, in the same period the age standardised five year survival for lung cancer only increased from 5% to 10%, increasing to around 15% by 2014.(9, 10) Despite longstanding ambitions to hasten diagnosis,(11) the proportion of those diagnosed with early stage lung cancer in the UK (and survival) has been considered disappointing, particularly in comparison to other high income economies. A comparison of cancer survival by the International Cancer Benchmarking Partnership (ICBP) in Australia, Canada, the Republic of Ireland, New Zealand and the UK estimated that the UK's five year survival for lung cancer was 14·7% (95% CI 14.5% to 15.0%) between 2010 and 2014, the lowest of all countries in the study.(10) Although stage of diagnosis was not reported in this study, in a previous ICBP study for the period 2004-07, higher proportions of late stage disease were reported for the UK than comparator countries.(12)

Several possible explanations have been proposed for the UK's adverse survival and stage distribution of lung cancer compared to other settings. Populations in the UK are likely to have a greater burden of co-morbidities than many of their counterparts in other Western European countries.(13) A comparison between prospective patient cohorts in Teesside in England and Varese in Italy found that the English patients were more likely to have smoked, had more co-morbidities and poorer performance status than those in Italy, although each cohort was not necessarily representative of the respective countries.(14) A population survey based in the countries represented in the ICBP found that the UK had the second highest proportion of those who reported they would wait over four weeks before seeking help from a clinician. (15) Other research has demonstrated that GPs in the UK tend to organise investigations less readily their counterparts in other affluent countries,(16, 17) which could in turn be related to the relative lack of capacity to undertake imaging such as computed tomography but may also be related to the 'gatekeeping' function GPs have in the UK.(18, 19) Obtaining comparable data on treatments between jurisdictions is challenging, but differences in uptake of therapies could account for some of differences in survival observed for patients with the same stage of disease.(12, 20) Unwarranted geographical and socio-economic variations in utilisation of optimal treatments for lung cancer could also be a contributory factor given the extent to which these disparities affect the UK.(21-24) Finally, it is possible that disparities in cancer outcomes between settings may be exaggerated by the varying assiduity and consistency with which cancer statistics are recorded in different states,(25) although the countries studied as part of ICBP were selected for inclusion because their systems of recording cancer diagnoses and outcomes were deemed to be broadly comparable.(26)

Recent cancer policy in England continues to prioritise earlier diagnosis of cancer with the aim of diagnosis of 75% of cancers at stage I or II by 2028.(27) Given that lung cancer is both among the most common cancers and also has one of the most adverse stage distributions at diagnosis,(28) improving earlier lung cancer diagnosis is likely to be crucial if this target is to be met.

Advances in the systemic treatment of advanced lung cancer with the use of tyrosine kinase inhibitors and immunotherapy has led to significant survival benefits for some patients.(29-31) The relatively infrequent expression of targets for these treatments and poor prognosis associated with advanced lung cancer have prevented these advances significantly impacting on overall survival so far but since these therapies entered mainstream practice only very recently, positive impacts on outcomes may become evident in the near future. The introduction of stereotactic radiotherapy has increased the radiotherapy treatment rate for early stage lung cancer without reducing surgical resection rates.(32) Lung cancer

outcomes differ according to stage at diagnosis, with one-year survival of 81.7% for stage I and 15.5% for stage IV lung cancer in England and Wales (Figure 1.1).(33) Therefore, despite the substantial promise offered by novel therapies, achieving earlier diagnosis is likely to remain a crucial strategy in improving outcomes.

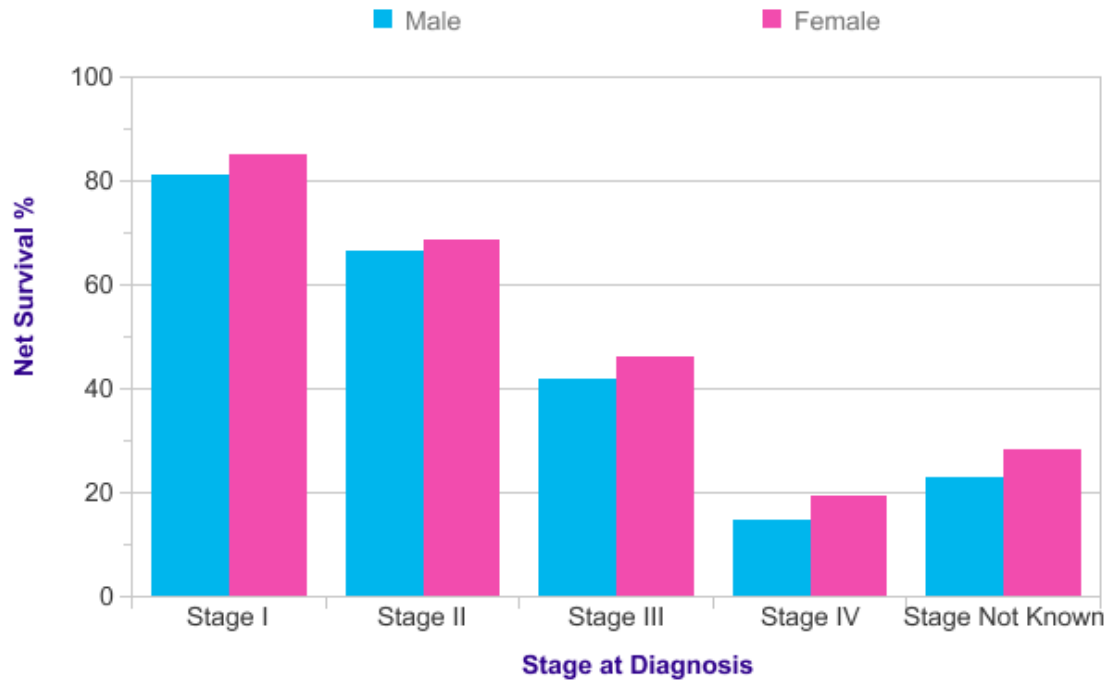


Figure 1.1 One-year net survival (%) by stage, adults aged 15-99. Statistics presented by Cancer Research UK(34)

Most patients with lung cancer first present to their GP.(35-38) Lung cancer often presents with symptoms that are very commonly encountered in primary care, making early diagnosis challenging. A large UK based population study demonstrated that although cough is one of the most frequent symptoms of lung cancer, only 0.2% of patients who had a cough for three weeks were ultimately diagnosed with lung cancer.(39) The UK's National Cancer Diagnosis Audit reported that the median primary care interval (time from first presentation to GP referral to specialist) for lung cancer was 14 days, the second highest of 15 cancers reported. Prolonged primary care intervals of 60 and 90 days were experienced by 17.9% and 10.8% of patients respectively.(40) A third of patients diagnosed with lung cancer have attended their GP with symptoms attributable to their cancer three or more times before diagnosis.(41) Unfortunately, most lung cancers are still diagnosed at an advanced

stage(42) and almost a third of lung cancers were diagnosed following emergency presentations in 2017.(43)

Despite the remaining challenges there have been several positive developments with respect to lung cancer in recent years in England and the UK. As mentioned above, while emergency presentations remain common, the proportion of patients diagnosed via this route has reduced from 39% to 32% between 2006 and 2017.(43) Proportions of patients receiving surgical resection have increased(44) which may be contributing to recent improvements in five year survival(10, 34) while increases in the proportions of patients receiving early stage diagnosis may be related to higher rates of imaging (prior to the pandemic).(45, 46) In recent years the UK has also achieved reductions in rates of tobacco smoking which should result in reductions in the prevalence of lung cancer in coming years and decades.(47)

1.3 Symptoms and Signs

The referral recommendations from the National Institute for Health and Care Excellence (NICE) are outlined in Figure 1.2.(48) This guidance was updated in 2015 with new recommendations that GPs refer all patients over age 40 years with unexplained haemoptysis and that consideration be given to chest x-ray for patients with thrombocytosis and/or appetite loss.

Refer people using a suspected cancer pathway referral (for appointment within 2 weeks) for lung cancer if they:

- have chest x-ray findings that suggest lung cancer **or**
- are aged 40 and over with unexplained haemoptysis

Offer an urgent chest x-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over if they have 2 or more of the following unexplained symptoms, **or** if they have ever smoked and have 1 or more of the following unexplained symptoms:

- cough
- fatigue
- shortness of breath
- chest pain
- weight loss
- appetite loss

Consider an urgent chest x-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over with any of the following:

- persistent or recurrent chest infection
- finger clubbing
- supraclavicular lymphadenopathy or persistent cervical lymphadenopathy
- chest signs consistent with lung cancer
- thrombocytosis

Figure 1.2 Recommendations from NICE guideline [NG12] suspected cancer: recognition and referral. (48)

The most common symptoms associated with lung cancer tend to be both common in benign presentations in the community and particularly amongst smokers. Therefore, the discriminative utility of most of these symptoms in isolation is low. Positive predictive values (PPVs) for different symptoms of lung cancer, both alone and in combination have been determined from a case-control study and are presented in Figure 1.2. Importantly PPVs for each symptom are higher in smokers and those over the age of 70 years.(49) With the highest PPV of 2.4-7.5%,(50) unexplained haemoptysis almost always warrants further investigation. Haemoptysis, however, is a feature of a minority of lung cancers cases (51, 52) and is becoming more unusual as a presenting symptom. In a cohort of patients diagnosed with lung cancer who presented with symptoms in the year before diagnosis, in

the period 2000-17 (n=6781), 15% (n=1043) presented with haemoptysis for the entire period but in the final year of the cohort only 2% presented with that symptom.(53) This trend may be because we are succeeding in diagnosing lung cancer earlier but it means that relying upon this 'red flag' symptom is not an effective strategy for lung cancer detection since its absence does not exclude the presence of lung cancer.

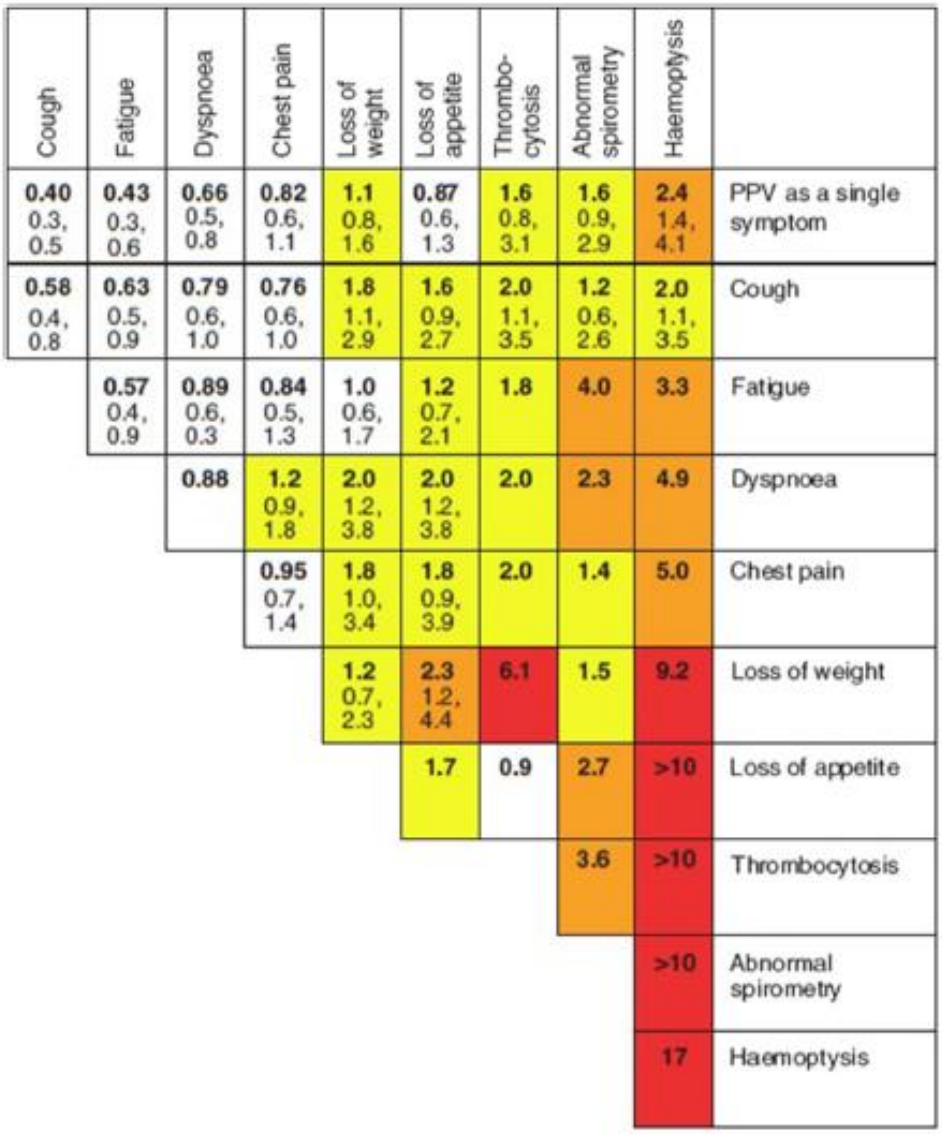
While guidelines have streamlined access to diagnosis for some, concern has been raised that this approach might prioritise patients with classical presentations, such as haemoptysis, at the expense of those with symptoms which reflect less advanced disease and would therefore have the most to gain from early diagnosis.(35) In fact, in 2017 only 26.9% of lung cancer cases in England were diagnosed through the country's 'two week wait' urgent referral pathway.(43) In many cases, appropriately urgent action may have occurred outside the two week wait pathway, for example through automatic referral following a chest x-ray or through routine surveillance for pulmonary nodules. Although declining as a proportion, diagnoses following emergency presentations remained the commonest route of diagnosis at 31.5%.(43) Such diagnoses are associated with the poorest outcomes, although the reasons for this are likely to be complex and probably include the poorer performance status, more advanced disease, greater levels of socioeconomic deprivation of patients who present in this way and because of the complications of the cancer which may have led patients to present as an emergency.(54, 55)

In order to reduce the time intervals between patients experiencing symptoms and presenting to their GP significant efforts have been made to improve public awareness of the symptoms of cancer. Evaluations of England's 'Be Clear on Cancer' campaign have suggested the programme contributed to encouraging increases in presentations to primary care with prolonged cough and an increase in the proportions diagnosed with early stage lung cancer.(45, 56) A longer term assessment, however, has suggested that such campaigns require sustained commitment in order to maximise their impact.(57) In Australia, a cluster randomised trial of a complex intervention which included a public awareness campaign showed no reduction in the interval between symptoms and diagnosis,(58) although the authors speculate that the intervention may not have achieved the breadth of media coverage required to show an effect.

A risk assessment tool has been developed which can generate PPVs for one symptom or two symptoms in combination stratified for smokers and non-smokers(59). Assessment of this tool, reproduced in Figure 1.3, has shown that, when used, it is associated with

increased investigations such as chest x-ray, urgent referrals and lung cancer diagnoses.(60) Two algorithms have also been created which incorporate symptoms as well as other risk factors to generate risk scores.(39, 61)

Positive examination findings are usually only associated with advanced disease, so examination findings may be unremarkable in those who present to primary care. Since an individual GP will, on average, encounter only one new case of lung cancer each year(62) the prospects of identifying lung cancer through rare signs such as hypertrophic pulmonary osteoarthropathy and Horner's syndrome are exceedingly unlikely. In clinical practice, patient and physician intuition of the possibility of serious underlying disease is probably much more important.(63) Given that the 'risk threshold' NICE has adopted for urgent referral for suspected cancer is 3%,(48) GPs are encouraged to refer patients at relatively low levels of risk.(64)



Cough	Fatigue	Dyspnoea	Chest pain	Loss of weight	Loss of appetite	Thrombo-cytosis	Abnormal spirometry	Haemoptysis	
0.40 0.3, 0.5	**0.43** 0.3, 0.6	**0.66** 0.5, 0.8	**0.82** 0.6, 1.1	**1.1** 0.8, 1.6	**0.87** 0.6, 1.3	**1.6** 0.8, 3.1	**1.6** 0.9, 2.9	**2.4** 1.4, 4.1	PPV as a single symptom
0.58 0.4, 0.8	**0.63** 0.5, 0.9	**0.79** 0.6, 1.0	**0.76** 0.6, 1.0	**1.8** 1.1, 2.9	**1.6** 0.9, 2.7	**2.0** 1.1, 3.5	**1.2** 0.6, 2.6	**2.0** 1.1, 3.5	Cough
	0.57 0.4, 0.9	**0.89** 0.6, 0.3	**0.84** 0.5, 1.3	**1.0** 0.6, 1.7	**1.2** 0.7, 2.1	**1.8**	**4.0**	**3.3**	Fatigue
		0.88	**1.2** 0.9, 1.8	**2.0** 1.2, 3.8	**2.0** 1.2, 3.8	**2.0**	**2.3**	**4.9**	Dyspnoea
			0.95 0.7, 1.4	**1.8** 1.0, 3.4	**1.8** 0.9, 3.9	**2.0**	**1.4**	**5.0**	Chest pain
				1.2 0.7, 2.3	**2.3** 1.2, 4.4	**6.1**	**1.5**	**9.2**	Loss of weight
					1.7	**0.9**	**2.7**	**>10**	Loss of appetite
							3.6	**>10**	Thrombocytosis
								>10	Abnormal spirometry
								17	Haemoptysis

Figure 1.3 Positive predictive values (%) for lung cancer for individual risk markers, and for pairs of risk markers in combination.
PPVs were calculated against a background risk of 0.18%). (1) The top row (bold) gives the PPV for an individual feature. The cells along the diagonal relate to the PPV when the same feature has been reported twice. Other cells show the PPV when a patient has two different features. (2) The top figure in each cell is the PPV. It has only been calculated when a minimum of ten cases had the feature or combination of features. The two other figures are the 95% confidence intervals for the PPV. These have not been calculated when any cell in the 2 x 2 table was below 10.(59)

1.4 Investigation of possible lung cancer

The first line investigation of suspected lung cancer in the UK remains chest x-ray. Current NICE guidance for the investigation of lung cancer in primary care suggests an immediate

referral to secondary care only for patients with haemoptysis, with other symptoms to be investigated first with CXR. Since haemoptysis accounts for only a very small minority of lung cancer presentations(51-53) adequate performance of CXR is therefore crucial for the success of the entire pathway in detecting lung cancer following patient presentation to primary care. In other high income countries in Western Europe, North America and Australia more extensive use is made of computed tomography, although no comparative data is available on the frequency of different imaging modalities for detection of symptomatic lung cancer specifically.(18, 65) Higher rates of computed tomography use in the United States have been identified as a concern given the resulting radiation exposure.(66) Low dose computed tomography (LDCT) uses an estimated radiation dose of 2 milliSieverts (mSv), compared to 7mSv from conventional computed tomography.(67) Increased availability of LDCT in the future could help reduce the total radiation exposure of computed tomography investigations. Although sensitivity and specificity of LDCT have been determined in the screening context for asymptomatic patients(68) the performance characteristics of the investigation for symptomatic patients are much less well understood.

Chest x-ray has the advantages of being cheap and accessible,(63) with a low radiation dose of 0.02mSv, equivalent to 3 days of natural background radiation.(69) Unfortunately, chest x-ray has a significant false negative rate, with a sensitivity of approximately 75-80%, although only a small number of studies have been conducted to determine sensitivity of the modality in the symptomatic context.(70-73) Sensitivity of chest x-ray is lower still when used in screening,(74) possibly due to a lower prevalence of cancer in that setting and possibly also smaller lesions associated with asymptomatic disease.(75) One study has reported that 10% of the CXRs of lung cancer patients were initially reported as normal, with a further 13% which were reported as abnormal but with no suspicion of lung cancer.(70) Due to concerns over ‘missed’ lung cancers on chest x-ray GPs have been advised not to take complete reassurance from a ‘negative’ chest x-ray in patients whom they consider to be at high risk of having lung cancer.(76) However given the dearth of evidence on chest x-ray in symptomatic patients or guidelines on what actions to take following a negative chest x-ray, this situation is likely to be challenging for many GPs.

Despite its limitations, evidence suggests that strategies to increase chest x-ray uptake can yield improvements in referral rates and possibly improve early detection of lung cancer.(45, 77) Traditional guidance that all patients with radiologically demonstrated community acquired pneumonia should have a repeat chest x-ray after six weeks to confirm resolution has been refined to include only those at highest risk of malignancy, such as smokers and those aged over 50 years.(78) Evidence from a population-based cohort study provides

some reassurance that such an approach is reasonable, given that only one in 57 patients who did have lung cancer one year following their pneumonia was under the age of 50.(79)

Computed tomography scans of the chest are much more sensitive than chest x-ray, although the majority of available evidence relates to screening contexts, rather than the investigation of symptomatic patients. In the National Lung Screening Trial,(NLST) low dose CT yielded sensitivity and specificity of 93.8% and 73.4% compared to 73.5% and 91.3% for chest x-ray, respectively.(80) In current clinical practice conventional computed tomography continues to be used much more frequently than LDCT for symptomatic investigations. NICE recommends contrast-enhanced computed tomography thorax including also the liver and adrenal glands.(81) This is usually arranged from secondary care following an urgent referral from a GP for suspected lung cancer. In the UK the National Optimal Lung Pathway(82) has set out standards for lung cancer service providers to improve the quality and efficiency of pathways for patients with suspected lung cancer, including the timing of investigations. This pathway aims to reduce the time between referral, computed tomography scan and review by respiratory physician with an interest in lung cancer.

Widening access to urgent computed tomography scans for GPs (sometimes termed ‘direct access’ investigations) has been proposed as a means to improve early stage diagnosis.(83) In some regions of the UK direct access computed tomography has been made available to GPs, although this reflects the development of local initiatives rather than national health policy.(84, 85) Denmark, which has a similar ‘gatekeeper’ role for GPs, until recently also relied upon chest x-ray for investigation of suspected lung cancer but has instituted imaging with LDCT as the first line test.(86) The policy followed a cluster-randomised controlled trial in which GPs were given access to LDCT to investigate possible lung cancer, although this was not found to have led to a statistically significant decrease to the time to diagnosis in the trial. Following adjustment for non-engagement in the intervention group it was found that patients in the control group were at a higher risk of experiencing a long diagnostic interval.(87) (88) The relatively low level of engagement, which reached only around half of eligible GPs, might suggest that achieving uptake of direct access investigations requires a broader shift in practice rather than simply permitting their use. Patients with haemoptysis have also routinely been investigated with bronchoscopy to exclude lung cancer. Diagnostic evaluations of computed tomography have suggested that bronchoscopy can be omitted in most cases if malignancy is not identified on computed tomography.(89, 90)

As new methods and technology are developed to reduce the radiation dose associated with computed tomography, this modality may well become increasingly favoured over chest x-ray as a first line investigation for lung cancer in coming years.(91, 92) In the UK, workforce

shortages in radiology seem likely to preclude a wholesale transition to computed tomography in the immediate future.(93) In addition, increased utilisation of computed tomgoraphy may result in harms from incidental findings and detection of benign lesions and disease which would not have caused symptoms within a patient's lifetime (overdiagnosis) but which require further investigations or which may cause patients inconvenience and distress, once detected. (94, 95). Digital Tomosynthesis may offer some improved diagnostic performance over chest x-ray while producing images which are less labour intensive to interpret than computed tomography and may also be less likely to identify incidental findings and lesions which require follow up before they are deemed not to be concerning.(96) Few centres in the UK currently have digital tomosynthesis and its performance in diagnosis of lung cancer in symptomatic patients has not yet been established.

1.5 Screening

The United States Prostate, Lung, Colorectal and Ovarian screening trial has provided the largest and most conclusive body of evidence that screening asymptomatic populations with CXR does not reduce lung cancer mortality.(97) The NLST trial demonstrated a 20% (95% CI 7% to 27%) reduction in lung cancer mortality with annual LDCT in an asymptomatic high risk population. The trial also demonstrated an all-cause mortality benefit of 7% (95% CI 1% to 14%). NLST remains the only screening trial which has shown reduced all-cause mortality.(98) The United States Preventative Task Force has since recommended annual screening with LDCT for those aged 55-80 who have a 30 pack-year smoking history and are current smokers or have smoked within the last 15 years.(99) Uptake of screening in the United States, however, remains low.(100, 101) This may be due to the lack of a fully co-ordinated national approach.(102) The European Union position statement on lung cancer screening set out specific actions that were required before the widespread implementation of lung cancer screening.(103)

The Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) study was published in February 2020 and is the only trial of LDCT screening aside from NLST which was adequately powered to demonstrate a lung cancer mortality benefit.(104) The findings were broadly comparable to NLST, despite the differing comparators (NLST used chest x-ray as a control), with a relative reduction in lung cancer mortality of 24% at 10 years of follow up (95% CI 6 to 39%) for men.(105). 92-133 individuals needed to be screened per round to prevent one lung cancer death.(106) There was a greater reduction in mortality in

the screened female population, but this cohort was smaller and this difference did not reach statistical significance.

The UK National Screening Committee does not recommend lung cancer screening but is currently reviewing this decision following the publication of the NELSON trial.(107) In England, lung cancer LDCT screening 'pilots' have been established in several localities targeting high risk populations (108, 109) with a commitment to expand the schemes under the NHS long term plan.(27)

Potential harms of LDCT screening must be weighed against any potential benefits. These include increased exposure to ionised radiation(110) invasive investigation and follow up for benign changes and overdiagnosis of cancers which if left undiscovered would not have affected patients.(111) (112) (113, 114) Overdiagnosis in NLST has been estimated at 3%.(115) Unfortunately, evidence from the US suggests that in discussing lung cancer screening, clinicians' communication of the possible harms is very limited.(116) These harms may be reduced by targeting screening programmes on the population at highest risk of lung cancer.

Analysis of the Surveillance, Epidemiology and End Results database has shown that only 26.7% of patients with lung cancer in the United States would have been eligible for LDCT screening by NLST criteria.(117) The use of composite risk prediction tools, such as The Liverpool Lung Project(118) or $PLCO_{M2012}$ models,(119) may better identify the high risk population and increase the proportion of lung cancers that may be detected by screening. Using current risk stratification approaches, significant proportion of patients who go on to develop lung cancer will not have been eligible for LDCT screening.(120) Of those who are eligible, some will choose not to undergo screening and the possibility remains of developing lung cancer between annual LDCT screening (interval cancers).

Lung cancer screening with LDCT remains controversial and the balance of benefits against harms and uncertainties appears to be finely balanced.(121) While lung cancer screening may have a role in improving outcomes, even if it is widely instituted it is likely that the majority of patients with lung cancer will continue to be diagnosed following presentation with symptoms to primary care since those who are eligible for screening comprise only a minority of the patients who develop lung cancer.(120)

1.6 Methodological challenges

While the strong association between improved survival for earlier stage lung cancers means there is a persuasive case for promoting earlier detection in order to improve outcomes it is important to acknowledge biases that can lead to overestimation of these benefits. As mentioned above, investigations may lead to overdiagnosis, whereby a diagnosis of cancer is made which would never have resulted in a symptomatic presentation if the cancer had remained undiagnosed. Length time bias is particularly a feature of screening interventions and refers to the tendency of asymptomatic detection to uncover cancers which are more indolent and with a better prognosis than cancers that would have presented symptomatically.(122) Early detection of cancer can also convey a misleading impression that survival has been improved by lengthening the duration between the time at which it is known that a cancer is present and the time at which an outcome such as death occurs. Lengthening of this 'lead time' may not in itself alter the eventual outcome and indeed lengthening the period during which a patient knows that they have cancer may actually impair their quality of life.(122)

Such biases mean that there are challenges in interpreting evidence on cancer detection, particularly observational data whereas evidence from studies such as well conducted randomised controlled trials facilitates a comparison of benefits and harms between those who do and do not receive particular investigations. However, because of the relatively low prevalence of the disease of interest, even where interventions are restricted to 'high risk' populations, very large numbers of participants would be required.(123) When interpreting observational data, examining differences between those who did and did not receive investigations, or those who did or did not receive diagnoses following these investigations it must be remembered that there are likely to be important differences between these populations aside from the intervention or outcome of interest. For example, if one were to compare patients who had received a test versus those who had not, the former group would already be more likely to have pathology since they had been selected for a test.(124) Similarly comparing survival or stage at diagnosis for those who had accurate test results versus those whose results did not correspond to the true diagnosis may also be problematic since the likelihood that a test is positive might well be independently associated with the speed of disease progression, as smaller or slower growing cancers could be less detectable.

These biases limit the inferences that can be reliably drawn from observational clinical data but the availability of data that is routinely collected by health services compared to the barriers in generating experimental data from randomised controlled trials means that

exploration of such data is often warranted, even if only to generate hypotheses or to demonstrate that further, more definitive experimental research is required.

1.7 Outstanding questions and rationale for thesis

Remarkably little evidence exists regarding the performance of chest x-ray, or computed tomography, as a test for lung cancer amongst symptomatic patients. Prior to this doctoral research, no systematic reviews had been performed on either modality in symptomatic patients and studies that have been performed in screening populations cannot be extrapolated to symptomatic populations.(74, 75) Reflecting the predominant role of the modality in the diagnosis of lung cancer in UK primary care, this thesis focusses on the performance of chest x-ray.

It may be questioned whether the UK's reliance on chest x-ray for lung cancer diagnosis is anachronistic(125, 126) and whether greater use of computed tomography should be pursued instead. Accurately determining whether such a transition would be warranted is far from straightforward and would require reference to not only the accuracy of both chest x-ray and computed tomography in the context of symptomatic primary care patients, but also costs and harms such as incidental findings and overdiagnosis.(95) Current health economic models are based on assumptions, including expert opinion, regarding the natural history of lung cancer and limited data on the healthcare resources used in the course of diagnosis.(127)

The purpose of this thesis is to assess the performance of imaging, as currently employed and mandated by guidelines in UK general practice. While the thesis will not determine whether alternative imaging strategies should be employed, the resulting findings on diagnostic accuracy and frequency and variation of investigations with chest x-ray and the possible consequences of x-ray results on patient outcomes may well inform assessments of this question.

1.8 Thesis objectives

The purpose of this thesis is to assess the diagnostic performance of chest x-ray for the detection of lung cancer in primary care, to understand how different chest x-ray results may affect patient outcomes and to determine how utilisation of chest x-ray varies between practices.

The specific objectives of the thesis are:

1. To determine the sensitivity and specificity of chest x-ray for the detection of lung cancer in symptomatic patients in primary care.

2. To determine the risk of a diagnosis of lung cancer following a negative chest x-ray with respect to different symptoms.

3. To determine if there are differences in outcomes between patients diagnosed with lung cancer who had a chest x-ray which identified their lung cancer and those who had a chest x-ray which did not identify their lung cancer.

4. To quantify the volume of chest x-rays undertaken by English general practices and to determine the extent to which variation in numbers of these investigations are due to differences in patient populations and the practices themselves.

1.9 Thesis overview

A brief overview of each chapter is presented below:

Chapter 2: Diagnostic accuracy of LDCT versus chest x-ray and sensitivity of chest x-ray for lung cancer in symptomatic people

A systematic review summarising existing sensitivity of chest x-ray and LDCT for lung cancer, excluding data from screening studies.

Chapter 3: What is the sensitivity of primary care chest x-ray for lung cancer and what are the differences in time to diagnosis and outcomes between patients who have a true positive and those who have a false negative chest x-ray?

An observational study using routinely collected data from Leeds Teaching Hospitals Trust to estimate the sensitivity of general practice requested chest x-ray for lung cancer, to outline the volume of chest x-rays performed by general practice in the year prior to diagnosis and to compare time to diagnosis, survival and stage at diagnosis between patients who had a 'true positive' chest x-ray versus those who had a 'false negative' chest x-ray.

Chapter 4: What is the risk of lung cancer in people who have symptoms but who have who have had a negative chest x-ray result?

A retrospective cohort study using data from a population who attended a 'self request' chest x-ray service because they had symptoms, to estimate the sensitivity and specificity of chest x-ray for lung cancer and also the risk of lung cancer following a negative chest x-ray for particular symptoms.

Chapter 5: Associations between general practice characteristics with investigation using chest x-ray

An observational study examining the volume of chest x-rays performed by general practices in England and the extent to which differences are attributable to characteristics of patient populations and general practices themselves.

Chapter 6: Conclusions

A summary of the findings of the studies included in these thesis, how these results should inform clinical practice in primary care along with policy more broadly and recommendations for further research.

2. Diagnostic accuracy of LDCT versus chest x-ray and sensitivity of chest x-ray for lung cancer in symptomatic patients: systematic review

2.1 Overview

- Research objectives:
    - What is the diagnostic accuracy of LDCT compared with chest x-ray for the detection of lung cancer in symptomatic patients
    - What is the sensitivity of chest x-ray for the detection of lung cancer in symptomatic patients?
- Background: LDCT has been proposed as an alternative first line investigation to chest x-ray for the detection of lung cancer, however no systematic review evidence exists regarding the performance of LDCT compared with chest x-ray. While chest x-ray is currently the first line investigation for suspected lung cancer in the UK no systematic review evidence exists as to the accuracy of chest x-ray for the detection of lung cancer.
- Methods: Two systematic reviews were conducted. The first review examined the sensitivity of chest x-ray for the detection of symptomatic lung cancer while the second review included studies which compared the diagnostic accuracy of LDCT and chest x-ray for the detection of symptomatic lung cancer.
- Results: 21 studies met the eligibility criteria for the systematic review examining the sensitivity of chest x-ray for symptomatic lung cancer. However, only one study was identified for which determining diagnostic performance of chest x-ray was a primary objective and almost all included studies were at high risk of bias. Several were drawn from non-generalisable patient populations, for example with non-typical presentations and/or histology or co-morbidity. Only three studies were assessed as being at low risk of bias, these yielded sensitivities of chest x-ray for lung cancer of 79.3% (95% CI 67.6% to 91.0%), 76.8% (95% CI 69.5% to 84.2%) and 79.8% (95% CI 72.7% to 86.8%). No studies were identified which compared the diagnostic accuracy of LDCT versus chest x-ray for the symptomatic detection of lung cancer.
- Conclusion: No published evidence was identified on the comparative diagnostic accuracy of low-dose CT compared to chest x-ray for the detection of symptomatic lung cancer. Although there is a paucity of high quality evidence relating to the

sensitivity of chest x-ray for lung cancer, the highest quality studies suggested that chest x-ray has an approximately 77-80% sensitivity for lung cancer.

2.2 Introduction

2.2.1 Chest x-ray

As discussed in chapter one chest x-ray remains the first-line investigation for lung cancer from primary care in the United Kingdom. This is reflected in the current NICE lung cancer guideline (81) in which GPs are advised to first evaluate all patients, aside from those aged over 40 and who have unexplained haemoptysis, with chest x-ray and to refer those who have a chest x-ray suspicious of malignancy via the two week wait pathway. While the guideline suggests that an immediate two week wait referral rather than initial assessment with chest x-ray is warranted in those aged over 40 with unexplained haemoptysis, data which precedes the guideline suggests that only a minority of patients diagnosed with lung cancer present with this symptom.(51) NICE guideline 12 - suspected cancer: recognition and referral,(48) advocates direct access computed tomography for GPs for suspected intra-abdominal cancers but not for lung cancer.

2.2.2 Low-dose CT

The radiation exposure associated with conventional computed tomography has provoked concerns of promoting malignancy.(66, 128, 129) Although radiation doses vary depending on the equipment and protocols used, LDCT delivers a much reduced radiation dose, estimated at around 2 millisieverts (mSv) compared to 7 mSv of conventional computed tomography for a chest study.(67) The radiation dose of chest x-ray is 0.02 mSv.(130)

LDCT has been evaluated and deemed to be a modality with satisfactory performance compared to conventional computed tomography in the evaluation of suspect lung cancer (131). Although the use of LDCT in detecting lung cancer is relatively well established in screening contexts,(132-138) it is rarely used in the UK for the evaluation of possible symptomatic presentations of lung cancer compared to chest x-ray and conventional computed tomography protocols.

2.2.3 Rationale for studies

The role of chest x-ray in the diagnosis of lung cancer is extremely well established and in the UK chest x-ray remains the first line investigation for suspected lung cancer from primary care. However, chest x-ray is widely understood to be less sensitive than computed

tomography in identifying lung cancer (139) leading to calls for GPs to have access to computed tomography.(83, 126, 140) In many jurisdictions, computed tomography is used more extensively than in the UK. For example, LDCT has been adopted in Denmark for the investigation of symptomatic lung cancer.(86) While individual studies have been published, no systematic reviews have been performed to determine the sensitivity of chest x-ray alone for lung cancer in symptomatic patients. There have also been no systematic reviews to compare the diagnostic accuracy of LDCT to chest x-ray for the diagnosis of lung cancer in non-screening settings.

2.3 Prospero Registration

The final protocol for this study was registered with the PROSPERO International Register of Systematic Reviews on 12th March 2018.(141)

2.4 Objectives

1. To systematically identify and review studies where patients with a diagnosis of lung cancer were previously investigated (within a year) using chest x-ray as a result of a symptomatic presentation.
2. To systematically identify and review studies that compare the diagnostic accuracy of chest x-ray and LDCT for the detection of lung cancer in symptomatic patients.

2.5 Study Questions

1. What proportion of patients who are investigated with a chest x-ray in the year prior to diagnosis with lung cancer had a chest x-ray in which features suspicious of lung cancer were identified?

2. What is the diagnostic accuracy, expressed as sensitivity and specificity, of LDCT compared to chest x-ray for lung cancer in symptomatic patients?

2.6 Sensitivity of Chest x-ray for Lung Cancer

2.6.1 Methods

2.6.1.1 Literature searches

Searches were carried out on the following databases with no language restrictions, from 1999 to 27th June 2017:

- The Cochrane Library (Central, DARE, Cochrane CDSR, NHS EED, HTA)
- CINHAL
- Clinical Trials.gov
- Dissertation and Thesis (Proquest)
- Embase
- Medline
- Medline Epub Ahead of Print
- Medline in Process
- PROSPERO
- WHO ICTRP
- Web of Science Core Collection

The search strategy consisted of two parts:

- Terms to include the modality of chest x-ray ('chest' or 'thora*' and 'radiograph*' or 'bronchograph' or 'x ray' and other synonyms.
- Descriptors to identify lung cancer ('lung' and synonyms such as 'pulmon*' and 'respirator*' in combination with 'cancer' and synonyms including 'neoplas*' and 'tumo?r*'

The full search strategies are included in Appendix 1. Manual checks of reference lists were performed in order to identify any additional studies which had not been retrieved through database search. Foreign language studies were included. As over one year had elapsed since the search was originally conducted on 27th June 2017 when the review was submitted for publication, the search was repeated on 17th December 2018.

Provision of relevant grey literature was made through a restricted search of dissertations on the ProQuest database of dissertations and of abstracts via the web of science conference proceedings database. The grey literature search was carried out by Sarah Abraham (who will be referred to as SA from now on). The websites of the following organisations were also searched to identify any potentially eligible reports, guidelines and audits:

- Royal College of Radiologists

- American College of Radiology
- American Society of Clinical Oncology
- American Society for Radiation Oncology
- British Institute of Radiology
- European Society of Radiology
- European Society for Medical Oncology
- European Society for Radiotherapy and Oncology
- International Society of Radiology
- International Association for the Study of Lung Cancer
- British Thoracic Society
- British Thoracic Oncology Group
- National Cancer Registration and Analysis Service
- European Respiratory Society and American Thoracic Society
- Cancer and Primary Care Research Network

2.6.1.2 Inclusion criteria and definitions

Studies relating to patients who had a chest x-ray after presenting to a clinician with symptoms were included. Studies based on screening populations were excluded. It was recognised that, in some cases, patients may have had a chest x-ray for reasons incidental to any clinical presentation or that the indication for the chest x-ray may not have been stated. Where possible, it was intended that study data which was based on patients who had a chest x-ray for a reason incidental to their clinical condition would be excluded, however studies in which the indication for the chest x-ray was not stated were included.

In determining sensitivity of chest x-ray, any study which reported on the numbers of adult patients who had a chest x-ray in the year prior to a diagnosis with lung cancer and which reported the results of those chest x-rays was considered. This timescale was selected with reference to estimates of detectable, preclinical phase of lung cancer (mean sojourn time). Although unknowable,(142) the mean sojourn time for lung cancer has been estimated at between 5.5 months (143) to 2.2 years.(144) It is possible that lung cancer could arise anew within one year and therefore not have been present one year before diagnosis, for example when a chest x-ray was performed. However, given that the mean sojourn time is estimated to be at least 5.5 months, it was felt that the duration of one year was justifiably and this time period was chosen by clinical consensus of the study team.

In cases in which an explicit timeframe was not stated in the study, the paper was included if the context of the study or the authors' description suggested that the time between chest x-ray and diagnosis was less than one year, for example if this period was stated to be within one hospital admission. The study team was consulted on the inclusion of studies in which the timeframe was not clear. It was decided to include studies where, on the balance of probability, the period between chest x-ray and diagnosis was likely to be less than one year.

Intrathoracic malignancies, such as mesothelioma and lymphoma, which are not considered to constitute lung cancer, were excluded. Studies relating to children (under age 18 years), metastatic lung disease from a non-lung cancer primary tumour and post treatment or diagnostic surveillance of lung cancer were also excluded. Although not included in the inclusion and exclusion criteria of the study protocol, following discussion within the study team, it was decided to also exclude the results of imaging which had been undertaken as part of cancer staging. The reasons for this decision are documented in Appendix 2.

It was decided to exclude all studies prior to 1999 so as to derive evidence from clinical contexts which had used radiographic technology broadly comparable to contemporary practice. As chest x-ray has been in use for many decades, it was apparent that any search strategy which did not restrict by date would identify a great many papers from throughout the 20th Century which would have limited applicability to modern lung cancer detection. Advice was supplied by colleagues in clinical radiology that the most significant recent change in plain radiology technology was the transition from film to digital media in the early to mid 1990s.(145) A cut off of 1999 was therefore chosen, recognising that the publications were likely to report findings from some years prior to the date of publication.

While the inclusion and exclusion criteria were outlined in the study protocol prior to commencement of data extraction, a small number of refinements were made to these in order to clarify decision making. These clarifications were made during the data extraction process in response to instances in which reported study details required to determine inclusion or exclusion were absent or ambiguous. A summary of these decisions and their rationale are outlined in Appendix 2.

Inclusion criteria:

- Reported findings of chest x-ray taken up to one year prior to diagnosis with lung cancer
- Chest x-ray requested to investigate symptoms

Exclusion criteria:

- Screening studies
- Under 18 years of age
- Other intrathoracic malignancies and metastatic disease
- Investigations performed as part of post treatment surveillance or for identification of metastatic disease

Figure 2.1 Inclusion and exclusion criteria for sensitivity of chest x-ray for lung cancer

2.6.1.3 Definitions

Chest x-ray is defined as a plain radiograph, of either posterior anterior or anterior posterior projection, processed by either digital or conventional means. Where not explicitly defined, any use of the terms chest and x-ray and radiograph were accepted to satisfy our definition of chest x-ray.

The definitions of a positive and negative test corresponded to that used in a large radiograph screening study.(97) A test was considered positive if any abnormality considered suspicious for lung cancer was noted at the time of reporting. The test was be considered negative if no features suspicious of lung cancer were noted at the time of reporting.

'Lung cancer' was defined as disease which satisfies the International Classification of Diseases-10 (ICD-10) 2016 diagnosis code C34, *malignant neoplasm of bronchus and lung.*(146) Metastatic lung disease, tracheal cancer and other intrathoracic malignancies such as mesothelioma were excluded. Where lung cancer was not explicitly defined use of the term 'lung cancer', or of terms which are listed synonyms of ICD-10 C34 was accepted.

Any reference standard for diagnosis as stated by the study authors was accepted. It was anticipated that reference standards would include computed tomography, positron emission tomography computed tomography, bronchoscopy, biopsy or clinical or post mortem diagnosis.

Due to advances in radiography, particularly in digital modalities of computed radiography and direct radiography, which emerged in the early to mid-1990s,(145) studies based on older modalities may not be comparable to contemporary technology. For this reason, studies published before 1999 were excluded.

2.6.1.4 Application of inclusion and exclusion criteria

The studies retrieved from the search strategy were saved in EndNote (Figure 2.2). A full title and abstract search of all citations generated by the search strategy was undertaken by SB. A review of a random 20% of the total number of citations was undertaken by Adam Grice (from now on referred to as AG). The selection of the random 20% was undertaken according to an established method (147) which has been used elsewhere.(148) SB and AG reviewed the citations and allocated these to groups based on their eligibility, according to an established method.(149) All of AG's and the corresponding 20% of SB's selections were compared to ensure consistency. Although the study protocol envisaged an initial screen of titles, followed by review of abstracts on citations selected as potentially eligible, it was decided to review the titles and abstracts of all citations following discussions between SB and AG and SB and Richard Neal (from now on referred to as RN). The full abstract and title review was undertaken because it did not prove possible to make accurate decisions on potential eligibility from the title of the studies alone. Although this was a deviation from the process outlined in the protocol, it was decided that this was legitimate as it represented an enhancement of the scrutiny and a reduction in the risk that relevant studies would be mistakenly excluded. All citations which were deemed to be likely to be eligible or those in which there was insufficient information to make a decision regarding eligibility were selected for a full text review.

2.6.1.5 Data extraction

The following data (where present) were extracted, or calculated from the studies:

- Title
- Year of publication
- Country of study
- Study design
- Details of study population including:
    - number of patients
    - age, gender, smoking status, deprivation
    - type of requesting physician (primary, secondary, tertiary care)
    - reasons for investigation request, if stated, and including, for example

- because of suspicion of lung cancer
- people with specific symptoms -such as haemoptysis
- reason incidental to clinical presentation

- Number of patients initially testing positive for lung cancer on chest x-ray
- Number of patients who initially tested negative on chest x-ray for lung cancer
- Sensitivity of chest x-ray and confidence intervals
- The time-point reported at which the patients were either diagnosed or not diagnosed with cancer (e.g. 6 months or one year)
- Reference-standard of the diagnosis (as reported in the study)

The entirety of data extracted from eligible studies are presented in Appendix 3.

2.6.2 Results

2.6.2.1 Search Results

Figure 2.2 outlines the results of the literature search.

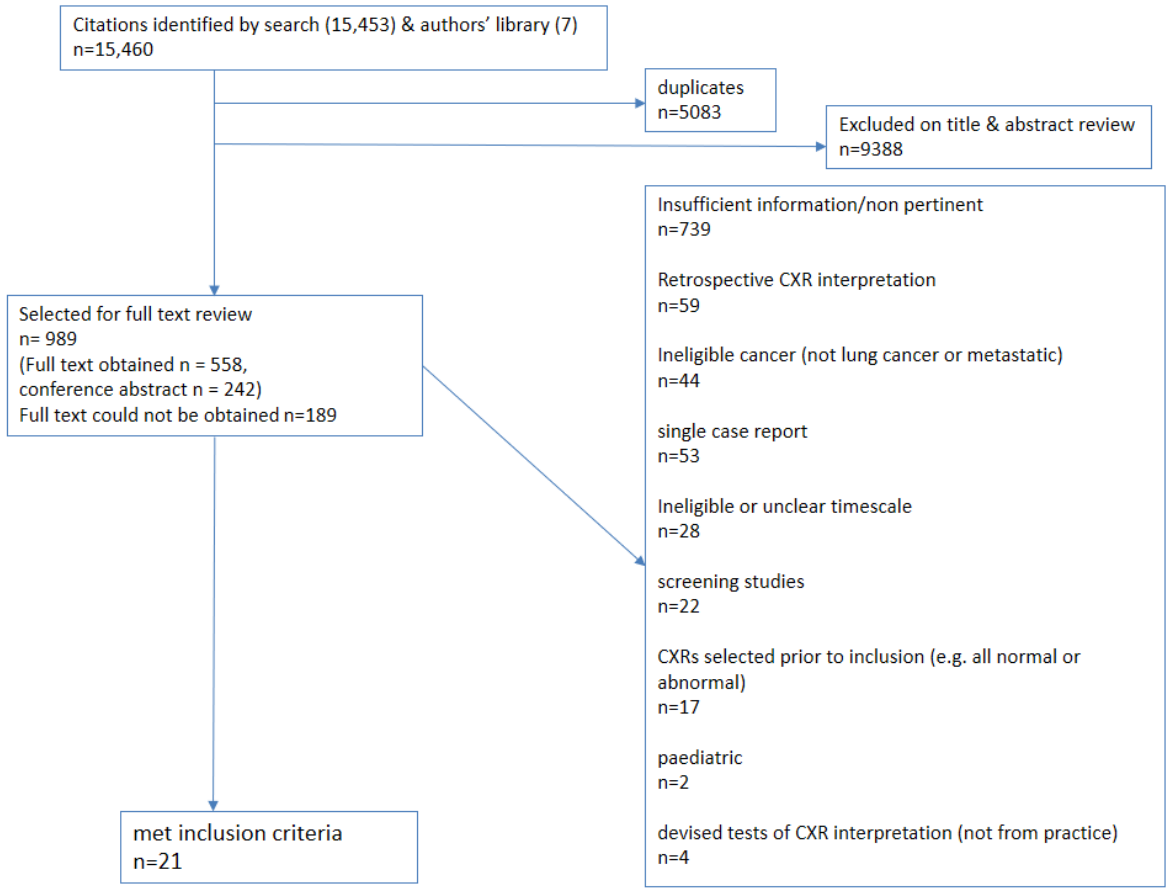


Figure 2.2 Flow chart for selection process of studies

Attempts were made to obtain all the texts, including contacting authors by email where the email was listed in the citation or where their email address could be located through an through internet search engines (such as Google) and also requesting the texts through the publication sharing platform ResearchGate. For 189 citations, the full text could not be obtained, leaving 800 full texts which were obtained and reviewed, although 242 of these were conference abstracts.

In the case of the citations where only the abstract was available (conference abstracts and citations for which the full text could not be obtained), these were considered for inclusion on the basis of the information contained in the abstract alongside the other texts during the full text review.

The most common reason for exclusion (n=739) was that the text 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.

59 citations were excluded because the interpretation of the imaging undertaken retrospectively and was therefore informed by the knowledge that the lung cancer had been diagnosed. 17 of the studies were not eligible because the patients had been chosen for inclusion on the basis of a chest x-ray that was known to be positive or negative for chest x-ray. Four studies were ineligible because they were devised evaluations of individual's performance in chest x-ray interpretation using films in which the presence or absence of lesions was already known to the study investigators, rather than observations of the accuracy of chest x-ray in clinical practice.

Other studies were excluded because the cancers the 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 one year or unclear (n=28), they were drawn from screening data (n=22) or patients were under 18 years old (n=2). 21 studies met the inclusion criteria.

2.6.2.2 Summary of studies which met the inclusion criteria

The 21 studies which met the inclusion criteria are summarised in Table 2.1. The entire data extracted for each study is outlined in Appendix 3. The majority of the studies included were case series. Several of these included very small numbers of patients, with eight studies

having less than ten patients. Detection of the diagnostic performance of chest x-ray for lung cancer was the primary aim of only one study.(70) The majority of the studies did not directly report the sensitivity or false negative rate of the chest x-ray, but have been included because they reported information which allowed for their calculation.

Many of the studies related to particular categories of lung cancer patients including uncommon histological types and symptomatic presentations or of particular population groups with lung cancer. Therefore the majority of the studies cannot be considered to be representative of typical lung cancer cases. Only four studies (70-72, 150) reported results for more than 10 patients from populations which were generalisable.

The sensitivity ranged from 40 to 100% and the numbers of patients ranged from 2 to 208.

Study	No.	CXR +ve (%)	95% C. I.	Total CXR –ve (%)	CXR –ve: normal (%)	CXR –ve: Abnormal (%)	Histology (%)	Mean Age	Male %	Population	Setting: primary or hospital	Country
Hamada 1999	31	22 (71.0)	52.0 to 89.9%	9 (29.0)			NSCLC (74.2), SCLC (25.8)	60.6	100.0	asbestos exposure	hospital	Japan
Tanaka 1999	3	3 (100.0)		0 (0.0)			NSCLC (33.3), pleomorphic (33.3), unknown (33.3)	72	100.0	gingival metastasis	hospital	Japan
Bini 2001	2	2 (100.0)		0 (0.0)			pulmonary blastoma (100)	62.5	100.0	pulmonary blastoma	hospital	Italy
Lee 2001	6	4 (66.7)	20.4 to 100%	2 (33.3)			SCLC (100)	62.5	50.0	paraneoplastic GI dysfunction	hospital	USA
Haro 2002	208[a]	185[a] (88.9)	84.4 to 93.5%	23[a] (11.1)				62[a]	84.4[a]	haemoptysis	hospital	Spain
Losa Gaspa 2002	93	84 (90.3)	84.0 to 96.6%	9 (9.7)				63.0	72.4[a]	metastatic cancer	hospital	Spain
Abraham 2003	23	19 (82.6)	65.6 to 99.7%	4 (17.4)				53.4	47.8	presented w/ facial pain		USA
Gomez 2004	41	36 (87.8)	77.1 to 98.5%	5 (12.2)			carcinoid (100)	50.0	66	bronchial carcinoid	hospital	Spain
Kitazaki 2005	2	2 (100.0)		0 (0.0)			NSCLC (100)	71.5	0.00	Bronchioalveolar treated w/ gefitinib	hospital	Japan
Bando 2006[b]	15	12 (80.0)	57.3 to 100%	3 (20.0)			SCLC (5), NSCLC (4),	68.3[a]	73.3	vocal cord paralysis	hospital	Japan

							others (2), unknown (4)					
Bjerager 2006	58	46 (79.3)	67.6 to 91.0%	12 (20.7)				66[c]	64.3[a]	primary care	primary	Denmark
Brock 2006	30	12 (40.0)	12.3 to 67.7%	18 (60.0)	9 (30.0)	9[d] (30.0)	NSCLC (85.9), SCLC (8.7), other (5.4)[a]	46[c]	67.4[a]	HIV infected patients	hospital	USA
Stapley 2006	164	126 (76.8)	64.5 to 84.2%	38 (23.2)	17 (10.4)	21 (12.8)	NSCLC (64.0), SCLC (21.1), unspecified carcinoma (10.9), unknown (4.0) [a]	70.8[a]	68.8[a]	primary care	primary	UK
Fernandez 2007[b]	102	97 (95.1)	90.8 to 99.4%	5 (4.9)	5 (4.9)		NSCLC (68.8), SCLC (20.5), anaplastic (9.9), unknown (1.8) [a]	68[a]	85.4[a]	hospital	hospital	Spain
Kato 2010	3	3 (100.0)		0 (0.0)			squamous cell (100)	64.7	100.0	Squamous cell carcinoma w/ necrotic cavities	hospital	Japan
Kikuchi 2010	2	2 (100.0)		0 (0.0)			pleomorphic carcinoma (100)	71.0	100.0	pleomorphic carcinoma	hospital	Japan
Uzun 2010[b]	51	50 (98.0)	94.2 to 100%	1 (1.9)			NSCLC (90.2), SCLC (5.9), other (3.9)	54.3[a]	76.4[a]	haemoptysis	hospital	Turkey

Mao 2011	10	6 (60.0)	39.2 to 99.2%	4 (40.0)			NSCLC (70.0), SCLC (30.0)	58.7	50.0	Diabetes insipidus from pituitary metastases	Hospital	China
Ozazaki 2012	2	2 (100.0)		0 (0.0)			SCLC (100)	75.0	50.0	gastric metastases from lung primary	hospital	Japan
Barry 2015	158	126 (79.8)	72.7 to 86.8%	32 (20.2)	23[e] (14.6)	9 (5.7)				hospital	hospital	Ireland
Ghimire 2016	7	7 (100.0)		0 (0.0)			NSCLC (100)	54.7[a]	76.0[a]	Patients undergoing bronchoscopy	hospital	Nepal

Table 2.1 Summary of eligible studies

a number includes cases which were not eligible, which could not be excluded

b interpretation of CXR reported as, 'abnormal' or 'normal' but authors did not state which abnormalities were contemporaneously considered to be suspicious for lung cancer at time of reporting CXR. 'Abnormal' processed as 'positive' for this review

c median

d 'non specific infiltrates'. Authors did not state if these were considered positive or negative

e abnormal but no follow up recommended

f all four patients had NSCLC with synchronous tumours, in one case combined NSCLC as well as SCLC

2.6.2.2 Assessment of risk of bias

The Newcastle-Ottowa scale was initially chosen (151) to assess the quality studies, as it allows for the categorisation of non-randomised observational studies as being either of low, moderate or high quality following application of an 8 point checklist. The scale is recommended by the Cochrane collaboration for the assessment of non-randomised studies.(152) However, the Newcastle-Ottowa scale facilitates only the assessment of comparative case control and cohort studies and was not appropriate for the assessment of any of the eligible studies all of which were essentially case series. One study was described as a 'cohort study', however it contained no comparative cohort.(70)

A modified QUADAS-2 tool (153) was instead used and assessment of risk of bias were undertaken by SB and AG. Agreement was achieved between both reviewers in all cases and no adjudication was required by a third reviewer. The QUADAS-2 tool required significant modification because the studies identified in the review were not diagnostic accuracy studies. The modified QUADAS-2 tool and the assessments of the risk of bias agreed by SB and AG are presented in appendix 4.

2.6.2.3 Meta-analysis

Meta-analysis was planned to provide pooled summary estimates of the sensitivity of chest x-ray for lung cancer.

However, the small number of studies with a low risk of bias (n=3) and the extensive heterogeneity between them meant that a meta-analysis was not appropriate and a descriptive synthesis of the results was produced instead.

2.6.2.4 Descriptive synthesis of results

Three studies were assessed as being at low risk of bias. These were Bjerager et al. (2006), Stapley et al. (2006) and Barry et al. (2015). The methods and results of these studies will be outlined in turn.

Bjerager et al. (2006) 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. The study is described as a 'population based observational case series'. The study data was derived from interviews with patients, their GPs and also some limited examination of medical records. The source of the

information on the results of the chest x-rays is not specifically explained, but it is likely that this was primarily gathered from the patients and their GPs and may have been supplemented with further reference to medical records in a small number of cases where the patients could not participate. Patients (n=58) had a chest x-ray arranged from general practice and 46 (79.3%) of these patients had chest x-rays which suggested the possibility of lung cancer. This included two cases in which pneumonia was indicated and a repeat chest x-ray was recommended to rule out lung cancer. The remaining chest x-rays (n=17, 20.7%), which the authors report 'raised no suspicion of lung cancer' are referred to as 'negative' results in the text.

Stapley et al (2006) was described as a retrospective cohort study, which examined chest x-ray results of patients of general practices in Exeter Primary Care Trust, Devon who were diagnosed with lung cancer between January 1998 and September 2002 and who were aged 40 or over. Of the 247 patients diagnosed with lung cancer in that period, 164 had a chest x-ray organised in primary care in the year prior to their diagnosis. The study authors categorised the chest x-ray results according to the radiologist's report into three categories. These were abnormal with possible malignancy, abnormal with no suspicion of lung cancer and normal. The authors considered the first category (abnormal with possible malignancy) to be positive, whilst the other two categories were considered negative. The study showed that in 126 (76.83%) of the patients the chest x-ray had indicated the possibility of lung cancer, while 38 (23.17%) of patients had a negative chest x-ray. Of the 38 'negative' chest x-rays, 21 (12.80%) were categorised as abnormal but not suspicious of malignancy while 17 (10.37%) were reported as 'normal'.

Barry et al. (2015) was a conference abstract containing a retrospective review of chest x-ray reports in a secondary care setting in the Republic of Ireland. This included 158 patients of whom 52 were identified as likely to have a lung malignancy and a further 74 were advised to have follow up. These groups have been considered to represent positive chest x-ray findings, which corresponds to a sensitivity of 79.8%. A further 23 patients had a chest x-ray in which the authors refer to as 'lesion not identified' (14.6%) and nine in which an abnormality was identified but no follow up recommended (5.7%). Although the setting for this study has been categorised in this review as secondary care, it is possible that the review included patients that were referred from primary care.

The remaining 18 studies were highly variable in terms of study design and all reported on populations that were not generalisable to symptomatic patients with lung cancer presenting to primary care, because they were restricted to patients who had either: 1) presented with

particular symptoms, 2) had particular (often atypical) lung cancer histology or 3) had particular co-morbidities or previous exposures.

2.6.3 Discussion

2.6.3.1 Strengths and limitations of the study

When undertaken, the study was the only systematic review which has attempted to determine the sensitivity of chest x-ray for lung cancer in symptomatic patients. The review was comprehensive in scope and led to title and abstract review of 7,942 citations and full text review of 774 citations. Foreign language papers were included and efforts were made to identify additional evidence through a grey literature search and manual checking of the websites of several organisations. The PRISMA statement for systematic reviews was not formally used in either the design or the reporting of the study, although the registration of the study prior to commencement did inadvertently ensure that almost all attributes of the guideline were adhered to.(154) Omissions mostly pertain to analyses which were not undertaken due to the nature of the data, which was not suitable for meta-analysis. These include the categories of items 'synthesis methods' and 'results of syntheses'. There was also no formal assessment of 'certainty of evidence' as recommended by PRISMA, although this was considered in a narrative terms.

The main limitation of the study is the restricted body of evidence that was been identified. The studies which satisfied the eligibility criteria were highly heterogeneous with almost all of the resulting evidence of low quality and/or related to very specific disease presentations and therefore was assessed as being at high risk of bias. Only three studies were identified which were at low risk of bias. The limitations of the evidence gathered for this systematic review is such that no meta-analysis could be performed and that no overall accurate estimate for sensitivity could be determined.

In order to capture all available evidence, no exclusions were placed on the settings in which the studies were performed. The prevalence of different diseases is known to vary across different test settings, for example primary or secondary care, which has implications for test performance.(155) The majority of the studies which met the eligibility criteria were based in secondary care, however two of the three studies which were assessed as being at low risk of bias were based in primary care settings.

Upon conducting the review a number of difficulties emerged in applying the eligibility criteria which required clarification to be agreed with the supervisory team, which were not sufficiently explicit in the study protocol (see appendix 2). These clarifications do not represent any significant deviation from the study protocol and remain consistent with the objectives and methods set out in the protocol.

Following the comparison of the selections made by SB and AG it was decided that in the selection of the texts all abstracts would be reviewed as it was considered that not enough information was contained within titles to determine which met the inclusion or exclusion criteria. This was agreed following consultation with the supervisory team. It was felt that this represented an improvement of the study selection process, although it had not been foreseen in the study protocol.

2.6.3.2 Comparisons with existing literature

That lesions can be frequently identified on chest x-ray retrospectively, which were not recognised contemporaneously has long been understood. For example, a 1993 study using chest x-rays from a screening study showed that of 71 of 131 stage I adenocarcinomas showed evidence of cancer for 2 years prior to diagnosis on a retrospective review of chest – x-ray.(156) Traditionally emphasis has been placed on the role of the performance of the individual interpreting the chest x-ray. When lesions are retrospectively identified following diagnosis of lung cancer these are typically framed as ‘misses’ connoting a failure on the part of the individual who interpreted the chest x-ray. In the United States in particular, the perceived failure to identify lung cancer on chest x-ray (157, 158) (159) is a leading cause of medical malpractice litigation. Focus on the role of the individual who interprets the chest x-ray implies a perspective in which one of two possibilities lead to the failure of chest x-ray to identify a lung cancer; either that the lung cancer was not visible on the chest x-ray (or perhaps was not even present at the time of imaging) or that the lung cancer was present as a visible lesion, but that it was not identified due to ‘human error’.

In designing this review the study team were informed by a broader perspective and were motivated to determine the performance of chest x-ray as a test for lung cancer in a real world setting. Chest x-ray as a diagnostic test was understood to constitute not only the technology of obtaining a radiological image but the clinical interpretation of this image by an individual. Therefore studies which examined radiographs retrospectively, in the knowledge of a lung cancer diagnosis were not included. Such studies included a retrospective review of 495 non small cell lung cancer cases from the Netherlands in which 19% were shown to have had a nodular lesion which had been ‘missed’ on the original interpretation.(160) In an

English study, of 28 histologically confirmed lung cancer cases in which a chest x-ray had been obtained prior to the imaging that led to diagnosis, 14 had ‘abnormal’ findings which included 19 ‘errors’ of interpretation identified by the authors.(161)

A separate literature exists around the role of ‘observer error’ which has been considered the principal cause of misdiagnosis of lung cancer.(162) Such errors have been categorised as errors of visual scanning, recognition of abnormalities and of decision making.(163) Other human factors have been explored such as the role of experience(164) and even the transient psychological factors such as the ‘mindset’ or level of concentration of the observer.(165)

Analysis of chest x-ray ‘misses’ has generated some understanding regarding the nature of those lesions which are less likely to be identified. Unsurprisingly smaller lesions are identified less frequently(160) and lesions of less than 1cm in diameter are said to be rarely detected on chest x-ray.(161) Other characteristics of the lesion itself that can adversely affect detection includes the absence of sharp borders(160, 166) and even the histologically determined pattern of tumour development, with some small adenocarcinomas tending to be less conspicuous than similarly sized malignant lesions with differing histology.(167) Location is also important with ‘missed’ lung cancer having been noted to be frequently located in the upper lobes and in particular the apices.(160, 166, 168-170) A 2014 national audit by the Royal College of Radiologists provides perhaps the most valuable recent evidence for the UK context of the locations where lesions are missed with 25% located at the right perihilar area compared to only 4% in the left middle zone.(171)

The tendency for anatomical structures to obscure pulmonary lesions appears to account for much of this pattern of where ‘missed’ lung cancers are most frequently located. Structures which frequently impair visualisation of tumours include ribs, lung vasculature, heart, mediastinum and diaphragm which can overlie each other on the two dimensional view of a plain radiograph creating what has been referred to as ‘anatomic noise’.(162)

Finally, the technical quality of the image 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.(165)

The determination that lung cancer was ‘missed’ in such studies is made when lesions which were not initially recognised are retrospectively identified through reinterpretation of the chest x-rays. In cases in which a lesion cannot be identified in retrospect the cancer can not

be said to have been ‘missed’ by the individual interpreting the chest x-ray. In such cases it is possible that the lung cancer was present but undectectable for example due to very small size or to obscuring overlying structures that rendered it invisible. It is also possible that in some cases lung cancer may not have been detected simply because the tumour was not then present at all. Attempts to understand the natural history of lung cancer remain necessarily largely speculative(142) although economic modelling has been conducted on the assumption that tumour growth begins slowly and accelerates during the progression of disease(127) and consensus seems to exist that in most cases malignant change will have commenced many months before symptomatic presentation.(144)

2.6.3.3 Studies published following completion of the systematic review

Following completion of this systematic review in 2019 it was discussed within the supervision team as to whether the review should be updated at the conclusion of the PhD. Given the very low yield of papers which were at low risk of bias which addressed the study question out of all the papers which were screened (3 out of 9391, or 0.03%) it was not considered proportionate to update the review for the period 2019 to 2021.

However two papers have been published since this systematic review was completed which warrant discussion. Dwer-Hemmings and Fairhead (2021) authored a systematic review and meta-analysis examining the performance of chest x-ray in the detection of lung cancer in symptomatic primary-care populations.(172) This review identified ten studies in total, five of which were deemed to be at low risk of bias and generated a summary sensitivity of 81% (95% CI 74 to 87%). In the systematic review described in this chapter, in order to be eligible for inclusion studies had to report the number of patients who were tested, the numbers of those who had positive and negative chest x-ray results and the numbers of those who had a diagnosis of lung cancer, which was confirmed by some other means than the chest x-ray itself. Dwyer-Hemmings and Fairburn’s review used different eligibility criteria and therefore different studies were identified. In particular, their review included studies in which confirmation of the diagnosis was made through the chest x-ray itself, rather than by any other comparator, or following an interval of up to one year as was used in the systematic review described in this chapter.

Foley et al. (2021) reported(173) the chest x-ray results for 1,488 patients who had been referred for the investigation by their GPs because of suspected cancer. Chest x-ray results for all patients were reported, categorised into three groups: those who had a normal test result, those with an ‘alternative diagnosis or indeterminate findings not sufficient to warrant further urgent investigation for lung cancer’ and those with findings of an alternative

diagnosis or indeterminate findings not sufficient to warrant further urgent investigation. If the test result categorisation corresponding to positive or negative results used in the systematic review were applied to the categories described by Foley et al, the normal category would be considered 'negative' and the other two groups may have been considered 'positive', since the intermediate group is likely to have contained diagnoses of pneumonia which by convention requires chest x-ray follow up to ensure resolution to exclude lung cancer. Out of the study population (n=1488), a total of 280 (18.8%) proceeded to computed tomography, of whom 88 (31.4%) were found to have lung cancer. Of these 88 patients, 10 (11.4%) had a normal chest x-ray, 29 (33.0%) had a chest x-ray which showed 'an alternative diagnosis or indeterminate findings not sufficient to warrant further urgent investigation' and 49 (55.7%) had a chest x-ray which was suspicious for malignancy, which could be interpreted, according to the methodology of the systematic review, as sensitivity of 88.6%. However the study may not have satisfied the eligibility criteria of the review as the outcome of whether or not patients were diagnosed with lung cancer was only reported for those patients who had computed tomography as well as chest x-ray. It is likely had the study been published at the time of conducting the systematic review that adjudication would have been sought regarding its eligibility for inclusion in the review.

2.7 Diagnostic accuracy of LDCT versus chest x-ray for the diagnosis of lung cancer in patients with symptoms

2.7.1 Methods

2.7.1.1 Literature searches

Searches were carried out on the following databases with no language restrictions, from 1946 to June 26th 2017:

- The Cochrane Library, which includes the Cochrane Database of Systematic Reviews (Cochrane CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Cochrane Central Register of Controlled Trials (CENTRAL), the NHS Economic Evaluation Database (NHS EDD) and the Health Technology Assessment Database (HTA)
- Cumulative Index of Nursing and Allied Health Literature (CINAHL)
- Clinical Trials.gov
- ProQuest
- Embase
- Medline, including Medline Epub Ahead of Print and Medline in Process

- The International Prospective Register of Systematic Reviews (PROSPERO)
- WHO International Clinical Trials Registry Platform (ICTRP)
- Web of Science Core Collection

The search strategy consisted of three parts:

- Descriptors to identify lung cancer studies ('lung' and synonyms such as 'pulmon*' and 'respirator*' in combination with 'cancer' and synonyms including 'neoplas*' and 'tumo?r*'
- Terms to include the modality of chest x-ray ('chest' or 'thora*' and 'radiograph*' or 'bronchograph' or 'x ray' and other synonyms.
- Terms to include the modality of low-dose CT including 'LDCT' and combinations of 'tomograph*' 'CT' and 'low*' or 'minim*' or 'ultralow*' or 'optim*' or 'reduc*' and ';dose?' or 'dosage?'

The full search strategies are included in Appendix 1. Manual checks of reference lists were performed in order to identify any additional studies which had not been retrieved through database search. Foreign language studies were included.

Provision of relevant grey literature was made through a restricted search of dissertations on the ProQuest database of dissertations and of abstracts via the web of science conference proceedings database. The grey literature search was carried out by SA. The websites of the following organisations were also searched to identify any potentially eligible reports, guidelines and audits:

- Royal College of Radiologists
- American College of Radiology
- American Society of Clinical Oncology
- American Society for Radiation Oncology
- British Institute of Radiology
- European Society of Radiology
- European Society for Medical Oncology
- European Society for Radiotherapy and Oncology
- International Society of Radiology
- International Association for the Study of Lung Cancer
- British Thoracic Society
- British Thoracic Oncology Group
- National Cancer Registration and Analysis Service

- European Respiratory Society and American Thoracic Society
- Cancer and Primary Care Research Network

2.7.1.2 Inclusion criteria & definitions

Studies comparing the diagnostic accuracy of LDCT and chest x-ray in patients who had presented with symptoms were included. Studies derived from screening populations were excluded.

Chest x-ray is defined as a plain radiograph, of either posterior anterior or anterior posterior projection, processed by either digital or conventional means. Where not explicitly defined, the terms ‘chest’ in combination with ‘x-ray’ and/or ‘radiograph’ were accepted.

There is no universally accepted definition of LDCT,(174) however it is generally accepted that this refers to computed tomography modalities which delivers radiation dose of less than 2.5 mSv (175). Computed tomography investigation of the chest or thorax in which the dose is quantified at less than 2.5 mSv was accepted as constituting a LDCT. Where the radiation dose was not stated, the terms ‘low dose CT’ or synonyms such as low dose computed tomography were accepted as constituting LDCT.

The definition of lung cancer used included disease which satisfied the ICD-10 2016 diagnosis code C34, *malignant neoplasm of bronchus and lung.*(146) Metastatic lung disease, tracheal cancer and other intrathoracic malignancies such as mesothelioma were excluded. Where lung cancer was not been explicitly defined, use of the term ‘lung cancer’, or of terms which are listed synonyms of ICD-10 C34 was accepted.

The reference standard for diagnosis was not defined in order to permit any standard used by the authors. It was anticipated plausible reference standards could include computed tomography, positron emission tomography computed tomography, bronchoscopy and biopsy. It was also anticipated that, in some cases, the diagnosis may have been determined once the disease has advanced. In this scenario, a clinical or post mortem diagnosis were considered acceptable.

Any definition of diagnostic accuracy employed by the authors of the study was accepted.

Intrathoracic malignancies, such as mesothelioma and lymphoma, which are not considered to constitute lung cancer were excluded. Studies relating to patients under 18 years of age,

metastatic lung disease from a non-lung cancer primary tumour and post treatment or diagnostic surveillance of lung cancer were also excluded.

Inclusion criteria:
- Reported diagnostic accuracy of LDCT compared to chest x-ray for detection of lung cancer
- Symptomatic patient population

Exclusion criteria:
- Screening studies
- Under 18 years of age
- Other intrathoracic malignancies and metastatic disease
- Investigations performed as part of post treatment surveillance or for identification of metastatic disease

Figure 2.3 Inclusion and exclusion criteria for diagnostic accuracy of low-dose CT versus chest x-ray for diagnosis of lung cancer

2.7.1.3 Screening

SB and SA independently screened the titles of the search results according to the inclusion criteria using EndNote. A third reviewer, RN, was designated to adjudicate any differences of opinion between SA and SB, however this was not required.

The original database search was conducted on 27th June 2017, yielding 952 papers following removal of duplicates. The search was repeated on 14th September 2018 and yielded an additional 278, papers of which 8 were duplicates.

The manual search of relevant organisations' websites was conducted by SA in July 2017. This yielded no relevant evidence. Given the investment of time required to undertake the manual website search, this was not repeated when updating the results in 2018.

2.7.2 Results

2.7.2.1 Search results

Figure 2.4 provides the results of the literature search. As no relevant citations were identified no data was extracted.

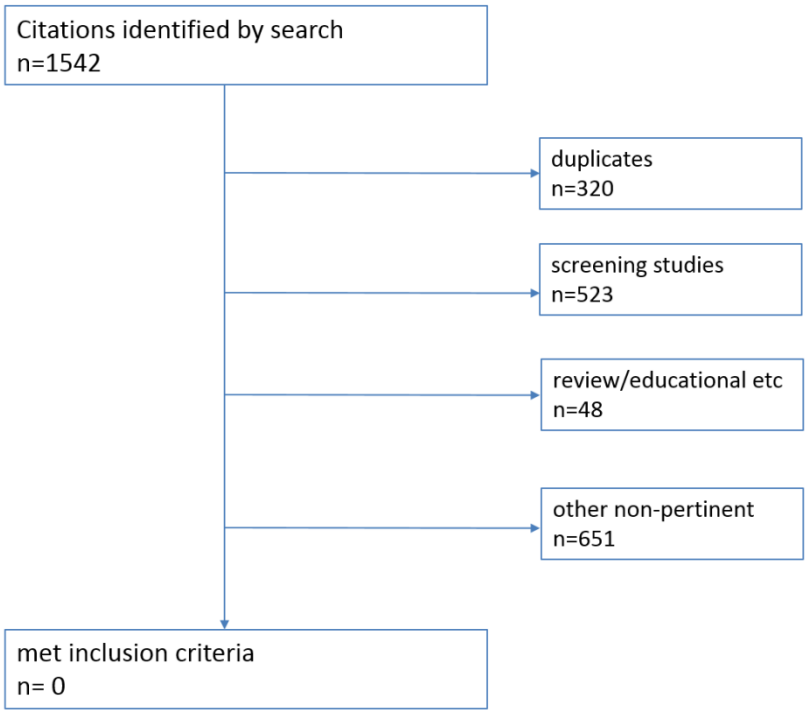


Figure 2.4 Flow chart representing selection process of studies

2.7.3 Conclusion

Although evidence exists around the performance of LDCT for the identification of lung cancer as a screening modality, this review has identified no evidence around the performance of LDCT in the diagnosis of symptomatic lung cancer, compared to chest x-ray. More surprisingly, given the ubiquity of chest x-ray in clinical practice, the second part of this review identified very little high quality evidence regarding the sensitivity of chest x-ray for lung cancer for a symptomatic patient population. Four studies reported from generalisable patient groups, however only three of these studies categorised the results in a consistent way and one of these was only documented as a conference abstract and was drawn from a secondary care population. It was striking that these three studies did report similar sensitivities of chest x-ray which ranged from 76.8% to 79.8%. The sensitivities of the two studies drawn from primary care populations, Bjerager et al. (2006) and Stapley et al. (2006) were 79.3% and 76.8% respectively.

This review demonstrates that the best available evidence yields a sensitivity of chest x-ray for symptomatic lung cancer of around 80%. Since this systematic review suggests that chest x-ray will fail to identify around 20% of lung cancers, this has serious consequences

for how chest x-ray is used and raises questions as to the thresholds which GPs should have for either repeating a chest x-ray or arranging more definitive testing such as computed tomography. In policy terms, the results of this review may support calls for greater access to additional modalities such as computed tomography or LDCT in instances in which GPs feel a patient is at sufficiently high risk of having lung cancer.

2.8 Acknowledgements

I am extremely grateful to Monica Koo, Marie Bourne, Nazia Ahmed, Sibel Saya and Dorota Karasek for their assistance in translation of non-English studies. I would also like to express my gratitude to the excellent team in information services at Leeds Institute of Health Sciences, including Judy Wright who provided advice regarding the conduct of the systematic review and Natalie King who provided advice on the practicalities of using EndNote to categorise citations. While undertaking this systematic review I emailed many authors of studies, many of whom were kind enough to provide further information which helped determine eligibility.

3. What is the sensitivity of primary care chest x-ray for lung cancer and what are the differences in time to diagnosis and outcomes between patients who have a true positive and those who have a false negative chest x-ray?

3.1 Overview

- Background: Chest x-ray is the first line investigation for lung cancer in many healthcare systems. The systematic review in chapter 2 demonstrated there is limited evidence on the sensitivity of chest x-ray for lung cancer in symptomatic patients. Even less is known regarding the consequences of false negative chest x-rays on time to diagnosis, stage and survival.
- Aims: To determine the sensitivity of chest x-ray for lung cancer and to compare stage at diagnosis, time to diagnosis and survival between those with chest x-ray which detected, or did not detect, lung cancer
- Design & Setting: Retrospective observational study using routinely collected healthcare data.
- Methods: All patients diagnosed with lung cancer in a large teaching hospital during 2008 – 2015 and who had a GP-requested chest x-ray in the year before diagnosis were categorised based on the result of the earliest chest x-ray performed in that period. Sensitivity of chest x-ray was calculated and analyses performed with respect to time to diagnosis, survival and stage at diagnosis.
- Results: Chest x-ray was positive in 1753 (82.3%) of 2129 patients. Median time from initial chest x-ray to diagnosis was 43 (IQR 27-78) and 204 days (IQR 105-287) following positive and negative results, respectively. Stage at diagnosis was I or II for 29.0% with a positive chest x-ray and 33.5% of those with a negative chest x-ray. Survival analysis demonstrated no adverse effect on survival for those with a negative chest x-ray result compared to those with a positive chest x-ray.
- Conclusion: Chest x-ray did not identify lung cancer in 17.7% (95% CI 15.9 to 19.4) of patients. Although there was a longer time to diagnosis for those with 'false negative' chest x-rays, there was no observed association with adverse stage or survival. Given the potential for confounding, these results warrant further investigation in a prospective study.

3.2 Introduction

Chapter two presented a systematic review of the sensitivity of chest x-ray, however the resulting estimate of sensitivity relied on only three studies with a total population of 380. In addition, evidence regarding the consequences of false negative chest x-ray results in terms of time to diagnosis, stage at diagnosis and survival is limited. A case series and two diagnostic audits suggests that those with false negative chest x-ray may experience a longer time to diagnosis,(72, 176) although a retrospective review of 24 patients found no adverse association between survival and 'missed' lung cancer on chest x-ray.(161) It is not understood whether the failure to detect lung cancer leads to adverse outcomes for patients. The purposes of the study detailed in this chapter is to generate an estimate for the sensitivity of chest x-ray for symptomatic lung cancer based on a large population sample and to use routinely collected data to explore if associations exist between chest x-ray result and duration to diagnosis, stage at diagnosis and survival.

Specificity as well as sensitivity is also important in evaluating the performance of a test. A high test sensitivity that comes at the expense of a very high false positive rate would impair the utility of the test since the capacity of the test to discriminate between those who do and do not have disease would be limited. Studies which estimate sensitivity based on those who are known to have the disease of interest and who have been tested, specifically patients who have been diagnosed with lung cancer and who have had a chest x-ray, as with the study described in this chapter and the majority of the studies considered in the systematic review in the previous chapter can not be used to determine specificity since they do not include patients who did not have lung cancer. Chapter four describes a study which did include patients who did and did not have lung cancer and who were investigated with chest x-ray and was used to determine test specificity.

3.3 Objectives

- To calculate the sensitivity of GP requested chest x-ray for lung cancer, in the year before diagnosis
- To compare time to diagnosis from chest x-ray, stage at diagnosis and survival between patients who had positive and negative chest x-ray results for lung cancer in the year before diagnosis

3.4 Methods

Leeds Teaching Hospital NHS Trust (LTHT) is a regional centre for lung cancer diagnosis and treatment, serving a population of approximately 750,000.(177) LTHT's lung cancer database is a comprehensive record of multi-disciplinary team confirmed lung cancer diagnoses which has previously been described.(45) From this database, a further file containing de-identified data on all patients diagnosed with a primary lung cancer between 1st January 2008 and 31st December 2015 within LTHT was created. Lung cancer cases which conformed to the international classification of diseases diagnostic code C34 were included; therefore other intrathoracic malignancies such as mesothelioma were excluded.(146) Patients who did not have a chest x-ray requested by their GP in the year before they were diagnosed with lung cancer were also excluded.

The study population was drawn overwhelmingly from patients who had GP requested chest x-rays, however a subgroup of 113 patients were included who had participated in a service whereby they could request their own chest x-rays (self-request chest x-ray service), because under that service these investigations were deemed to be primary care investigations. The study population included almost all of the patients who attended that service and who were diagnosed with lung cancer as reported in chapter four (113 out of 114). The one individual out of 114 who was not included in the study was excluded as their diagnosis occurred after 31st December 2015.

For the present study, all radiology reports for GP-requested chest x-rays in the year before diagnosis were coded according to criteria adapted from a national audit.(171) The chest x-ray report codes were as follows:

1. Suspicion of lung cancer identified/urgent investigation indicated
2. Abnormality identified/non-urgent investigation indicated, including diagnoses of pneumonia or consolidation even if repeat imaging was not explicitly suggested
3. Abnormality identified but no further investigation/assessment indicated
4. Normal chest x-ray. No abnormalities identified.

Codes 1 and 2 were considered 'positive' results while codes 3 and 4 were 'negative'. A sample of 100 chest x-ray reports were categorised by SB and a second independent reviewer (Nathaniel Luke Hatton) which yielded Cohen's kappa scores of 0.80 and 0.92 on comparing agreement across all four codes (1-4) and into the positive (1-2) versus negative (3-4) categories, respectively. The protocol for the validation of chest x-rays coding is included as appendix 5. Coding of chest x-ray reports was performed by SB with advice

obtained from Prof Mat Callister on categorisation of results, where the appropriate categorisation was not clear.

Patients were categorised according to the code of the earliest GP requested chest x-ray in the year prior to diagnosis (initial chest x-ray). This period was chosen as it is very likely that cancer would be present during this interval before diagnosis.(142)

3.5 Statistical Analysis

The overall sensitivity of chest x-ray was calculated as the proportion of patients who had initial chest x-rays which were coded either 1 or 2 with 95% confidence intervals calculated according to a method previously described.(178) Sensitivity of any subsequent chest x-rays that were also performed in the year prior to diagnosis was also calculated. The sensitivity of these subsequent chest x-rays were reported based on the report of that chest x-ray alone, rather than in combination with any prior chest x-rays that were performed. Pearson's chi-squared test was used to determine if a statistically significant association was present between early and late-stage disease and positive and negative chest x-ray results.

Kaplan-Meier survival curves were generated to compare 'true positive' and 'false negative' groups in terms of survival from initial chest x-ray and duration from initial chest x-ray to lung cancer diagnosis. The log rank test was used to test the null hypothesis that there was no difference in survival between these two groups. A Cox proportional hazards model was used to allow adjustment for age, sex, deprivation and lung cancer stage. To test the assumption of proportional hazards, interaction terms between time and each explanatory variable were included; significant effects for these interactions indicate violation of the assumption. Where this occurred, the interaction terms were adjusted for in the final model.(179)

Since detectability of lesions may be associated with size and stage, an exploratory analysis comparing stage at diagnosis and survival between cases diagnosed earlier and later than six weeks following initial chest x-ray was conducted. The period of six weeks was chosen for this analysis following discussion within the supervision team as a period within which it was felt to be likely that diagnosis would have been recorded had the diagnosis resulted from the same episode of symptomatic presentation which prompted the GP requested chest x-ray. The full analysis plan is reproduced in appendix 6.

3.6 Results

3.6.1 Summary

A total of 4,698 patients were diagnosed with lung cancer including 2,129 (45.3%) with at least one GP requested chest x-ray in the year before diagnosis (Figure 3.1). Sensitivity of chest x-ray was 82.3% (95% CI 80.6% to 84.1%). Median time from initial CXR to diagnosis for those with a 'positive' result was 43 days (IQR 27-78) compared to 204 days (IQR 185-287) for those who had a 'negative' CXR. Further detail on chest x-ray results, median durations to diagnosis and stage at diagnosis by group is presented in Table 3.1.

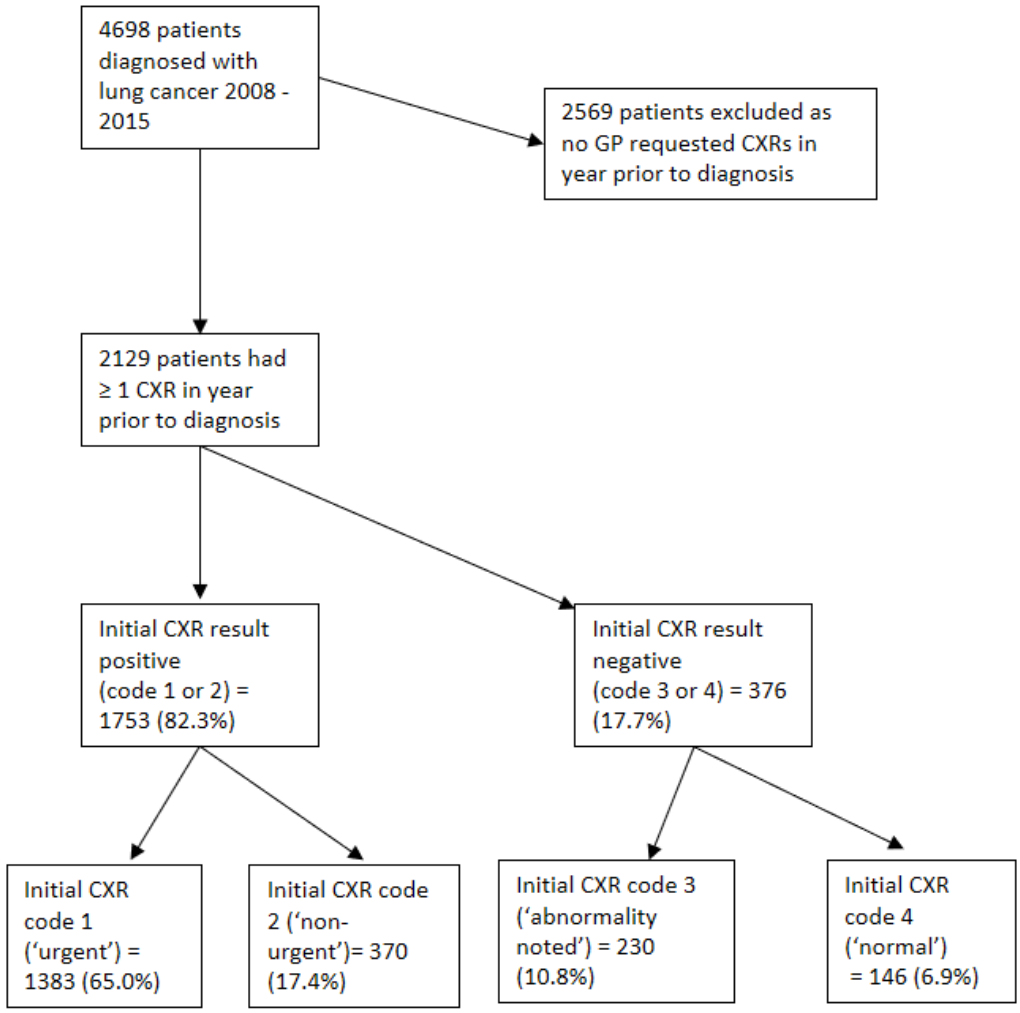


Figure 3.1 Number of patients included in study and result of initial chest x-ray (i.e. the earliest GP requested chest x-ray which was undertaken in the year prior to diagnosis).

Sensitivity was based on the dichotomous (positive or negative) result of the initial chest x-ray, which was 82.3%. CXR=chest x-ray

	Initial CXR code 1	Initial CXR code 2	Initial CXR code 3	Initial CXR code 4	'Positive' (code 1 or 2)	'Negative' (code 3 or 4)	Total
Number (%)[a]	1383 (65.0)	370 (17.4)	230 (10.8)	146 (6.9)	1753 (82.3)	376 (17.7)	2129
Age in years (mean)	71	72	75	70	71	73	72
Male (n, %)	753 (54.4)	189 (51.1)	121 (52.6)	72 (49.3)	942 (53.7)	193 (51.3)	1135 (53.3)
CXR to diagnosis (days)							
Median	36	93	211	193	43	204	51
IQR	(23-63)	(55-154)	(181- 296)	(87-279)	(27-78)	(105-287)	(29-107)
Stage							
I / II n (%)	397 (28.7)	111 (30.0)	83 (36.1)	43 (29.5)	508 (29.0)	126 (33.5)	634 (29.8)
III / IV n (%)	981 (70.9)	259 (70.0	147 (63.9)	103 (70.5)	1240 (71.0)	250 (66.5)	1490 (70.0)
Unknown n (%)	5 (0.4)	0	0	0	5 (0.3)	0	5 (0.2)
Survival from CXR (days)							
Median	313	400	408	420	328	412	345
IQR	(126-877)	(163-964)	(238-958)	(214-1117)	(135-899)	(225-1011)	(148-920)
Histology, n (%)							
Small cell	170 (12.3)	39 (10.5)	30 (13.0)	25 (17.1)	209 (11.9)	55 (14.6)	264 (12.4)
Non-small cell	961 (69.5)	257 (69.5)	123 (53.5)	87 (60.0)	1218 (69.5)	210 (55.9)	1428 (67.1)
Other histologies[b]	-	-	-	-	12 (0.7)	5 (1.3)	17 (0.8)
Unknown	244 (17.6)	70 (18.9)	76 (33.0)	30 (20.5)	314 (17.9)	106 (28.2)	420 (19.3)

Table 3.1 Study population by initial chest x-ray group

[a]Percentages in some cases ≠ 100 due to rounding.

[b] *In order to maximise anonymity, numbers for CXR groups 1–4 have not been reported.*

CI = confidence interval. CXR = chest x-ray. IQR = interquartile range.

3.6.2 Duration to diagnosis

The Kaplan Meier analysis survival presented in Figure 3.1 illustrates that for those who had a positive chest x-ray the probability of diagnosis was much higher at earlier time points, compared to those who had a negative chest x-ray. In simple terms, those who had a positive chest x-ray were much more likely to be diagnosed sooner than those who had a negative chest x-ray. This propensity to earlier diagnosis in those who had a positive chest x-ray persisted after adjusting for stage, performance status, deprivation, sex and age using Cox regression survival analysis (Figure 3.2) (hazard ratio 3.88, 95% CI 3.43 to 4.39, p<0.000)

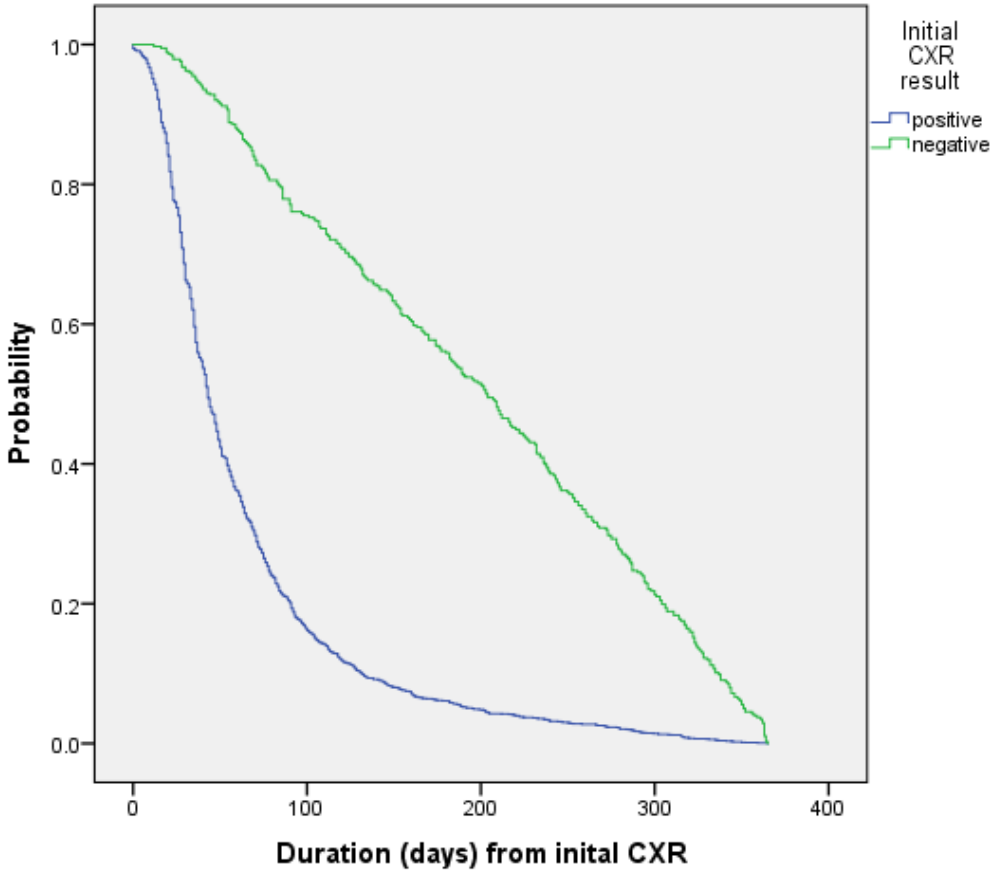


Figure 3.2 Kaplan Meier survival analysis for chest x-ray result with respect to duration to diagnosis from initial chest x-ray (days). Log rank test p<0.000

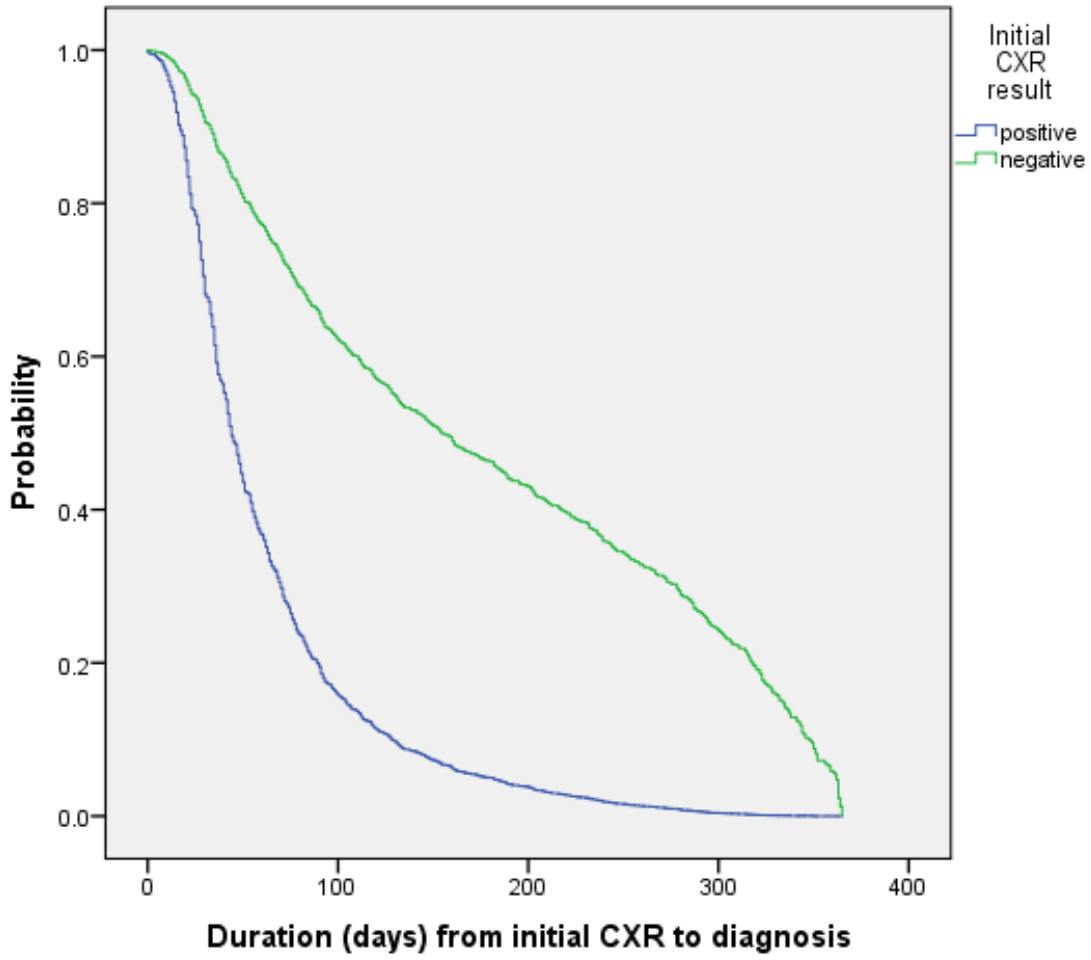


Figure 3.2 Cox regression survival analysis of chest x-ray result and duration to diagnosis in days from index chest x-ray with adjustment for stage, performance status, deprivation, sex and age. Hazard ratio 3.88 (95% CI 3.43 to 4.39, p<0.000)

3.6.3 Results of repeat chest x-rays

370 (17.4%) patients had an initial chest x-ray result which advised non-urgent further review or investigation (code 2). Of these patients, 191 (51.6%) then had a second chest x-ray, the median duration to second CXR was 42 days (IQR 28-57) and the result was falsely negative in 9.9% of cases (95% CI 6.4% to 13.5%).

A total of 324 patients (15.2%) had ≥2 chest x-rays before receiving a lung cancer diagnosis with sensitivity of these follow-up chest x-rays increasing only slightly from 82.3% (95% CI 80.6% to 84.1%) on initial chest x-ray to 83.6% (95% CI 79.2% to 88.0%) on the subsequent chest x-ray (Table 3.2). Of the 376 patients who had an initial CXR that was negative, 98 (26.1%) had at least one further CXR (Figure 3.3). The second chest x-ray for these patients was positive in 68 (69.4%, 95% CI 67.2 to 71.6), for whom urgent follow up (code 1) was

recommended in 52 (53.1%) and non-urgent follow up in the remaining 16 (16.3%) (Table 3.2).

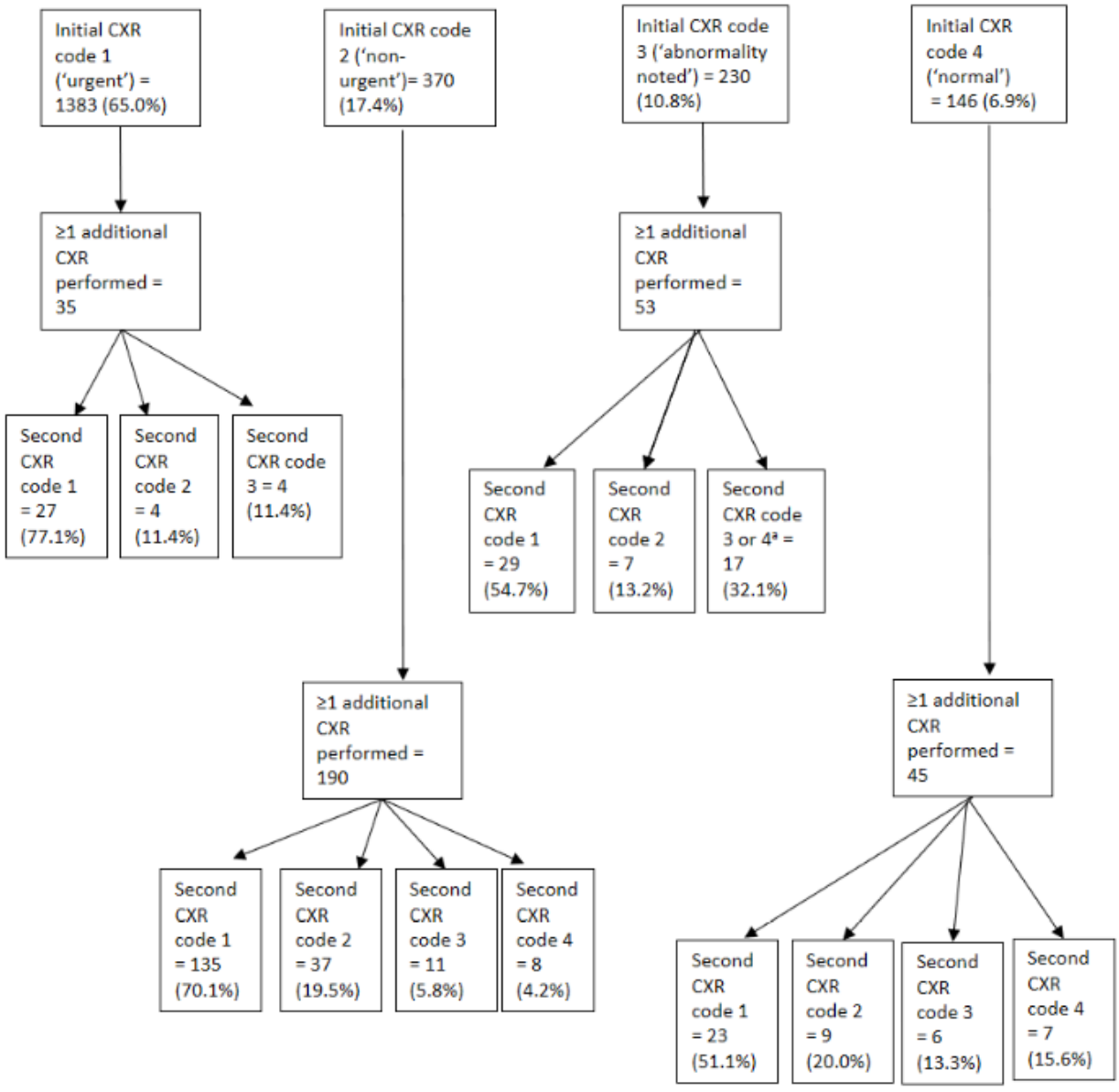


Figure 3.3 Chest x-ray results of second chest x-rays performed broken down by code of initial chest x-ray

CXR = chest x-ray

[a] Groups combined in order to maximise patient anonymity

Number of CXRs performed	Number of patients	Male (%)	Mean age	Positive CXR (%)	Previous CXR positive (%)	Stage I or II at diagnosis (%)	Median days from previous CXR (IQR)	Median days to diagnosis from initial CXR (IQR)
1	1805	978 (54.2)	72	1527 (84.6)		523 (29.0)		44 (57, 27-84)
2	277	126 (45.5)	72	244 (88.1)	185 (66.8)	83 (30.0)	49 (110, 29-139)	128 (144, 79-223)
3	43	21 (48.8)	70	37 (86.0)	26 (60.5)	13 (30.2%)	74 (97, 44-141)	239 (97, 186-283)
4	4	*	*	4 (100.0)	3 (75.0)	*	96 (132.5, 38.5-170.1)	339.5 (309, 54-363)
1, 2, 3 or 4 [a]	2129	1135 (53.3)	72	1753 (82.3)		634 (29.8)		51 (78, 29-107)
2, 3 or 4[a]	324	156 (48.1)	72	271 (83.6)[b]	226 (69.8)[c]	111 (34.3)	48.5(106, 29-134)	147.5 (167,84-251)
3 or 4[a]	47	23 (48.9)	70	40 (85.1)	28 (59.6)	14 (29.8)	67(102, 42-144)	251 (190, 114-304)

Table 3.2 Number of GP requested chest x-rays in year prior to diagnosis
IQR=interquartile range, CXR=chest x-ray
*** Demographic data has been excluded to maintain patient anonymity**
[a] Chest x-ray Results pertain to the first chest x-ray in each row, not to the total of all chest x-rays, e.g. for '1,2,3 or 4' indicates that the first chest x-ray was positive for 1753, row '2, 3 or 4' indicates that the second chest x-ray was positive in 271 out of 324 patients who had at least two chest x-rays.
[b] In those who had a negative initial chest x-ray and who had a second chest x-ray (98), the second chest x-ray code was 1 for 52 (53.1%), 2 for 16 (16.3%), 3 for 21 (21.4%) and 4 for 9 (9.2%)
[c] Of those who had two or more chest x-rays in the year prior to diagnosis, the initial chest x-ray code was 1 for 35 patients (10.8%), 2 for 191 (59.0%), 3 for 53 (16.4%) and 4 for 45 (13.9%)

3.6.4 Stage at diagnosis by initial chest x-ray group

Stage at diagnosis was similar across groups, with 634 (29.8%) patients diagnosed at stage I or II, including 508 (29.0%) of those who had a 'positive' initial chest x-ray and 126 (33.5%) who had a negative initial CXR. No statistically significant association between chest x-ray result and later stage (i.e. stage III or IV) diagnosis was found although the analysis may have not had sufficient power to find such an association if it was present, X^2 (1, N=2124) = 2.92, p = 0.09.

3.6.5 Chest x-ray result and stage for those diagnosed within six weeks of initial chest x-ray

Patients who were diagnosed within six weeks of initial CXR regardless of CXR result were more likely to have stage III or IV disease (*n* = 775/880, 88.1% versus *n* = 715/1244, 57.5%, *P*<0.001) (Table 3.3) and small cell histology (*n* = 115/884, 13.0% versus *n* = 109/1245, 8.8%, *P*<0.001) (Table 3.4). Among patients diagnosed ≥six weeks (42 days) after initial chest x-ray, there was evidence that those for whom the initial chest x-ray was negative were more likely to have stage III or IV disease than those for whom the initial chest x-ray was positive (*n* = 225/350, 64.3% versus *n* = 490/894, 54.8%, *P* = 0.002) (Table 3.5). Few patients who had an initial negative chest x-ray received a diagnosis of lung cancer within six weeks of initial chest x-ray (*n* = 26/376, 6.9%) (Table 3.6). Of those who did have a negative initial chest x-rays and were diagnosed within 6 weeks, almost all had stage III or IV disease (*n* = 25/26, 96.2%) (Table 3.7)

	Diagnosed *within* six weeks of initial CXR	**Diagnosed *after* six weeks of initial CXR**
Stage I/II	105 (11.9)	529 (42.5)
Stage III/IV	775 (85.1)	715 (57.5)
Totals	880	1244

Table 3.3 : Lung cancer stage and diagnosis with lung cancer within, or after six weeks (42 days) following initial chest x-ray.

Patients with unknown stage excluded to maintain anonymity. Pearson's chi squared demonstrated a statistically significant association between late stage and diagnosis within six weeks, X2 (1, N=2124) 230.36, p<0.001.

	Diagnosed *within* six weeks of initial CXR (%)	**Diagnosed *after* six weeks of initial CXR (%)**
Non small-cell/other/unknown	729 (82.4)	1136 (91.2)
Small-cell	155 (17.5)	109 (8.8)
Total (% of study population)	884 (41.5)	1245 (58.5)

Table 3.4 Lung cancer histology with respect to diagnosis with lung cancer within, or after six weeks (42 days) following initial chest x-ray.

Pearson's chi squared demonstrated a statistically significant association between small-cell histology and diagnosis within six weeks, X2 (1, N=2129) 36.68, P<0.001

	Patients diagnosed *after* six weeks of initial CXR (%)	Positive initial CXR (%)	Negative initial CXR (%)
Stage I/II	529 (42.5)	404 (45.2)	125 (35.7)
Stage III or IV	715 (57.5)	490 (54.8)	225 (64.3)
Total	1244	894	350

Table 3.5 Lung cancer stage at diagnosis and initial chest x-ray results for those who were diagnosed after six weeks (42 days) following initial chest x-ray.

Those with unknown stage are not included in order to maintain anonymity. Pearson's chi squared test did demonstrate a statistically significant association, X2, (1, N=1244) 9.24, p= 0.002.

	Diagnosed *within* six weeks of initial CXR (%)	Diagnosed *after* six weeks of initial CXR (%)
CXR Positive	858 (97.1)	895 (71.9)
CXR Negative	26 (2.9)	350 (28.1)
Total	884	1245

Table 3.6 Result of initial chest x-ray and diagnosis within or after six weeks (42 days)

Pearson's chi squared test demonstrated a statistically significant association between positive CXR and diagnosis within 42 days, X2 (1, N=2129) 225.24, p < 0.001.

	Patients diagnosed *within* six weeks of initial CXR (%)	Positive initial chest x-ray (%)	Negative initial chest x-ray (%)
Stage I/II	105 (11.9)	105 (12.3)	1 (3.8)
Stage III/IV	775 (88.1)	749 (87.7)	25 (96.2)
Totals	880	854	26

Table 3.7 Stage and initial chest x-ray results for those who were diagnosed within 42 days (six weeks).
Patient data with unknown stage excluded to maintain anonymity. Pearson's chi squared test did not demonstrated a statistically significant association between stage and chest x-ray result, X2 (1, N=880) 1.67, p=0.196. The result is not significant at p < .05, 1 degree of freedom.

3.6.6 Survival and initial chest x-ray result

Survival analysis demonstrated no adverse effect on survival for those with a negative chest x-ray result compared to those with a positive chest x-ray. Adjustment for co-variates using Cox proportional hazards regression found those with positive CXR results had poorer

survival relative to the negative CXR group (hazard ratio 1.35, 95% CI 1.19 to 1.52, *p*<0.000) (Figure 3.4).

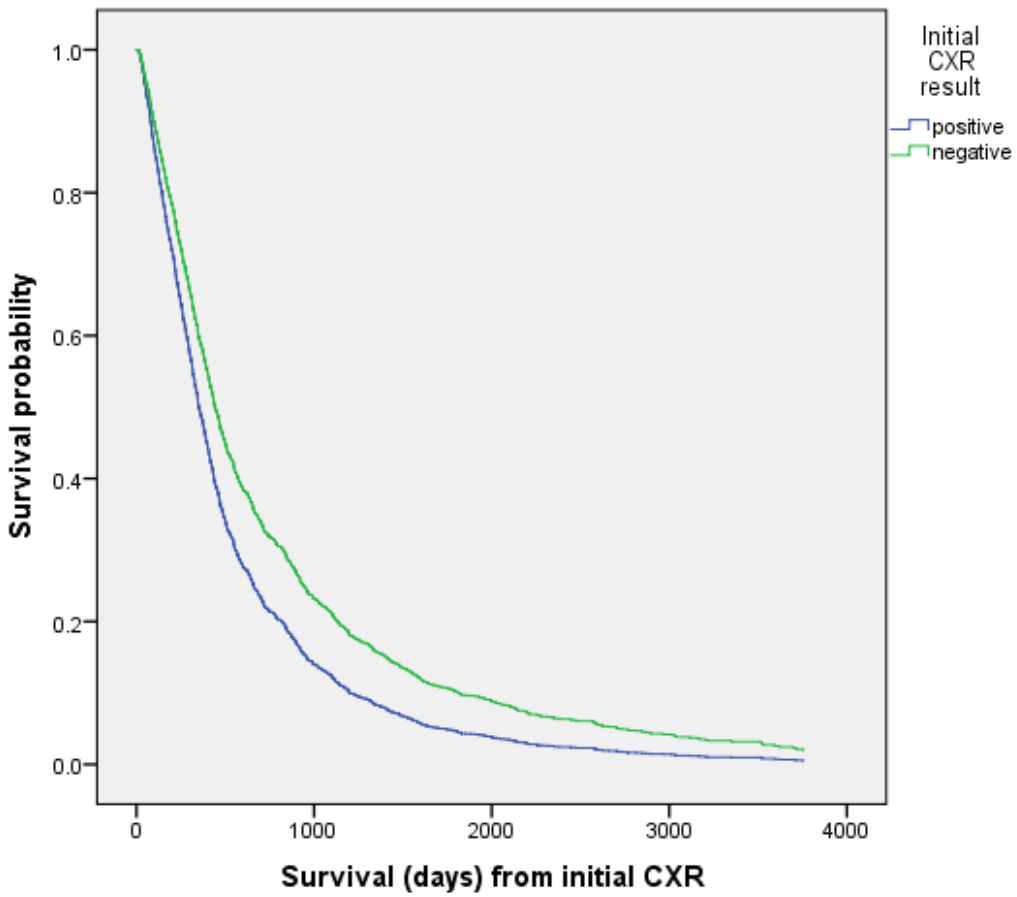


Figure 3.4 Cox regression survival analysis of chest x-ray result and duration of survival following initial chest x-ray adjusted for age, stage at diagnosis, deprivation, sex and performance status.

The blue line indicates positive chest x-ray result, the green line indicates negative chest x-ray result. CXR = chest x-ray

3.7 Discussion

3.7.1 Summary

This study estimates that the sensitivity of chest x-ray for lung cancer diagnosed within one year amongst patients presenting to primary care is 82.3% (95% CI 80.6 to 84.1%). The study builds on evidence from smaller studies that 'false negative' chest x-ray results are associated with additional delay to lung cancer diagnosis, compared to 'true positive' results.(70, 72) The study determined that, of the patients who have had a chest x-ray in the year prior to their diagnosis with lung cancer, those with positive results had a median

duration of 43 days compared to a duration of 204 days for those with an initially negative chest x-ray. The finding that patients who were diagnosed within six weeks of initial chest x-ray regardless of chest x-ray result were more likely to have stage III or IV disease, regardless of chest x-ray result, suggests that late-stage disease and small cell histology (which is associated with rapidly progressive disease) are more likely to be diagnosed rapidly, which could be due to the severity of presenting symptoms and/or more clear-cut radiological evidence of cancer.

No association was observed between failure to detect lung cancer on chest x-ray and adverse stage at diagnosis or survival. It is possible that such associations do exist but are obscured by confounding due to the retrospective observational study design or because the study lacked the statistical power to detect such associations.

3.7.2 Strengths and limitations

The study population exceeds by more than five-fold the total population of patients included in studies that were identified which had a low risk of bias which reported the sensitivity of chest x-ray for lung cancer (n=380) which were reported in chapter two. A systematic approach was used to classify chest x-ray results which was validated and refined using a sample of chest x-ray results prior to commencement of the study. The study is the first to report chest x-ray results with respect to time to diagnosis, stage at diagnosis and survival.

Smoking status, co-morbidities and the symptoms that prompted investigation with chest x-ray were not available. It is not possible to know whether chest x-rays were requested because of respiratory symptoms or symptoms stipulated in guidance from NICE.(48) However, this reflects real world clinical practice, and investigations that lead to a lung cancer detection may be initiated without malignancy having been initially considered as a likely diagnosis.

A period of one year from chest x-ray to diagnosis was chosen to determine sensitivity, reflecting much of the existing research documented in chapter two. One year was chosen as a period in which it would be likely that a macroscopic lesion would be present. The choice of time period has important consequences for sensitivity as choosing a longer period, for example two years, would be likely to lower sensitivity, while a shorter period, for example six months, would be likely to result in a higher sensitivity. Estimates derived from screening studies suggest that in a large proportion of cases lung cancer develops over years prior to detection,(142, 144, 180) although a small proportion of cancers develop more

rapidly.(144) It is possible that, in some cases, lung cancer was not present at the time at which the initial chest x-ray was performed.

A comparable proportion of the study population was diagnosed at stage I or II (29.8%) as in England as a whole (27.3%).(181) 44.9% of patients diagnosed with lung cancer had a GP requested chest x-ray in the year prior to diagnosis which is broadly similar to that found in a larger study,(182, 183) but less than that found in a cohort of 247 patients (66%).(70)

The study population included 113 patients (5.3% of the total study population) who attended a service which allowed them to request their own chest x-ray, if they had symptoms. The results of this service are described in chapter four. These chest x-rays had been allocated to GPs for administrative purposes and were therefore included in the study population. As patient data was anonymised at the point of analysis, data for these patients was not excluded. On subtracting the CXR results from the patients who requested their own chest x-rays described in chapter four (86 positive results and 28 negative results) sensitivity remains similar: 82.7% (95% CI 80.9 to 84.5) compared to 82.3% (95% CI 80.6 to 84.1%).

Due to the retrospective observational design of this study no definitive conclusions can be drawn from the lack of observed association between detection of lung cancer and stage at diagnosis or survival. It is likely that the detectability of lung cancers has an independent relationship with stage and survival. Larger tumours may have been more detectable and could also have been more likely to represent late-stage disease. Lesions which were initially not detected could, however, have been more likely to be faster growing tumours, with poorer prognosis, akin to 'interval cancers' described in screening studies.(184) Exploratory analyses in this study suggest that late stage disease is associated with diagnosis within six weeks. Since this effect is apparently not mediated by chest x-ray result, it is possible that patients with more advanced disease are more likely to be diagnosed early. While this may support the so called 'sick quick' theory, it is important to acknowledge that such observations in this context are speculative.(185)

3.7.3 Comparison with existing literature

In the systematic review discussed in the previous chapter the sensitivity of chest x-ray for lung cancer in symptomatic patients identified three studies with estimates of 79.3% (95% CI 67.6 to 91.0), 76.8%; (95% CI 64.5 to 84.2%) and 79.7%, (95% CI 72.7 to 86.8%). Sensitivity in the present study (82.3%) was consistent with previous estimates, although the larger sample size has yielded tighter CIs (95% CI 80.6% to 84.1%) than previous investigations.

As sensitivity is affected by the prevalence of the disease and the associated differing spectrum of disease, which also may contribute to the higher sensitivity in this study, since all of the patients had a diagnosis of lung cancer.(75)

In a Danish study 12 patients with lung cancer who had a negative chest x-ray result had a median duration from presentation to GP to diagnosis of 161 days to diagnosis compared to 27 days for those with a positive chest x-ray.(72) In another retrospective study, diagnosis was 'missed' on the chest x-rays of 14 patients who had experienced an additional median delay of 101 (48–339) days.(161)

The association between duration to diagnosis and survival is known to be complex. Tørring et al. found increasing mortality with longer diagnostic intervals; however, they also observed higher mortality with short diagnostic intervals. Redaniel et al. observed higher five year survival for patients with a diagnostic interval of 3-6 months, with lower survival for those with diagnostic intervals shorter and longer than this.(186, 187) A systematic review which examined time to diagnosis and outcomes for lung cancer presented 'mixed findings' with similar numbers of studies demonstrating positive, negative and no associations. Such observations are likely to be related to the clinical heterogeneity of cancer presentations. While cancers which are undetected will progress unchecked by treatment, rapidly progressive cancers which confer poor outcomes may also have shorter diagnostic intervals both through their more florid clinical presentation and shorter overall survival.(185) In this study it is possible that adverse consequences of failure to detect cancer have been obscured by comparison with cancers which were more advanced and therefore more likely to be detected on chest x-ray.

Some of the reasons why lung cancer may not be identified on chest x-ray have been explored in previous research, some of which has been considered in section 2.6.3.2. Smaller lung cancers are more likely to not be identified on chest x-ray.(160, 161) Tumours that lack well defined borders and those that are located in the lung apices can be harder to identify on chest x-ray. (160, 166, 168-171). Adenomas may be less identifiable on chest x-ray compared to other common histologies.(167)

3.7.4 Implications for research and practice

Chest x-ray does not identify lung cancer in around 18% of patients with lung cancer in the year before diagnosis. The study also demonstrated that for the 15.2% of patients who had a further chest x-ray in the year before diagnosis sensitivity increased only slightly from 82.3% on the initial chest x-ray to 83.6%. Meanwhile in almost 10% of those who had

another chest x-ray following a result which indicated non-urgent follow up, this result was negative. Therefore, even for patients who have a repeat chest x-ray which is negative GPs should not wholly dismiss the possibility of lung cancer if symptoms persist. In such circumstances, further actions could include reassessment after a suitable interval, requesting imaging with another modality such as computed tomography or asking for advice from colleagues in respiratory medicine.

While evidence for an association with adverse stage at diagnosis or survival was not found, it is possible that such associations do exist, but that a retrospective approach using routinely collected data was not sufficient to demonstrate this association. A prospective study comparing chest x-ray with a more sensitive modality such as computed tomography may be necessary to determine if such an association is present.

Since such a prospective imaging study would be costly and require the participation of many thousands of patients, the preliminary retrospective approach may help inform priorities for further research. It would not be appropriate to use the findings of this study to undermine the case for achieving early diagnosis of lung cancer, given the strong association between early stage diagnosis and survival.(188) However, the study suggests that before considering replacing the role of chest x-ray with a modality such as computed tomography, both modalities should be assessed in a prospective trial and cost-effectiveness analysis to determine if the potential gains in accuracy outweigh the harms and costs. In chapter six the rationale for such a trial, along with the some of the aforementioned issues with conducting such a study are considered more fully.

The study described in this chapter did not attempt to ascertain whether false negative chest x-ray results were due to human error. In chapter two the existing literature around ‘missed’ lung cancers on chest x-ray which can be attributed to such errors, and some of the explanations for such lapses, was discussed. If a substantial proportion of false negative chest x-ray results are due to human error and if technology such as artificial intelligence is successful in detecting abnormalities suggestive of lung cancer which human radiologists may not identify then it is possible this could be an important advance which enhances the performance of chest x-ray. There is emerging evidence that such technology may help radiologists to identify lesions suspicious of lung cancer on chest x-ray and further progress in this area is likely to be made in the coming years.(189)

From a clinical perspective, whilst this study brings greater understanding of the sensitivity of chest x-ray for lung cancer compared to the literature described in chapter two, understanding what risk a patient has of having lung cancer if they have symptoms but have had a negative chest x-ray, remains unknown. In practical terms it remains difficult for GPs

to decide what actions to take in this situation. The present study also provides little insight for the clinician as to how basic clinical information such as smoking status and symptoms should be used to stratify risk of lung cancer, following a negative chest x-ray. To address these gaps chapter four presents a study in which the risk of having lung cancer despite a negative chest x-ray with respect to particular symptoms is estimated.

3.8 Ethical approval

The study was approved following review from the University of Leeds School of Medicine ethics committee (SoMREC 18-035) and the Leeds Teaching Hospitals NHS Trust Data Oversight Committee (LTH19034)

3.9 Acknowledgements

I would like to thank Matt Barclay who provided additional advice regarding statistical aspects of the project.

4. What is the risk of lung cancer in people who have symptoms but who have who have had a negative chest x-ray result?

4.1 Overview

- Background: Chapters two and three have demonstrated that chest x-rays requested for patients who have symptoms do not detect lung cancer in about 20% of cases. But, these studies were unable to determine specificity of chest x-ray or the risk of lung cancer, with particular symptoms, following a negative chest x-ray.
- Aims:
    - To determine sensitivity, specificity, positive predictive value and negative predictive value of chest x-rays for detecting lung cancer in people aged ≥50
    - To determine the positive predictive values (PPVs) of symptoms (and thrombocytosis) for lung cancer in smokers and non-smokers aged ≥ 50
    - To develop a risk assessment tool to allow GPs to estimate the risk of lung cancer in people with symptoms who have had a negative chest x-ray result
    - To determine whether the symptoms associated with lung cancer are different in those who have had a positive chest x-ray compared to those who had a negative chest x-ray result
    - To determine which symptoms are associated with the highest risk of being diagnosed with lung cancer following a negative chest x-ray result
    - To determine if high platelet count (thrombocytosis) can be used in combination with symptoms to estimate the risk of lung cancer in patients who have either positive or negative chest x-ray result
- Design & Setting: A prospective cohort study based on routinely collected data from a service which allowed patients with symptoms to request a chest x-ray
- Methods: Symptom data was combined with a diagnostic category (positive or negative) for each chest x-ray. Sensitivity & specificity of chest x-ray for lung cancer was calculated. The PPVs of lung cancer associated with each symptom was estimated for those with a negative chest x-ray.
- Results: 114 (1.3%) out of 8996 patients were diagnosed with lung cancer within one year. Sensitivity was 75.4%, and specificity was 90.2%. Risk of lung cancer following a negative chest x-ray was low for all symptoms with the exception of haemoptysis, which had a positive predictive value of 2.9%.
- Conclusion: Chest x-ray has limited sensitivity. However, in a low prevalence population, its high specificity and negative predictive value means that lung cancer is very unlikely

to be present following a negative result. The study suggests that urgent referral for unexplained haemoptysis, regardless of chest x-ray result, is appropriate.

4.2 Introduction

The systematic review detailed in chapter two has demonstrated that lung cancer is only evident on chest x-ray in the year prior to diagnosis in approximately 77-80% patients based on three studies with a total population of 380. The subsequent chapter determined a sensitivity of 82.3% with a population of 2129. Neither chapter has addressed the specificity of chest x-ray for lung cancer or provided additional insight for clinicians to estimate the risk of lung cancer for individual patients who have an unremarkable chest x-ray.

That around a fifth of patients who do have lung cancer may have disease that is not detected on chest x-ray poses a conundrum for GPs. Since the capacity to perform computed tomography is limited in the United Kingdom compared to some similar countries(190) and the symptoms which could represent lung cancer are extremely common(39) it would not be practicable for GPs to request imaging with computed tomography on all patients with symptoms who have an unremarkable chest x-ray. A means of determining risk of lung cancer in the context of a negative chest x-ray could help rationalise further investigation decisions for GPs and help inform shared decision making between patients and GPs.

The practice of ‘safety netting’, conceptualised by Neighbour in the 1980s, involves GPs advising patients for whom a serious diagnosis such as cancer is considered not sufficiently likely to warrant immediate further investigations or referral on what actions they should take should their symptoms persist or worsen.(191) Safety netting may be considered appropriate for patients who have been investigated with a chest x-ray because of possible lung cancer symptoms (excepting haemoptysis) and for whom the chest x-ray result is unremarkable.(192). For example, a patient might be advised that their chest x-ray is normal which offers some reassurance that cancer is unlikely to be present but that if their symptoms are still present after a further duration then they should make a further appointment so that their GP can consider whether any further action or investigation is required. Understanding more about the eventual outcomes for patients with symptoms who have negative chest x-ray results might help inform whether, or for which patients, such safety netting approaches are appropriate.

A series of case-control studies have derived PPVs for particular symptoms and combinations of symptoms in smokers and non-smokers for common cancers, including lung cancer.(59) The PPVs derived from these studies have been used to create Risk Assessment Tools (RATs) which allow GPs to rapidly identify the risk of cancer associated with a symptom or two symptoms. For the lung cancer RAT 'symptoms' included two features which might be more accurately termed 'findings', rather than symptoms which patients might present with. These were 'abnormal spirometry' and 'thrombocytosis'.

4.3 Objectives

4.3.1 Primary Objectives

- To determine the sensitivity, specificity, positive predictive value and negative predictive value of chest x-rays in detecting lung cancer in smokers and non-smokers aged ≥50 years
- To determine the positive predictive values of symptoms (and thrombocytosis) for lung cancer in smokers and non-smokers aged ≥ 50
- To develop a tool to allow GPs to estimate the risk of lung cancer in people with symptoms who have had a negative chest x-ray result

4.3.2 Secondary objectives

- To determine whether the symptoms associated with lung cancer are different in those who have had a positive chest x-ray result compared to those who had a negative chest x-ray result
- To determine which symptoms are associated with the highest risk of being diagnosed with lung cancer following a negative chest x-ray result
- To determine if high platelet count (thrombocytosis) can be used in combination with symptoms to estimate the risk of lung cancer in patients who have either positive or negative chest x-ray result

4.4 Study design

The Leeds Teaching Hospitals NHS Trust (LTHT) self-request chest x-ray (SRCXR) service allowed patients aged 50 years and older who had symptoms for which chest x-ray was recommended by NICE to present for a chest x-ray without referral by GP.(193) Upon presentation to the service, patients were asked to complete a form (Appendix 7) in which they indicated the presence of particular symptoms for at least three weeks (cough,

haemoptysis, shortness of breath, chest pain, weight loss, change in voice) and their smoking status. The forms were checked by a radiographer to ensure that necessary information was entered and to confirm eligibility for the chest x-ray prior to the investigation being performed. Patients who had a prior chest x-ray performed within three months of presentation were not eligible for SRCXR. For patients who underwent >1 SRCXR during the study, each SRCXR was considered a separate event.

A study database was created by supplementing the routinely collected data for the SRCXR service for the period 2011 to 2016 with:

- data on whether or not each individual was subsequently diagnosed with lung cancer within one and two years following SRCXR
- data on whether or not the patient had a full blood count performed in the one or two years prior to diagnosis and whether or not thrombocytosis, defined as a platelet count of > 400 x 10^9 / L (a widely used cut-off in clinical practice and in a previous investigation of thrombocytosis with respect to cancer risk).(194)
- coded chest x-ray results, which were categorised as positive or negative according to the system detailed on chapter 3
- lung cancer histology, if applicable

The database was de-identified with all patient identifiable data removed including name, address, NHS number, LTHT hospital number, date of diagnosis and detailed lung cancer diagnostic information. The full list of variables held in the study database is listed in appendix 8.

Patients who were diagnosed with lung cancer prior to attending for SRCXR were excluded as the purpose of the investigation was to be able to determine risk of lung cancer in patients who did not already have a risk of lung cancer, since most GPs would be likely to already have a higher index of suspicion for a recurrence of lung cancer in that group. Patients who were diagnosed with another intrathoracic malignancy, such as mesothelioma within one or two years of SRCXR were also excluded. These patients were excluded because the rationale of the study was to generate evidence to support the early detection of lung cancer which has strong evidence of prognostic benefit. The prognostic benefit for early detection of other intrathoracic malignancies such as mesothelioma is less clear and also analysing heterogeneous malignancies together was not considered appropriate. Whether or not to include other cancers as cases was discussed extensively within the supervision team. In these discussions it was felt that the detection of other cancers could be an important outcome but that interpretation of such findings as ‘cases’ would be problematic because the SRCXR service was established with the explicit objective of detecting lung cancer, rather

than all potential pathologies and it would also not have been feasible to design the study with definitions of what diseases or cancers should be included as cases since 'cancer' represents a heterogeneous spectrum of disease.

4.5 Statistical analysis

Incidences of lung cancer diagnosis within one and two years following a negative chest x-ray were calculated. This was followed by calculation of the incidence of lung cancer within one and two years for each symptom and symptom combination. These incidences are equivalent to the observed PPVs of each symptom or symptom combination. Patients who reported multiple symptoms were included in calculations for individual symptoms and also for symptom combinations. Estimates of PPVs adjusted for age, sex and smoking status were obtained from the marginal distributions of separate logistic regression models predicting lung cancer diagnosis within one and two years of a negative chest x-ray for each symptom and symptom combination. By comparing the average risk for people with a symptom to people without that symptom a percentage estimate of the additional risk of cancer for those with each symptom or symptom combination was derived. As all patients within the study population had symptoms, non-smoking, female patients aged 50-55 were used as a reference category, since these patients had the lowest risk of lung cancer.

A further logistic regression model predicting lung cancer diagnosis within two years was constructed for each symptom and symptom combination, which included the interaction between the indicator for that symptom/combination and chest x-ray result, as well as the main effects for both variables. These interactions explored whether the association of each symptom and symptom combination with lung cancer diagnosis differed between patients with a positive chest x-ray to those with a negative chest x-ray.

Statistical analysis was undertaken using SPSS (IBM) version 25.

4.6 Results

The study database initially contained records for 9367 patients. 342 records were excluded due to administrative errors in capture of patient information at the time of presentation for SRCXR:

- On 227 forms NHS number was not properly recorded so they could not be linked to a patient record.

- For 102 forms no corresponding chest x-ray could be located, suggesting the investigation had not been performed.
- On 13 forms no symptoms were recorded

Measures were considered in order to identify the 227 patients for whom NHS numbers were not recorded, such as undertaking a manual inspection of CXRs performed on the date of completion of the form. However, this was deemed to be not feasible due to the large volume of CXRs where are performed in LTHT (approximately 200 per day) and because chest x-ray reports did not note consistently if the chest x-ray was performed as part of the SRCXR service, so could not be reliably differentiated from non self-request chest x-rays. A manual check of the SRCXR paper forms was also not possible as these had been destroyed, following creation of the SRCXR service database. Whilst it is impossible to state that the data entry error occurred entirely at random across the patient population, no temporal or other pattern has been found to exist between these 227 records that suggests the introduction of a systemic source of bias.

16 further patients were excluded because they had a diagnosis of lung cancer prior to attending for SRCXR while 13 patients were excluded because they were diagnosed with an intrathoracic malignancy other than lung cancer within two years. Data suppression requirements agreed upon granting ethical approval for this project means that subgroups containing only small numbers of patients which could lead to identification of individual patients could be reported. Therefore it is not possible to report a breakdown of the specific malignancies other than lung cancer, other than that the majority of these were mesothelioma.

Figure 4.1 illustrates the number of patients in the study and the numbers who had positive and negative SRCXRs. Following the above exclusions 8996 patient records remained which were de-identified and included in the study database. 771 (8.6%) of these records were for patients who had previously had a SRCXR (Appendix 9).

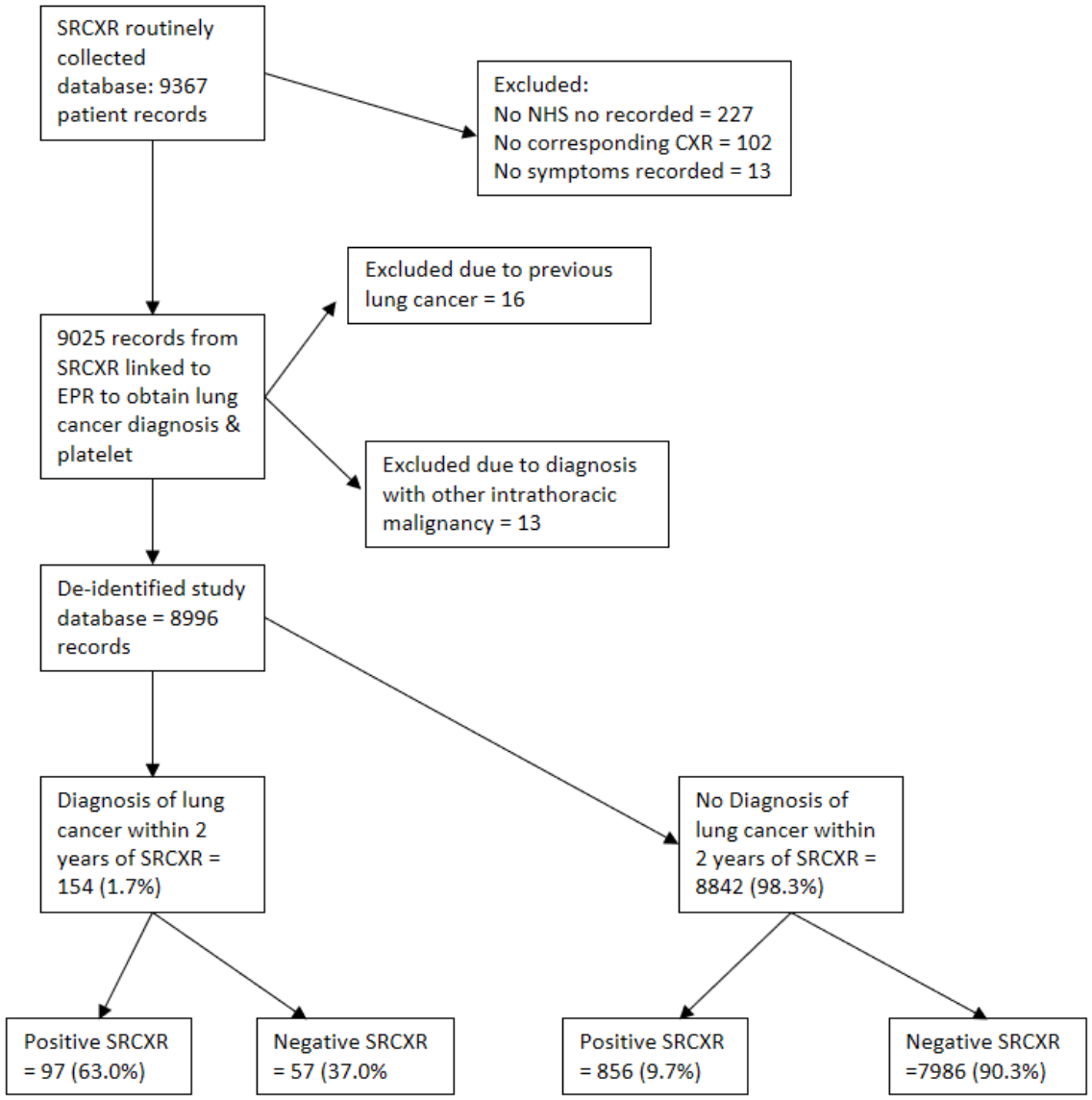


Figure 4.1 Numbers of patients included in study, lung cancer diagnoses and positive and negative chest x-ray results at 2 years

Table 4.1 outlines the basic characteristics of the SRCXR study database. Table 4.2 outlines the characteristics of patients who subsequently had a diagnosis of cancer including stage and histology. Table 4.3 and table 4.4 outlines the sensitivity, specificity, positive and negative predictive values for SRCXR for a diagnosis of lung cancer at 1 and 2 years.

Characteristic	Number	%
Sex		
Male	4441	49.4
Female	4555	50.6
*Smoking status**		
Smoker status not recorded	60	0.7
Smoker/Ex-smoker	5951	66.2
Never Smoker	2985	33.2
Age Category		
Age 50 – 55	1485	16.5
Age 56 – 60	1484	16.5
Age 61 – 65	1777	19.8
Age 66 – 70	1598	17.8
Age 71 – 75	1205	13.4
Age 76 – 80	845	9.4
Age > 80	602	6.7
No. Symptoms Recorded		
1	3527	39.2
2	3240	36.0
3	1674	18.6
≥4	555	6.2
Thrombocytosis		
Thrombocytosis in 24 months prior to SRCXR (out of number who had FBC)	395 (5524)	7.2
Index of Multiple Deprivation		
1st Decile (Most deprived)	2844	31.6
2nd Decile	2233	24.8
3rd Decile	1350	15.0
4th Decile	1652	18.4
5th Decile	753	8.4
6th Decile	29	0.3
7th Decile	38	0.4
8th Decile	37	0.4
9th Decile	35	0.4
10th Decile (Least deprived)	25	0.3

Table 4.1 Patient characteristics

(FBC = full blood count, is the blood test routinely used to detect thrombocytosis).
*** indicates category in which stated percentages do not total 100 due to rounding.**

	Diagnosed with lung cancer in period 0-12 months following SRCXR	Diagnosed with lung cancer in period 0-24 months following SRCXR
Summary statistics		
Number	114	154
Mean age	69 Years	70 Years
Male	45 (39.5%)	64 (41.6%)
Ever smokers	107 (93.9%)	145 (94.2%)
Chest x-ray result		
Positive	86 (75.4%)	97 (63.0%)
Negative	28 (24.6%)	57 (37.0%)
Stage at Diagnosis		
Stage I-II	34 (29.8%)	50 (32.5%)
Stage III-IV	80 (70.2%)	104 (67.5)
Tumour Histology		
Adenocarcinoma	38 (33.3%)	50 (32.5%)
Squamous cell carcinoma	31 (27.2%)	41 (26.6%)
Small cell carcinoma	15 (13.2%)	22 (14.3%)
Non-small not otherwise stated & Large cell*	17 (14.9%)	18 (11.7%)
Unknown	13 (11.4%)	23 (14.9%)

Table 4.2 characteristics of patients diagnosed with lung cancer within 1 and 2 years of SRCXR.
*** Categories combined due to data suppression requirements**

	Lung cancer diagnosis (within 1 year of SRCXR)	No diagnosis of lung cancer (within 1 year of SR-CXR)	Totals
Positive X-ray	86	867	953
Negative X-ray	28	8015	8043
Totals	114	8882	8996
Sensitivity (95% CI)	75.4% (67.5-83.3)		
Specificity	90.2% (89.6-90.9)		
PPV	9.02% (7.21-10.8)		
NPV	99.7% (99.5-99.8)		

Table 4.3 Test characteristics of chest x-ray in the study population for one year

PPV = positive predictive value, NPV = negative predictive value.

	Lung cancer diagnosis (within 2 year of SRCXR)	**No diagnosis of lung cancer (within 2 year of SR- CXR)**	**Totals**
Positive X-ray	97	856	953
Negative X-ray	57	7986	8043
Totals	154	8842	8996
Sensitivity (95% CI)	63.0% (54.8-70.6)		
Specificity	90.3% (90.0-90.9)		
PPV	10.2% (9.0-11.5)		
NPV	99.3% (99.1-99.4)		

Table 4.4 Test characteristics of chest x-ray in the study population for two years.

PPV = positive predictive value, NPV = negative predictive value

114 patients (1.3%) were diagnosed with lung cancer in one year following SRCXR of whom 86 (75.4%) had a positive chest x-ray and the remaining 28 (24.6%) had a negative chest x-ray. At two years following SRCXR, a total of 154 patients (1.7%) were diagnosed with lung cancer, of whom 97 (63.0%) had a positive chest x-ray.

Observed cancer incidence for patients with a negative chest x-ray for one and two years was 0.35% (95% CI 0.22% to 0.48%) and 0.71% (95% CI 0.53% to 0.89%), respectively. Adjusted one and two year incidences were 0.27% (95% CI 0.13% to 0.55%) and 0.56% (95% CI 0.37%-0.84%). Figure 4.2 contains the observed PPVs of single symptoms demonstrating the PPVs of the entire study population and of those who had a negative chest x-ray, for the period up to one year following SRCXR. Figures 4.3 and 4.4 contain the observed PPVs of symptom combinations of those who had a negative chest x-ray within one and two years of SRCXR respectively.

For context, figures 4.5 and 4.6 show the one and two year observed PPVs of symptom combinations for the entire study population, regardless of chest x-ray result. These may be interpreted as the percentage chance of being diagnosed with cancer within one or two years following chest x-ray for the respective symptom or symptom combinations, irrespective of the result of the chest x-ray Figures 4.7 and 4.8 contain the adjusted PPVs (marginal means) for symptom combinations within one and two years following a negative chest x-ray. The marginal means may be understood as the additional absolute risk of lung cancer that is attributable to each symptom or symptom combination for patients who had a negative chest x-ray. The largest marginal means for symptoms for which there were at least five cases was for haemoptysis, which was 0.0222 (0.0071 - 0.0690) at one year and 0.0319 (0.0142 - 0.0715) at two years. That the magnitude of these marginal means are modest in absolute terms reflects the overall prevalence of lung cancer in the population and have little clinical application, beyond demonstrating that haemoptysis was the most important symptom indicating possible lung cancer in patients who had a negative chest x-ray.

4135 and 5524 patients had full blood counts obtained in the 12 and 24 months prior to chest x-ray, of whom 217 and 395 had thrombocytosis respectively. In all analyses of thrombocytosis with other symptoms confidence intervals included 0, or could not be calculated due to insufficient cases. Therefore inclusion of thrombocytosis did not add any discriminative utility in this study. The one year PPVs for the entire study population for thrombocytosis were 1.03 (95% CI 0 to 2.45) when in combination with cough, 2.17 (95% CI 0 to 6.39) in combination with chest pain and 6.67 (95% CI 0 to 15.59) in combination with weight loss.

There was no evidence that there was a difference in risk of lung cancer from particular symptoms between those who had a negative versus positive chest x-ray (all interaction *p*-values >0.05). In other words, the study did not identify that there were any symptoms that were particularly associated with a negative chest x-ray result and the risk of lung cancer diminished substantially for all symptoms following a negative result.

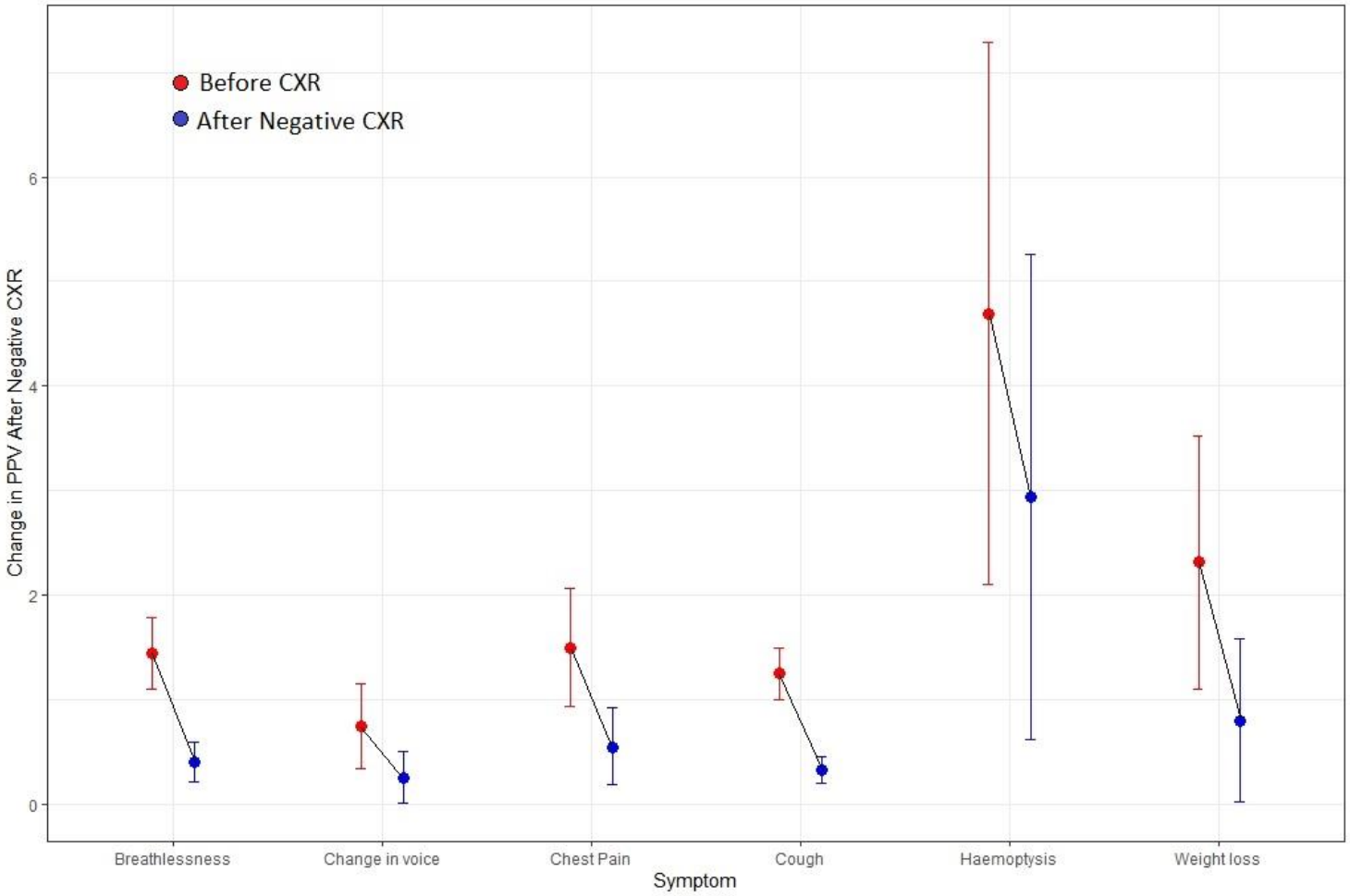


Figure 4.2 Individual symptoms PPVs as a percentage (unadjusted) with respect to diagnosis with lung cancer in the period 0-12 months following SRCXR

PPVs for the entire study population are marked in red, while the PPVs following a negative chest x-ray are marked in blue. Since thrombocytosis was not used as a qualifying symptom for chest x-ray it has not been included in the figures. CXR= chest x-ray

Cough, as a percentage (95% CI)	Haemoptysis, as a percentage (95% CI)	Breathlessness, as a percentage (95% CI)	Chest pain, as a percentage, (95% CI)	Weight loss, as a percentage (95% CI)	Change in voice, as a percentage (95% CI)	PPV
0.33 (0.20 - 0.46)	2.94 (0.62 - 5.26)	0.40 (0.21 - 0.60)	0.55 (0.19 - 0.91)	0.80 (0.02 - 1.58)	0.26 (0.01 - 0.51)	As single symptom
	2.63 (0.36 - 4.91)	0.42 (0.21 - 0.63)	0.55 (0.17 - 0.94)	0.86 (0.02 - 1.70)	0.27 (0.01 - 0.53)	Cough
		3.15 (0.11 - 6.19)	1.41 (0.00 - 4.15)	7.69 (0.00 - 17.94)	1.75 (0.00 - 5.16)	Haemoptysis
			0.37 (0.01 - 0.73)	0.86 (0.00 - 1.83)	0.30 (0.00 - 0.64)	Breathless
				0.70 (0.00 - 2.07)	0.48 (0.00 - 1.14)	Chest Pain
					0.68 (0.00 - 2.01)	Weight loss

Figure 4.3 Symptom combination PPVs as a percentage for diagnosis with lung cancer in the period 0-12 months following SRCXR for those who had a negative chest x-ray result.

Since thrombocytosis was not used as a qualifying symptom for chest x-ray it has not been included in the figures. Cells which contain data from fewer than five cases are shaded grey.

Cough, as a percentage (95% CI)	Haemoptysis, as a percentage (95% CI)	Breathlessness, as a percentage (95% CI)	Chest pain, as a percentage, (95% CI)	Weight loss, as a percentage (95% CI)	Change in voice, as a percentage (95% CI)	PPV
0.67 (0.49 - 0.86)	3.92 (1.26 - 6.59)	0.93 (0.63 - 1.23)	0.92 (0.46 - 1.39)	1.40 (0.37 - 2.43)	0.71 (0.29 - 1.12)	As single symptom
	3.68 (1.01 - 6.36)	0.92 (0.61 - 1.23)	0.90 (0.41 - 1.39)	1.5 (0.4 - 2.60)	0.67 (0.26 - 1.08)	Cough
		4.72 (1.03 - 8.41)	2.82 (0.00 - 6.67)	11.54 (0.00 - 23.82)	1.75 (0.00 - 5.16)	Haemoptysis
			0.93 (0.36 - 1.50)	1.43 (0.19 - 2.68)	1.00 (0.38 - 1.62)	Breathless
				2.10 (-0.00 - 4.45)	0.72 (0.00 - 1.53)	Chest Pain
					0.68 (0.00 - 2.01)	Weight loss

Figure 4.4 Symptom combination PPVs as a percentage for diagnosis with lung cancer in the period 0-24 months following SRCXR for those who had a negative chest x-ray result.

Since thrombocytosis was not used as a qualifying symptom for chest x-ray it has not been included in the figures. Cells which contain data from fewer than five cases are shaded grey.

Cough, as a percentage (95% CI)	Haemoptysis, as a percentage (95% CI)	Breathlessness, as a percentage (95% CI)	Chest pain, as a percentage (95% CI)	Weight loss, as a percentage (95% CI)	Change in voice, as a percentage (95% CI)	PPV
1.24 (1.01 - 1.48)	4.67 (2.09 - 7.25)	1.44 (1.09 - 1.79)	1.49 (0.93 - 2.05)	2.31 (1.11 - 3.50)	0.75 (0.34 - 1.15)	As single symptom
	4.24 (1.67 - 6.80)	1.45 (1.08 - 1.82)	1.43 (0.85 - 2.01)	2.31 (1.07- 3.56)	0.66 (0.27 - 1.05)	Cough
		5.10 (1.66- 8.54)	3.70 (0.00- 7.82)	9.38 (0.00- 19.47)	1.45 (0.00 - 4.27)	Haemoptysis
			1.17 (0.56 - 1.77)	2.34 (0.91 - 3.77)	0.81 (0.28 - 1.34)	Breathless
				1.81 (0.00 - 3.83)	0.86 (0.02 -1.71)	Chest Pain
					1.18 (0.00 -2.80)	Weight loss

Figure 4.5 Symptom combination PPVs as a percentage for entire study population with respect to diagnosis with lung cancer in the period 0-12 months following SRCXR.

Since thrombocytosis was not used as a qualifying symptom for chest x-ray it has not been included in the figures. Cells which contain data from fewer than five cases are shaded grey.

Cough, as a percentage (95% CI)	Haemoptysis, as a percentage (95% CI)	Breathlessness, as a percentage (95% CI)	Chest pain, as a percentage, (95% CI)	Weight loss, as a percentage (95% CI)	Change in voice, as a percentage (95% CI)	PPV
1.66 (1.39 - 1.93)	5.45 (2.67 - 8.22)	2.11 (1.69 - 2.53)	1.99 (1.35 - 2.64)	3.14 (1.75 - 4.52)	1.27 (0.74 - 1.79)	As single symptom
	5.08 (2.29- 7.89)	2.07 (1.63- 2.50)	1.93 (1.26 - 2.60)	3.20 (1.75 - 4.67)	1.08 (0.59 - 1.58)	Cough
		6.37 (2.55 - 10.19)	4.94 (0.22 - 9.66)	12.50 (1.04 - 23.96)	1.45 (0.00 - 4.27)	Haemoptysis
			1.83 (1.07 - 2.59)	3.27 (1.59 - 4.98)	1.62 (0.88 - 2.36)	Breathless
				3.61 (0.78 - 6.45)	1.30 (0.27 - 2.33)	Chest Pain
					1.76 (0.00 - 3.74)	Weight loss

Figure 4.6 Symptom combination PPVs as a percentage for entire study population with respect to diagnosis with lung cancer in the period 0-24 months following SRCXR.

Since thrombocytosis was not used as a qualifying symptom for chest x-ray it has not been included in the figures. Cells which contain data from fewer than five cases are shaded grey.

Cough, as a percentage (95% CI)	Haemoptysis, as a percentage (95% CI)	Breathlessness, as a percentage (95% CI)	Chest pain, as a percentage, (95% CI)	Weight loss, as a percentage (95% CI)	Change in voice, as a percentage (95% CI)	PPV
0.0025 (0.0013 - 0.0051)	0.0240 (0.0071 - 0.0814)	0.0030 (0.0015 - 0.0060)	0.0049 (0.0022 - 0.0107)	0.0054 (0.0017 - 0.0171)	0.0020 (0.0007 - 0.0064)	As single symptom
	0.0222 (0.0071 - 0.0690)	0.0033 (0.0016 - 0.0068)	0.0049 (0.0022 - 0.0110)	0.0058 (0.0018 - 0.0182)	0.0021 (0.0007 - 0.0066)	Cough
		0.0257 (0.0073 - 0.0900)	0.0124 (0.0017 - 0.0929)	0.0476 (0.0093 - 0.2431)	0.0159 (0.0022 - 0.1162)	Haemoptysis
			0.0033 (0.0011 - 0.0093)	0.0058 (0.0016 - 0.0205)	0.0024 (0.0007 - 0.0076)	Breathless
				0.0061 (0.0008 - 0.0442)	0.0043 (0.0011 - 0.0174)	Chest Pain
					0.0056 (0.0008 - 0.0388)	Weight loss

Figure 4.7 Adjusted symptom combination marginal means for lung cancer in the period 0-12 months following negative chest x-ray as a percentage.

Cells which contain data from fewer than five cases are shaded grey. Marginal means are the average risks of cancer for different groups of people – for example, people with or without a symptom – taking into account the characteristics of the people within each group, such as their age and sex. When we compare the average risk for people with a symptom to people without that symptom, we have an estimate of the additional risk of cancer for people with the symptom.

Cough, as a percentage (95% CI)	Haemoptysis, as a percentage (95% CI)	Breathlessness, as a percentage (95% CI)	Chest pain, as a percentage, (95% CI)	Weight loss, as a percentage (95% CI)	Change in voice, as a percentage (95% CI)	Cough, as a percentage (95% CI)
0.0054 0.0036 - 0.0080	0.0323 0.0139 - 0.0750	0.0073 0.0047 - 0.0113	0.0084 0.0046 - 0.0155	0.0080 0.0031 - 0.0202	0.0064 0.0032 - 0.0125	As single symptom
	0.0319 0.0142 - 0.0715	0.0073 0.0046 - 0.0117	0.0081 0.0042 - 0.0156	0.0086 0.0034 - 0.0218	0.0061 0.0030 - 0.0122	Cough
		0.0406 0.0166 - 0.0988	0.0275 0.0067 - 0.1121	0.0797 0.0213 - 0.2977	0.0166 0.0023 - 0.1222	Haemoptysis
			0.0084 0.0040 - 0.0177	0.0083 0.0029 - 0.0237	0.0088 0.0045 - 0.0173	Breathless
				0.0155 0.0041 - 0.0581	0.0073 0.0024 - 0.0228	Chest Pain
					0.0050 0.0007 - 0.0357	Weight loss

Figure 4.8 Adjusted marginal means for lung cancer in the period 0-24 months following negative chest x-ray as a percentage.

Cells which contain data from fewer than five cases are shaded grey. Marginal means are the average risks of cancer for different groups of people – for example, people with or without a symptom – taking into account the characteristics of the people within each group, such as their age and sex. When we compare the average risk for people with a symptom to people without that symptom, we have an estimate of the additional risk of cancer for people with the symptom.

4.7 Conclusions

4.7.1 Summary

This study presents the PPVs for developing lung cancer with respect to particular symptoms when reported in a service which allowed patients to request a chest x-ray. Although similar methodology has been employed before(59), this is the first time that risk of developing lung cancer has been estimated in relation to chest x-ray results. This has demonstrated that for most symptoms, the risk of lung cancer following a negative chest x-ray remains very low, with the exception of haemoptysis which had a PPV of 2.94%. This finding is important because it provides evidence to support the current NICE guidance which uses an abnormal chest x-ray result as the main criterion for a two week referral, with the exception of haemoptysis, which warrants referral, even in the absence of concerning findings on chest x-ray.

This study is also the first to provide diagnostic accuracy estimates including specificity of chest x-ray for the detection of lung cancer in symptomatic patients. Although the sensitivity of chest x-ray may appear modest when interpreted in isolation, when coupled with a negative predictive value of over 99%, this suggests that chest x-ray is well suited to its role as a first line investigation in a low prevalence setting. The performance of chest x-ray could be different in populations with a higher prevalence of lung cancer, for example patients for whom a GP has referred for chest x-ray because of a high index of suspicion for lung cancer.(192)

4.7.2 Strengths and limitations

Although previous studies have examined symptoms associated with lung cancer diagnosis, predominantly through case-control studies, this is the first study that systematically explores symptoms with respect to chest x-ray result. The large sample size of the study population is a strength of this study along with its prospective design. However, the study population had a low prevalence of lung cancer with only 154 diagnosed with lung cancer within two years (1.7%), of whom 57 (37.0%) had a negative chest x-ray. This meant that insufficient cases were present to calculate PPVs for several symptom combinations. The lack of a control group meant that the calculation of adjusted PPVs was calculated using a within study comparator based on the lowest risk patients (female non-smokers aged 50-55). While it was an objective of the study to develop a risk assessment tool for GPs to use with patients who have symptoms but have had a negative chest x-ray, the resulting Figure 4.3 has little practical clinical utility, since the relevant clinical information is easily summarised that haemoptysis confers a PPV of 3%, while for all other symptoms it is less than 1%.

In determining which patients developed lung cancer, it was assumed that patients did not move outside of the region following their chest x-ray. It is possible the prevalence of lung cancer was underestimated if some patients moved and were subsequently diagnosed elsewhere.

It is also possible that some cancers diagnosed one and two years following chest x-ray were not actually present at the time of imaging. Although the natural history of undetected lung cancer is necessarily unknown, estimates derived from screening studies suggest that in a large proportion of cases lung cancer develops over some years prior to detection.(142, 144, 180) However a small proportion of cancers develop more rapidly.(184) Therefore the assumption that a lung cancer which was not detected on chest x-ray constitutes a 'false negative' result requires some qualification, particularly at the two year interval.

The study population had a chest x-ray following their own request for this investigation. There might be important differences between the study population and the patient population who are referred for a chest x-ray by their GP. It is possible that the prevalence of lung cancer in this population is lower than patients who report their symptoms to a GP and are then referred for a chest x-ray. This could be the case if patients had a lower threshold for accessing a SRCXR than for seeing their GP regarding their symptoms and/or if GPs on seeing patients with symptoms did not refer patients who had respiratory symptoms onward for a chest x-ray. If this was the case, the pre-test probability of lung cancer would be lower and would result in lower PPVs and sensitivity and higher NPVs and specificity than in the referred population who see their GP before a chest x-ray was arranged. The inverse might also apply, it could the case that patients had a higher threshold for arranging their own SRCXR than for consulting a GP first about their symptoms. Symptom PPVs for the whole population in this study (i.e. including all irrespective of chest x-ray result) was higher than that of the previously developed RAT which probably reflects that patients who had sufficient concern to arrange a SRCXR were a higher risk population than all those who might have a symptom recorded in the primary care record for by a GP if they mentioned symptoms during a consultation, since the previous RAT study was based on patients who had symptoms recorded by GP, not those who were selected for further investigation.(59) It has previously been observed that patients who are selected for testing by their GP constitute a higher risk group, merely because they have been selected for testing.(124) The same could well be true of patients who choose themselves to be tested.

It is possible that the patient group who attended for a self-request chest x-ray could have different levels of socio-economic deprivation than those who attend for chest x-rays following referral from their GP. However, socio-economic status is not linked to differences

in stage of lung cancer diagnosis, and is unlikely to alter the performance characteristics of the test itself.(28)

While the study population were deemed eligible for chest x-ray because they had symptoms listed in NICE guidance, it is important to acknowledge that NICE guidance was based on GP appraisal of patient symptoms and did not envisage patient requested investigations. The study population was also limited to individuals aged 50 and over, while NICE guidelines suggests investigation for those with symptoms aged over 40 years. It is also likely that GPs are less prescriptive and may not always require specific symptoms before requesting a chest x-ray when concerned about lung cancer.

In contrast to the previously produced lung cancer RAT the 'symptoms' included in this study did not include 'abnormal spirometry'(59) as incorporating this data would have required access to the primary care record, which was not obtained for this study. Had this data been obtained it is likely that only a small proportion of the patients would have had spirometry performed and had this coded in their records than was found for thrombocytosis, so it is likely that this finding would have also generated PPVs with confidence interval that included 0.

Symptoms were declared by patients and this information was recorded by radiographers on a pro-forma (Appendix 7). Such a means of data collection was appropriate for the large numbers of patients who attended the service, but does have limitations as noted in a consensus statement on improving design and reporting of studies on early cancer diagnosis.(195) Duration of symptoms was recorded as free text on forms but the range of ways in which this was recorded prevented consistent categorisation and duration of symptoms were not considered in the analyses. It is also possible that when symptoms were being declared by patients, where multiple symptoms were present, these may not have all been recorded once one symptom which qualified for the service was marked on the form. However, symptom recording may be also incomplete for studies that use different types of data, such as data entered during primary care consultations, or indeed for any type of study that relies on reporting and recording of symptoms.

4.7.3 Comparison with existing literature

This study has confirmed the finding of previous studies that haemoptysis is the symptom most strongly associated with a subsequent diagnosis of lung cancer(39, 59, 61). Hamilton 2009 was a case-control study which linked cancer registry data to general practice paper and electronic health record symptom records(59). That study did not report chest x-ray

results. Symptom PPVs for this study population were much higher than in Hamilton's work. The populations are unlikely to be directly comparable, since patients' decisions to self-request a chest x-ray could have reflected a greater underlying concern that serious disease was present, compared with attending to see a GP with symptoms, or mentioning symptoms to a GP whilst attending for other reasons. Though it is also possible that patients who would be reluctant to 'bother their doctor' might have more readily attended the SRCXR rather than arranging to see a GP about symptoms.(15)

Previous findings that thrombocytosis is associated with increased risk of lung cancer(194) were not replicated in this study. The relatively small numbers of patients diagnosed with lung cancer and the number of those with thrombocytosis is likely to have rendered this study underpowered to detect such an association. Another possibility is that the population selected for a full blood count and the population that requested a chest x-ray in this study were at already elevated risk of serious disease compared to the wider population by having been selected for testing by their GP with a blood test, or having opted to undergo a chest x-ray themselves.(124) This related mechanism of test selection bias may have obscured the capacity to differentiate elevated risk from thrombocytosis *as well as* patient self-selection to undergo chest x-ray.

The point estimate for sensitivity in this study was lower than that reported in chapter three (75.4% in the present study, 95% CI 67.5 to 83.3% versus 82.3%, 95% CI 80.6% to 84.1%) the previous chapter but the confidence intervals for both overlapped. Sensitivity is affected by the prevalence of the disease and the associated differing spectrum of disease, which could have contributed to the higher point estimate for sensitivity reported in chapter three, since all of the patients in that study had a diagnosis of lung cancer.(27)

4.7.4 Implication for research and/or practice

Increasing access to computed tomography has been proposed as a means of increasing the proportion of patients diagnosed at earlier stages.(126) In many high income countries more extensive use is made of computed tomography than in the UK. In Denmark, Guldbrandt et al investigated offering GPs access to investigation with computed tomography, as an alternative to chest x-ray, providing evidence which has informed a policy shift away from chest x-ray in that country.(86-88, 196) Whilst replacing chest x-ray with computed tomography might expedite diagnoses in some, it remains unknown whether the benefits of earlier diagnosis would outweigh the harms incurred by such a strategy, including over-diagnosis and the additional burdens resulting from findings such as nodules requiring

surveillance. Current guidance advocates urgent referral for the symptom with the highest predictive value for lung cancer (haemoptysis) or in the case of significant intuition or 'gut feeling' from the referring GP. Transitioning to a diagnostic pathway which makes greater use of computed tomography, instead of chest x-ray could have unwelcome implications including the opportunity costs of adopting a more expensive modality, capacity implications for the wider health system as well as the possible harms of over-diagnosis. This study suggests that chest x-ray's present role in lung cancer diagnosis may be appropriate and that any policy decision to replace chest x-ray should not be undertaken without careful health economic evaluation.

This study also supports the approach of using safety netting when a chest x-ray is negative in patients who are at risk of lung cancer and continue to have symptoms. Clinicians can with confidence inform patients who have not had haemoptysis that a diagnosis of lung cancer following a negative chest x-ray is very unlikely and that the benefits of immediate further investigation are in most cases unlikely to justify the harms, costs and inconvenience to patients. Since the precise level of risk that might be considered acceptable will vary between individuals and clinicians, a shared decision making approach is prudent when considering what action to take when symptoms continue despite a negative chest x-ray. Clinicians should remember that even in patients who appear to be at low risk, a negative chest x-ray does not eliminate the possibility of lung cancer and in some cases further investigation should be considered if symptoms persist or evolve.

4.8 Funding

The study was awarded £14,987.90 in funding from the Mason Medical Foundation. This funding was used to support the secondment of a clinical research assistant, Dr Luke Hatton and for the article processing charge for British Journal of General Practice.

4.9 Ethical approval

The study was approved following review from the University of Leeds School of Medicine ethics committee SoMREC 17-107 and the Leeds Teaching Hospitals NHS Trust data oversight committee LTH19015.

4.10 Acknowledgement

I would like to thank Mr Pete Wheatstone who provided advice regarding data governance and public/patient perspectives on the study.

5. What are the associations between characteristics of general practices and their populations with rate of investigation with chest x-ray rate?

5.1 Overview

- Background**:** The studies reported in chapters two and three have demonstrated that although chest x-ray in those who have lung cancer may give a 'false negative' result in around 20% of cases, the study reported in chapter four suggests that the modality does perform well in excluding the disease for people who have respiratory symptoms other than haemoptysis. Previous research has suggested that higher referral rates for suspected cancer and rates of investigation with chest x-ray are associated with improved outcomes.
- Aim**:** To explore the associations between characteristics of general practice services and their practice populations and frequency of investigation with chest x-ray
- Design & Setting**:** Retrospective observational study of English general practices
- Method**:** A database of English general practices containing number of chest x-rays requested per practice and data on population and practice characteristics for 2018 was constructed. Recorded characteristics included patient demographics, smoking prevalence, deprivation, staff demographics and patient satisfaction indicators. Mixed effects Poisson modelling was used to adjust for variation due to chance and to estimate the amount of remaining variation that could be attributed to practice and population characteristics.
- Results**:** There was substantial variation in GP chest x-ray rates (median 34 per 1000 patients, IQR 26-43). Only 18% of between-practice variance in chest x-ray rate was accounted for by recorded characteristics. Higher practice scores for continuity and communication skills and higher proportions of smokers, Asian and mixed ethnic groups, and patients aged ≥65 were associated with increased chest x-ray rates. Higher patient satisfaction scores for access and with greater proportions of male and patients of black ethnicity were associated with lower chest x-ray rates.
- Conclusion: Substantial variation was found in chest x-ray rates beyond that expected by chance, which could not be accounted for by practice and population characteristics. Increasing chest x-ray rates in practices which currently investigate

less often that their peers might offer an effective strategy to improve lung cancer outcomes.

5.2 Introduction

Across many healthcare systems, including that of the UK, GPs have a crucial role in timely diagnosis of lung cancer.(197) Most cancer patients are seen by a GP before diagnosis(186, 198, 199) and analysis of routes to diagnosis in England has demonstrated that almost half of all lung cancer diagnoses result from GP referrals.(200) The previous chapter has suggested that despite its limited sensitivity, chest x-ray remains a useful test for identifying lung cancer, particularly for patients who do not have haemoptysis. Accordingly, investigation with chest x-ray in response to symptoms is likely to be the most frequent way in which lung cancers are first identified through imaging.(201)

Chest x-ray is requested for reasons other than suspected lung cancer from general practice, for example for suspected pneumonia or tuberculosis. However the overlap between lung cancer symptoms and those of common respiratory disorders means that 'incidental' detection of lung cancer on chest x-ray in patients for whom the diagnosis had not been explicitly considered is likely to be common.(202)

Patients who are diagnosed at earlier stages of lung cancer have favourable outcomes compared to those diagnosed with advanced disease.(9) Previous research has demonstrated that patients with cancer who are registered with general practices which have higher rates of urgent referral for suspected cancer (all types, excluding non-melanoma skin cancer) are more likely to be diagnosed with earlier stage disease and have improved survival.(203, 204)

Although guidelines support urgent referral for patients with haemoptysis even in the absence of suspicious chest x-ray findings, less than a tenth of cases present with this symptom and it is quite likely that in many cases GPs choose to first investigate with chest x-ray even when a history of haemoptysis is ascertained.(53) Therefore investigation with chest x-ray is a crucial part of the diagnostic pathway for almost all patients referred urgently by GPs because of suspected lung cancer. Research examining uptake of chest x-ray by GPs during a symptom awareness campaign has indicated that higher utilisation of chest x-ray was associated with earlier stage diagnosis and improved outcomes.(45)

In order to facilitate comparative evaluation of the performance of general practices in cancer diagnosis, a number of activity indicators for all general practices in England have been compiled and made publically available.(205) These include frequency of urgent

referrals for suspected cancer and endoscopic investigations, which are presented alongside data on demography and practice disease registers. Analysis of this data has demonstrated that substantial variation in these activity indicators exists between general practices, beyond that which can be accounted for by chance variation, even after adjusting for differing practice populations.(206) As well as characteristics of patient populations, variation in practice use of endoscopy has been associated with the characteristics of general practice services themselves, although all of these attributes combined account for less than half of the variation that was demonstrated.(207) Despite being a more widely used and accessible test,(208, 209) no comparable investigation has been undertaken with respect to chest x-ray. The objective of this study was to determine whether recorded population and practice characteristics are associated with frequency of investigation with chest x-ray by different general practices.

5.3 Methods

Data for all English general practices with list sizes greater than 1,000 patients and for which the numbers of patients who were investigated by general practices with chest x-ray was available, was obtained. Using methods similar to those described by Mendonca et al who explored variation in gastrointestinal endoscopy, the associations between chest x-ray use and characteristics of the practices and their populations were examined.(207)

5.3.1 Data

Numbers of patients for each practice who had at least one chest x-ray in 2018 which was requested by their GP was obtained from the Diagnostic Imaging Data set (DID).(210) Due to de-identification requirements these numbers are rounded to the nearest five with counts of less than three suppressed in order to preserve patient anonymity. For the purposes of this study these suppressed counts were assumed to be two. Data on general practices and populations was obtained from Public Health England's general practice profiles, the quality and outcomes framework (QOF), the general practice patient survey and NHS General and Personal Medical Services (GPMS) dataset.(205, 211, 212) All data pertained to 2018, except for index of multiple deprivation and ethnicity which are not reported directly for practice populations but are aggregated estimates based on the 2011 national census and the Index of Multiple Deprivation (IMD) 2015. The formulation of IMD measures and ethnicity estimates for practices populations has been described previously.(213, 214)

Data on the following six parameters relating to practice populations were obtained: the percentage who were male, the percentage aged 65 or over, the index of multiple deprivation fifth of the practice, the percentage who were on disease registers for chronic obstructive pulmonary disease and heart failure and an estimate of the population ethnicity. The data on ethnicity used were estimates of the percentage of each practice categorized into the following groups: white, mixed ethnic group, Asian, black or other ethnic group.

Data on eight parameters relating to the general practices themselves were also obtained. These were the number of patients per full time equivalent GP, the practice list size, the percentage of GPs who were male, the mean GP age, whether or not the practice was involved in postgraduate GP training, whether or not the practice was a 'single-handed' practice, the designation of the practice as either rural or urban and the percentage of respondents who gave the most positive response to the general practice survey for items relating to access, continuity of care and communication. Survey responses were adjusted for age, long term conditions, ethnicity and deprivation as described elsewhere.(215)

5.3.2 Analysis

A mixed-effects Poisson regression model including a random effect for general practice was used to determine the extent to which variation in numbers of patients who had a chest x-ray between practices could be attributable to recorded population and/or practice characteristics. Mixed effects models can estimate the overall underlying variation between practices after removing the role of chance due to small numbers.(216)

Three further iterations of the model were run. These included in turn, the variables relating to the practice population characteristics, the variables relating to practice characteristics and both groups of variables combined. The percentage of the variation in frequency of investigation with chest x-ray which each model could account for was estimated. In addition, the median incidence rate ratio (MIRR)(217) was calculated as an alternative means of expressing the degree of variation that was accounted for by each version of the model. MIRR is a statistic which measures the median relative change in a rate when two identical subjects (i.e. practices) from randomly selected clusters ordered by rate are compared. The ratios of MIRR in a model with no co-variates to the models with practice characteristics, population characteristics and both sets of characteristics combined was calculated to express the between-practice variance in rates of chest x-ray that can be attributed by each set of characteristics. Continuous exposure variables have different

distributions in different practices and were therefore standardized as previously described.(207)

Given the large sample size and the multiple variables being studied, statistically significant associations with little clinical importance were anticipated. There was no way to determine the effect size that was likely to be of any clinical importance. Results therefore were presented with 'cut offs' similar to those which have been used in previous similar practice level analyses with a difference of 4% or greater (i.e. 0.96 or smaller or 1.04 or greater) and with $P < 0.01$.(207, 215) The full analysis plan was pre-registered (Appendix 10).(218)

5.4 Results

Following exclusion of practices with fewer than 1,000 patients (n=173), data for 6,909 practices remained. A further 234 practices (3.4%) were excluded because data was not available (Table 5.1). The characteristics of the 6,675 practices included in the analysis are outlined in Table 5.2. A median of 33.8 chest x-rays were performed per 1,000 patients, with substantial variation (IQR 25.5-42.6) between practices. Less than a fifth of this variation was accounted for by combined population and practice characteristics (Table 5.3). Of the two, population characteristics were found to be more important, resulting in a 16.4% reduction in between-practice variance compared to only 2.8% for practice characteristics. A hypothetical example of how changes in population and practice characteristics could be expected to affect numbers of chest x-rays performed is presented in Table 5.4. The median incidence rate ratio was 1.95 for the model which included both sets of characteristics, and 1.95 and 2.05 for models with only population and practice characteristics, respectively. Adjusted and unadjusted associations between chest x-ray rate and population and practice characteristics are presented in Tables 5.5 and 5.6. A small proportion of practices were found to have undertaken fewer than three chest x-rays (n=127, 1.9%). The characteristics of these practices are described in Table 5.7. In case such low rates of investigation with chest x-ray could represent an error of reporting, a post hoc sensitivity analysis was undertaken on associations between population and practice characteristics, excluding these practices. The sensitivity analysis (Table 5.8) provided broadly consistent findings with the main analysis, with differences noted below.

	Available Observations (%)	Median (IQR)	10-90th centiles
Outcome variable			
chest x-rays per 1000 patients	234 (100.0)	33.6 (25.1-44.2)	15.5-53.4
Total number of chest x-rays	234 (100.0)	162.5 (81.3-287.5)	45-412
Practice population characteristics			
% who are male	234 (100.0)	50.2 (48.9-51.8)	48.3-54.1
% who are aged >65	234 (100.0)	16.0 (10.5-22.4)	6.3-26.5
% who are smokers	152 (65.0)	20.3 (16.6-25.8)	12.9-31.5
% who are on practice register for Chronic Obstructive Pulmonary Disease	152 (65.0)	2.3 (1.4-3.3)	0.8-3.9
% who are on practice register for Heart Failure	152 (65.0)	0.8 (0.5-1.1)	0.3-1.5
Ethnicity category estimates[a]			
% white	201 (85.9)	96.0 (83.1-97.9)	53.2-98.5
% mixed/multiple ethnic groups	201 (85.9)	1.3 (9.8-2.3)	0.7-4.5
% Asian/Asian British	201 (85.9)	1.7 (0.8-7.4)	0.5-26.3
% Black/ African/Caribbean/Black British	201 (85.9)	0.5 (0.2-2.2)	0.1-8.7
% Other ethnic groups	201 (85.9)	0.3 (0.1-0.9)	0.1-3.0
General practice characteristics			
Number of patients per full time equivalent GP	156 (66.7)	2209 (1550-3046)	1152-4523
% of GPs who are male	162 (69.2)	50.0 (33.0-74.0)	11.6-100.0
% of GPs who are UK qualified	118 (50.4)	75.0 (33.3-100)	0.0-100.0
Mean GP age	110 (47.0)	44.8 (41.3-50.0)	37.5-55.1
Practice list size	234 (100.0)	4855 (3328-7365)	2290-11174
% who gave highest rating given for general practice survey			
Helpfulness of reception staff (access)	228 (97.4)	48.0 (38.8-59.0)	31.2-68.3
Ability to see preferred GP (continuity)	228 (97.4)	53.8 (46.6-60.4)	42.7-66.7

Ability to book appointment (access)	228 (97.4)	25.2 (17.6-35.5)	14.0-48.1
Healthcare professional communication skills	228 (97.4)	78.1 (71.3-83.8)	65.1-87.7
Categorical variables		**Number (%) by variable category**	
Deprivation fifth (F1=least deprived, F5=most deprived) [b]	219 (93.6)	F1: 19 (8.7%); F2: 22 (10.0%); F3: 44 (20.1%); F4: 64 (29.2%); F5: 70 (32.0%)	
Single-handed status	234 (100.0)	Yes: 87 (37.2%); No: 147 (62.8%)	
Practice location	234 (100.0)	Urban: 204 (87.2%); rural: 30 (12.8%)	
Practice involved in post-graduate GP training	234 (100.0)	Yes: 42 (17.9%); No 192 (82.1%);	

Table 5.1 Practice level variables and practice characteristics of 234 practices for which data was not available

All data which does not pertain to 2018 is indicated by a footnote. For 200 practices one item of data (GP staffing, smoking/disease prevalence, index of multiple deprivation, ethnicity estimates) were unavailable. For 34 practices more than one of these items of data was unavailable.

[a] The ethnic composition of practice populations estimated by applying 2011 census data to the 2015 practice populations. These estimates were obtained from Public Health England

[b] Derived from Index of Multiple Deprivation practice scores for 2015

	Median (IQR)	**10-90th centiles**	**Median (IQR) for general practices within 0-10th centiles of CXR rate (<16.5 per 1000 patients)**	**Median (IQR) for general practices within 90-100th centiles of CXR rate (>51.2 per 1000 patients)**
chest x-rays per 1000 patients	33.8 (25.5-42.6)	16.5-51.2		
Total chest x-rays per practice[a]	250 (135-395)	70-560	35 (5-85)	368 (255-570)
Practice population characteristics				
% who are male	49.7 (48.9-50.8)	48.2-52.7	50.2 (49.1-52.2)	49.5 (48.6-50.1)
% who are aged >65	17.6 (12.4-21.9)	8.2-26.0	11.4 (6.7-18.7)	21.1 (17.3-25.4)
% who are smokers	16.5 (12.9-20.6)	10.4-24.1	16.8 (13.2-20.5)	17.0 (13.5-21.1)
% who are on practice register for Chronic Obstructive Pulmonary Disease	1.9 (1.3-2.5)	0.9-3.2	1.4 (0.7-2.1)	2.7 (2.2-3.3)
% who are on practice register for Heart Failure	0.9 (0.6-1.7)	0.4-1.5	0.6 (0.4-0.9)	1.8 (0.9-1.5)
Ethnicity category estimates[b]				
% white	92.4 (75.3-97.3)	50.6-98.2	80.8 (58.6-96.3)	96.8 (92.1-98.1)
% mixed/multiple ethnic groups	1.7 (1.0-3.5)	0.7-5.2	3.2 (1.0-4.9)	1.1 (0.8-1.7)
% Asian/Asian British	3.6 (1.2-11.0)	0.7-25.6	8.1 (1.9-15.5)	1.4 (0.8-3.8)
% Black/ African/Caribbean/Black British	1.0 (0.3-4.9)	0.2-12.0	3.7 (0.5-11.4)	0.4 (0.2-1.3)
% Other ethnic groups	0.4 (0.2-1.5)	0.1-3.5	1.4 (0.2-3.1)	0.2 (0.1-0.5)
General practice characteristics				
Number of patients per full time equivalent GP	1881 (1440-2459)	1157-3404	2110 (1630-2829)	1629 (1290-2196)
% of GPs who are male	51.1 (36.2-68.7)	21.3-97.3	53.0 (36.8-75.8)	53.4 (38.1-70.4)
% of GPs who are UK qualified	75.0 (50.0-100.0)	0-100	69.6 (33.3-92.9)	75.0 (50.0-100.0)
Mean GP age	46 (43-50)	40-56	47 (43-53)	45 (42-50)

Practice list size	7622 (4869-11141)	3258-14782	6829 (4486-11008)	6345 (4274-9595)
% who gave highest rating given for general practice survey				
Helpfulness of reception staff (access)	48.5 (39.7-58.2)	32.7-67.1	49.7 (41.2-58.8)	51.5 (42.1-62.1)
Ability to see preferred GP (continuity)	54.7 (48.8-60.8)	43.5-66.5	54.3 (47.8-60.4)	56.9 (51.2-63.1)
Ability to book appointment (access)	25.0 (17.4-34.7)	13.0-46.4	27.9 (20.1-38.0)	25.1 (16.6-36.5)
Healthcare professional communication skills	78.4 (72.3-84.0)	66.1-88.3	78.4 (71.4-83.9)	79.6 (73.6-85.6)
Categorical variables	**Number (%) by variable category** [d]			
Deprivation fifth (F1=least deprived, F5=most deprived)[c]	F1: 1360 (20.4%); F2: 1357 (20.3%); F3: 1337 (20.0%); F4: 1444 (21.6%); F5: 1177 (17.6%)		F1: 75 (11.2%); F2: 106 (15.9%); F3: 151 (22.6%); F4: 226 (33.9%); F5: 109 (16.3)	F1: 83 (12.4%); F2: 148 (22.2%); F3: 133 (19.9%); F4: 154 (23.1%); F5: 150 (22.5%)
Single-handed status	Yes: 410 (6.1%); No: 6265 (93.9%)		Yes: 60 (9.0%); No: 607 (91.0%)	Yes: 39 (5.8%); No: 629 (94.2%)
Practice location	Urban: 5695 (85.3%); rural: 980 (14.7%)		Urban: 551 (82.6%); rural: 116 (17.4%)	Urban: 569 (85.2%); rural: 99 (14.8%)
Practice involved in post-graduate GP training	Yes: 2486 (37.2%); No: 4189 (62.8%)		Yes: 184 (27.6%); No: 483 (72.4%)	Yes: 277 (41.5%); No: 391 (58.5%)

Table 5.2 Practice level variables and practice characteristics used in analysis.

All data which does not pertain to 2018 is indicated by a footnote

[a] In order to maintain patient anonymity, Diagnostic Imaging Dataset rounds chest x-ray counts for each practice to nearest 5 and counts of <3 are suppressed. In this study '2' was substituted for practices with counts of <3

[b] The ethnic composition of practice populations estimated by applying 2011 census data to the 2015 practice populations. These estimates were obtained from Public Health England

[c] Derived from Index of Multiple Deprivation practice scores for 2015

[d] Due to rounding not all percentages add precisely to 100

Model	Random effects variance [a]	% reduction in variance	Median incidence rate ratio (MIRR) [b]	Ratio of MIRR to that of null model
Null (random effect only)	0.58		2.07	
Population characteristics only	0.50	16.4	1.95	0.95
Practice characteristics only	0.56	2.8	2.05	0.99
Both population & practice characteristics	0.49	17.9	1.95	0.94

Table 5.3 Extent of between-practice variation explained by each model expressed as % reduction in random effects variance and by median incidence rate ratio

[a] This is the variance between practices measured on the log-scale

[b] This is the ratio of the chest X-ray rate for a practice at the 75th centile of the chest X-ray utilisation against the chest X-ray rate for a practice at the 25th centile of chest X-ray utilisation, estimated using the random effects variance

	Distribution of characteristics			Difference in number of CXRs between 75th & 25th centile (95% confidence intervals)		
	Overall mean (SD)	25th Percentile	75th Percentile	25th Centile	75th Centile	
Practice population characteristics						
Male %	50.1 (2.4)	48.6	51.7	277 (273-281)	265 (252-269)	8 (4 – 19)
Aged >65 %	17.4 (6.8)	12.8	22.0	226 (219-233)	316 (309-323)	97 (76-104)
Smokers %	17.1 (5.7)	13.3	20.9	247 (241-253)	295 (289-301)	54 (35 – 61)
Heart Failure practice register %	0.9 (0.4)	0.6	1.2	260 (253-267)	282 (278-287)	28 (14 – 32)
Ethnicity category:						
Mixed/multiple ethnic groups %	2.4 (1.8)	1.2	3.6	260 (253 – 267)	282 (275-289)	29 (7-36)
Asian/Asian British %	9.3 (13.4)	0.2	18.0	248 (243-253)	294 (289 – 299)	51 (35 – 56)
Black/ African/Caribbean/Black British	4.1 (6.7)	0.00	8.6	280 (275-286)	262 (256-268)	13 (7-30)
General practice variables						
Highest rating given for general practice survey for:						
Helpfulness of reception staff % (access)	49.4 (13.1)	40.5	58.2	279 (274-285)	263 (257-268)	11 (6- 27)
Ability to book appointment (access) %	27.6 (13.3)	18.6	36.6	281 (276-285)	263 (257-268)	15 (10-28)
Ability to see preferred GP (continuity) %	54.9 (8.8)	48.9	60.8	261 (256-266)	281 (276-286)	25 (9-30)

Healthcare professional communication skills %	77.7 (8.6)	71.9	83.5	264 (259-269)	278 (273-283)	19 (4-24)
Categorical Variables						
	Difference in number of chest x-rays expected to result from theoretical change in deprivation from Fifth 1 (95% Confidence Intervals)					
Deprivation Fifth 3	35 (19-50)					
Deprivation Fifth 4	44 (26 – 61)					

Table 5.4 Theoretical example of how changes in population and practice characteristics determined from the adjusted model would be expected to affect the number of patients receiving chest x-rays in a year in a practice with 8,000 patients.

Based on the mean chest x-ray rate of 34 chest x-rays per 1000 patients. In the cases of variables for which moving from 25th to 75th centile would result in fewer chest x-rays, these differences are indicated in blue in the rightmost columns. The example assumes that the variables follow a normal distribution. Only variables with effect sizes ≥1.04 or ≤0.96 ($p<0.01$) are included. CXR = chest x-ray SD=Standard deviation

	Rate Ratios * (95% Confidence intervals)	P value
Practice population characteristics		
Male %	**0.96 (0.93-0.99)**	**0.004**
Aged >65 %	**1.36 (1.30-1.42)**	**<0.001**
Smokers %	**1.18 (1.13-1.24)**	**<0.001**
Chronic Obstructive Pulmonary Disease practice register %	1.05 (1.01-1.10)	0.018
Heart Failure practice register %	**1.09 (1.05-1.12)**	**<0.001**
Ethnicity category		
Mixed/multiple ethnic groups %	**1.08 (1.03-1.14)**	**0.003**
Asian/Asian British %	**1.17 (1.13-1.22)**	**<0.001**
Black/ African/Caribbean/Black British	**0.93 (0.89-0.97)**	**0.002**
Other ethnic groups	0.97 (0.94-1.01)	0.099
Deprivation Fifths (highest fifth is most deprived)		
Fifth 2	0.94 (0.88-0.99)	0.019
Fifth 3	**0.87 (0.82-0.93)**	**<0.001**
Fifth 4	**0.84 (0.77-0.90)**	**<0.001**
Fifth 5	0.93 (0.84-1.03)	0.161
General practice characteristics		
Number of patients per full time equivalent GP	1.00 (0.98-1.03)	0.729
GPs who are male %	0.97 (0.95-0.99)	0.017
GPs who are UK qualified %	1.00 (0.97-1.03)	0.853
Mean GP age	0.99 (0.96-1.02)	0.590
Practice list size	**0.95 (0.92-0.97)**	**<0.001**
Single handed practice	0.99 (0.91-1.07)	0.814
Practice involved in post graduate GP training	1.02 (0.98-1.07)	0.369
Rural location	1.03 (0.99-1.09)	0.165
Highest rating given for general practice survey for:		
Helpfulness of reception staff (access) %	**0.94 (0.90-0.98)**	**0.002**
Ability to book appointment (access) %	**0.93 (0.90-0.96)**	**<0.001**
Ability to see preferred GP (continuity) %	**1.07 (1.04-1.11)**	**<0.001**
Healthcare professional communication skills %	**1.05 (1.01-1.09)**	**0.007**

Table 5.5 Adjusted associations between chest x-ray rates with population and general practice characteristics in English general practices in 2018.

The rate or odds ratios correspond to the change in the rate resulting from moving from the 25th to the 75th centile of the exposure variable (practice team or practice population characteristic) of interest. Bold fonts used for rate ratio values ≥1.04 or ≤0.96 where P<0.01.

*** For categorical values these are Odds Ratios**

	RR (95% Confidence intervals)	P value
Practice population characteristics		
Male %	**0.90 (0.88-0.92)**	**<0.001**
Aged >65 %	**1.31 (1.28-1.34)**	**<0.001**
Smokers %	1.01 (0.99-1.04)	0.346
Chronic Obstructive Pulmonary Disease practice register %	**1.24 (1.21-1.27)**	**<0.001**
Heart Failure practice register %	**1.29 (1.26-1.32)**	**<0.001**
Ethnicity category		
Mixed/multiple ethnic groups %	**0.83 (0.81-0.85)**	**<0.001**
Asian/Asian British %	**0.90 (0.88-0.93)**	**<0.001**
Black/ African/Caribbean/Black British	**0.83 (0.81-0.85)**	**<0.001**
Other ethnic groups	**0.85 (0.83-0.87)**	**<0.001**
Deprivation		
Quintile 2	1.01 (0.95-1.07)	0.823
Quintile 3	0.91 (0.86-0.97)	0.002
Quintile 4	**0.85 (0.80-0.90)**	**<0.001**
Quintile 5	0.98 (0.92-1.04)	0.493
General practice characteristics		
Number of patients per full time equivalent GP	**0.95 (0.93-0.98)**	**<0.001**
GPs who are male %	0.98 (0.95-1.00)	0.047
GPs who are UK qualified %	**1.06 (1.03-1.08)**	**<0.001**
Mean GP age	**0.95 (0.93-0.98)**	**<0.001**
Practice list size	1.00 (1.00-1.00)	0.007
Single handed practice	0.91 (0.84-0.98)	0.016
Practice involved in post graduate GP training	**1.10 (1.06-1.14)**	**<0.001**
Rural location	0.99 (0.94-1.05)	0.770
Highest rating given for general practice survey for:		
Helpfulness of reception staff %	1.00 (0.98-1.03)	0.719
Ability to book appointment (access) %	**0.94 (0.92-0.97)**	**<0.001**
Ability to see preferred GP (continuity) %	**1.05 (1.03-1.08)**	**<0.001**
Healthcare professional communication skills %	1.04 (1.01-1.06)	0.003

Table 5.6 Unadjusted associations between investigation with chest x-ray and practice and population characteristics.
Because no adjustment is made for each variable in this table, limited interpretation is possible for variables, for which other important co-variables also have a relationship with chest x-ray rate. The rate or odds ratios correspond to the change in the rate resulting from moving from the 25th to the 75th centile of the exposure variable (practice team or practice population characteristic) of interest.

	Median (IQR)	10-90th centiles
Practice population characteristics		
% who are male	49.8 (48.8-51.3)	47.9-53.5
% who are aged >65	18.2 (12.3-21.2)	9.1-24.5
% who are smokers	18.4 (14.8-20.7)	11.8-23.7
% who are on practice register for Chronic Obstructive Pulmonary Disease	2.5 (1.7-3.4)	1.2-4.2
% who are on practice register for Heart Failure	1.0 (0.7-1.3)	0.4-1.5
Ethnicity category estimates[a]		
% white	96.6 (88.5-97.7)	56.3-98.3
% mixed/multiple ethnic groups	0.9 (0.6-1.8)	0.5-5.2
% Asian/Asian British	1.9 (1.1-7.1)	0.8-17.1
% Black/ African/Caribbean/Black British	0.5 (0.2-1.5)	0.2-13.2
% Other ethnic groups	0.3 (0.2-0.9)	0.1-2.1
General practice characteristics		
Number of patients per full time equivalent GP	1844 (1441-2407)	1186-3346
% of GPs who are male	56.7 (38.5-80.2)	25.8-100.0
% of GPs who are UK qualified	66.7 (25.0-87.8)	0.0-100.0
Mean GP age	46.0 (42.5-52.5)	40.2-57.5
Practice list size	5935 (4298-8699)	3143-11144
% who gave highest rating given for general practice survey		
Helpfulness of reception staff	50.5 (41.6-62.0)	34.1-72.6
Ability to see preferred GP (continuity)	54.4 (48.3-61.1)	45.0-67.1
Ability to book appointment (access)	27.6 (18.8-38.7)	14.2-51.1
Healthcare professional communication skills	77.1 (72.2-84.5)	66.0-90.0
Categorical variables	**Number (%) by variable category**	
Deprivation quintile (Q1=least deprived, Q5=most deprived) [b]	Q1: 7 (5.5%); Q2: 16 (12.6%); Q3: 35 (27.6%); Q4: 54 (42.5%); Q5: 15 (11.8%)	
Single-handed status	Yes: 12 (9.4%); No: 115 (90.6%)	
Practice location	Urban: 108 (85.0%); rural: 19 (15.0%)	
Practice involved in post-graduate GP training	Yes: 45 (35.4%); No 82 (64.6%)	

Table 5.7 Practice level variables and practice characteristics of 127 practices for which <3 chest x-rays were recorded in 2018

The Diagnostic Imaging Dataset reports numbers of chest x-rays rounded to the nearest 5, with numbers less than 5 categorised as either 0 or 1-2. Of the 127 practices with <3 chest x-rays recorded, 80 were recorded as having had 1-3 chest x-rays, and 27 were reported as having had 0 chest x-rays. All data which does not pertain to 2018 is indicated by a footnote.

[a] The ethnic composition of practice populations estimated by applying 2011 census data to the 2015 practice populations. These estimates were obtained from Public Health England

[b] Derived from Index of Multiple Deprivation practice scores for 2015

	Rate Ratios [*] (95% Confidence intervals)	**P value**
Practice population characteristics		
Male %	**0.96 (0.94-0.98)**	**<0.001**
Aged >65 %	**1.26 (1.21-1.30)**	**<0.001**
Smokers %	**1.11 (1.07-1.14)**	**<0.001**
Chronic Obstructive Pulmonary Disease practice register %	**1.16 (1.12-1.20)**	**<0.001**
Heart Failure practice register %	**1.07 (1.04-1.09)**	**<0.001**
Ethnicity category		
Mixed/multiple ethnic groups %	0.99 (0.95-1.03)	0.62
Asian/Asian British %	**1.14 (1.11-1.17)**	**<0.001**
Black/ African/Caribbean/Black British	0.98 (0.95-1.02)	0.311
Other ethnic groups	0.98 (0.96-1.01)	0.236
Deprivation Fifths (highest fifth is most deprived)		
Fifth 2	0.95 (0.91-0.99)	0.020
Fifth 3	**0.92 (0.88-0.97)**	**0.001**
Fifth 4	**0.91 (0.86-0.97)**	**0.002**
Fifth 5	0.93 (0.87-1.00)	0.054
General practice characteristics		
Number of patients per full time equivalent GP	1.00 (0.99-1.02)	0.635
GPs who are male %	0.98 (0.97-1.00)	0.093
GPs who are UK qualified %	0.99 (0.99-1.01)	0.251
Mean GP age	0.99 (0.97-1.01)	0.318
Practice list size	**0.93 (0.90-0.94)**	**<0.001**
Single handed practice	0.97 (0.92-1.03)	0.381
Practice involved in post graduate GP training	**1.06 (1.02-1.09)**	**0.001**
Rural location	1.03 (0.99-1.06)	0.137
Highest rating given for general practice survey for:		
Helpfulness of reception staff (access) %	**0.95 (0.92-0.98)**	**0.001**

Ability to book appointment (access) %	**0.95 (0.93-0.98)**	**<0.001**
Ability to see preferred GP (continuity) %	**1.06 (1.03-1.09)**	**<0.001**
Healthcare professional communication skills %	1.03 (1.00-1.06)	0.052

Table 5.8 Sensitivity analysis of adjusted associations between chest x-ray rates with population and general practice characteristics for 2018, excluding practices which performed three chest x-rays or less in 2018

127 practices performed three chest x-rays or less in 2018 (1.9%). The characteristics of these practices are outlined in Table 5.7. The rate or odds ratios correspond to the change in the rate resulting from moving from the 25th to the 75th centile of the exposure variable (practice team or practice population characteristic) of interest. Bold fonts used for rate ratio values ≥1.04 or ≤0.96 where P<0.01.
*** For categorical values these are Odds Ratios**

5.4.1 Population characteristics

Practices with higher proportions of smokers, patients on heart failure registers and those aged 65 or older had higher rates of investigation with chest x-ray (Table 5.5). On excluding practices which performed fewer than three chest x-rays an association between higher chest x-ray rates and proportions of patients on COPD registers was demonstrated (Table 5.8). Practices with higher estimated proportions of patients belonging to mixed/multiple ethnic groups or Asian/Asian British ethnic categories also had higher chest x-ray rates. Chest x-ray rates were lower in practices with higher proportions of male patients and estimated proportions of patients in the Black/African/Caribbean/Black British ethnic category. When practices which performed fewer than three chest x-rays were excluded the associations between mixed/multiple ethnic groups and increased chest x-ray rates and the Black/ African/Caribbean/Black British ethnic category with reduced chest x-ray rates were not demonstrated (Table 5.8). There was no consistent relationship with deprivation, with some suggestion that more deprived groups had lower adjusted rates of investigation, with odds ratios for the deprivation fifths 4 and 5 versus deprivation fifth 1 of 0.84 (95% CI 0.77 to 0.90, p<0.001) and 0.93 (95% CI 0.84 to 1.03, p<0.161) respectively (Table 5.5). An exploratory, post-hoc, analysis including the index of multiple deprivation score as a linear continuous variable found no evidence of a relationship (p=0.7, data not shown).

5.4.2 Practice characteristics

Practices with larger list sizes had lower rates of chest x-ray, although higher numbers of patients per full time equivalent GP was not shown to be associated with lower rates of chest

x-ray. General practice location, GP age, single-handed status and involvement in GP training were not associated with differences in chest x-ray rate. On excluding practices which performed three or fewer chest x-rays an association between involvement in GP training was associated with increased chest x-ray rates was demonstrated (Table 5.8). Practices which achieved the highest scores for General Practice survey items pertaining to access (helpfulness of receptionist and ability to book appointment) had reduced chest x-ray rates while items pertaining to continuity (ability to see preferred GP) and healthcare professional communication skills were associated with higher practice chest x-ray rates. An association between healthcare professional communication skills and increased chest x-ray rates did not meet pre-defined significance thresholds when practices which fewer than three chest x-rays were excluded (Table 5.8).

5.5 Discussion

5.5.1 Summary

This is the most comprehensive investigation undertaken to date on the population and practice characteristics associated with rates of chest x-ray investigation by GPs. The resulting insights are primarily of interest due to the role of chest x-ray in lung cancer detection from general practice, although the study included counts of all chest x-rays, regardless of indication. Several population and practice characteristics were found to be associated with differences in chest x-ray rates, but the effect size of most of these was small. The characteristic with the largest effect size was the proportion of patients aged 65 or over. Characteristics relating to practice populations were found to have a much greater association with differences in chest x-ray rates than characteristics of the practices themselves. As well as age, the most important population characteristics associated with higher chest x-ray rates were smoking and heart failure prevalence and higher estimated proportions of patients from Asian and mixed ethnicity groups. Lower chest x-ray rates were associated with practices with higher proportions of black patients and male patients. However, in combination, all population characteristics could only account for around a sixth of observed between-practice variation in investigation with chest x-ray. Characteristics of the practices themselves (e.g. staffing, training status and location) accounted for even less of this variation and few of these individual practice characteristics were linked to appreciable differences in chest x-ray rates. Practices that scored highly for GP survey items relating to access were associated with lower rates of chest x-ray and higher rates for practices that scored highly in survey items relating to continuity of care and communication skills.

5.5.2 Strengths and Limitations

This study used a large national sample of General Practices with analysis performed according to a pre-registered plan. In studies of this type, with a large sample size and numerous co-variates there is a risk that statistically significant differences are observed which have no or negligible importance. In the present study, the use of pre-specified cut-off values provides some confidence that the observed associations reflect meaningful differences in investigation rates.(219)

Suspected lung cancer is only one possible indication for investigation with chest x-ray from general practice. When GPs suspect other illnesses, they may also arrange chest x-ray, although several of these pathologies, may cause similar symptoms such as cough and shortness of breath, and in many instances one rationale for organising chest x-ray may be to exclude malignant disease as well as to confirm a primary differential such as heart failure or pneumonia. Previous audit evidence suggests that investigation with chest x-ray because of symptoms, even when lung cancer is not explicitly suspected, is an important route to diagnosis.(73) In this study it was not possible to capture the indication for chest x-ray and it is important to acknowledge that the proportion of chest x-rays which were arranged for suspected lung cancer is unknown.

A small proportion of practices (3.4%) were excluded from the analysis because data for the practice was not available for one or more of the sets of variables which were studied (Table 5.1). Excluded practices had a similar rate of chest x-ray, however these practices had fewer registered patients (median of 4855 vs 7622), higher rates of smoking (median 20.3% vs 16.5%), were more frequently located in the most deprived fifth (32.0% vs 17.6%) and were more often single-handed practices (37.2% vs 6.1%). A proportion of practices (1.9%) were recorded as having performed fewer than three chest x-rays. As it is possible that the number of chest x-rays is recorded incorrectly in the Diagnostic Imaging Dataset for these practices, associations excluding these practices were also reported (Table 5.8).

Variations in chest x-ray use could be influenced by geographical differences in practice, which could in turn be influenced by complex cultural factors such as the perceived benefits or drawbacks of arranging chest x-ray for patients at different thresholds of risk and perceptions around local radiology capacity to undertake chest x-rays. Geographical variation in test use within different countries has been outlined.(220, 221)

The locations of the general practices in this study was available within the study data however geographical variations in chest x-ray use within England was not explored. Had this been explored, additional insights may have been gleaned, if there were substantial differences in chest x-ray utilisation between regions (such as those covered by cancer alliances), or localities within those regions (such as clinical commissioning groups).

5.5.3 Comparison with existing literature

A study by O'Dowd et al. determined age and sex-standardised chest x-ray rates for 71 general practices in England and reported a similar median rate (4 chest x-rays per 100 patients per year) to the present study but an even wider variation in chest x-ray rates (IQR 3-6).(182) Another study based in a single city has also demonstrated wide variation in chest x-ray rates.(222) The present study draws from a much larger sample of practices (n=6775) and provides a more detailed exploration of the variation in chest x-ray rates and the factors associated with this variation.

A recent study found that urgent referrals for suspected cancer (USC) over ten years (to 2018/19) more than doubled to over 2 million with significant variation between practices in cancer detection.(223) Use of urgent referral and detection of cancer was associated with larger practices and those with younger GPs, though the association with GP age became attenuated over time. In 2019/20 of the 2.3 million urgent suspected cancer referrals, only 65,000 were for suspected lung cancer (2.8% of all referrals) with 32% of lung cancers detected via USC, compared to over 50% of all cancers detected via USC.(224) Another paper which analysed trends in USC referrals over the ten year period (to 2019/20) that while referral rates for suspected lung cancer had increased by 5.4%, this increase was lower for that observed in many other cancer types.(225) Neither study determined the proportion of USC referrals that were made because of chest x-ray findings.

This study is similar to an investigation by Mendonca et al which considered general practice and population characteristics with respect to urgent referrals for suspect cancer and referrals for a range of gastrointestinal endoscopic investigations.(207) A greater degree of between-practice variation in endoscopic investigation was found to be attributable to population and practice characteristics than for chest x-ray in the present study. In Mendonca et al practice characteristics accounted for less than 4% of variation for all three endoscopic investigations studied, while population characteristics accounted for proportions of variance of 17.5% for sigmoidoscopy, 22.2% for colonoscopy and 25.1% for gastroscopy. In the present study less than 3% of variation could be attributed to practice characteristics

with population characteristics accounting for 16%. Of the endoscopic investigations sigmoidoscopy is less invasive and expensive than gastroscopy and colonoscopy. Chest x-ray is more inexpensive than all forms of gastrointestinal endoscopy and is non-invasive.(226) Chest x-ray is also a much more common investigation.(208, 209) Investigations which are less invasive, expensive and more widely used are probably considered more acceptable to clinicians and patients. It is plausible that chest x-ray is deployed more readily and at lower levels of risk of cancer than invasive investigations like endoscopy, which might explain the lower proportion of variation accounted for population factors with chest x-ray rate. In the present study no association was found between GP age and chest x-ray rate, while Mendonca et al. found practices with older GPs had reduced referral rates for suspected cancers and gastroscopies.(207)

In the present study it was found that practices with higher proportions of male patients had lower chest x-ray rates. Reduced rates of urgent and suspect cancer referrals (all cancer types) in Mendonca et al were found for practices with higher proportions of men. This may reflect differences in responses to symptoms and promptness of presentation to GP between men and women.(227)

Findings related to ethnicity were the inverse of those described by Mendonca et al. with respect to endoscopy. In the present study practices with higher estimated proportions of patients categorised ‘Asian’ and ‘other ethnicities’ were associated with higher rates of chest x-ray and those with higher estimated proportions of black patients were associated with lower rates of investigation with chest x-ray. The explanation for this discordance is likely to be complex and could be related to the nature of the tests and their indications and may also intersect with barriers to access certain investigations which may not be uniformly experienced across different communities. For example, it is possible that uptake of chest x-ray is higher in practices with higher proportions of immigrant populations reflecting a higher index of suspicion for tuberculosis in those populations.(228)

Data from the GP patient survey were explored in relation to endoscopy in Lyratzopoulos et al.(215) This found that found that practices that scored highly for a survey items relating to ease of patient access to appointments and continuity of care were correlated with reduced rates of endoscopic investigation whereas higher investigation rates were observed in practices which had the highest scores for communication skills. In the present study it was observed that practices which achieved the highest scores for access to appointments were associated with a lower chest x-ray rate but items relating to continuity of care as well as clinician communication skills was associated with higher chest x-ray rates. Continuity of

care has previously been associated with increased delay in cancer diagnosis, leading to suggestion that 'discontinuity' may precipitate a fresh perspective from another clinician.(229) The apparent disparity in the present study which demonstrated increased chest x-ray rates in practices with high attainment for continuity of care may still be consistent with this paradigm. GPs who know their patients well may be less willing to subject their patients to invasive testing but might be more prepared to consider a less invasive test like chest x-ray.

Previous studies that have use of vignettes and surveys with GPs may help explain the consequences of and reasons for variation between chest x-ray investigation rates. In Rose et al. referral and investigation decisions of general practitioners across several jurisdictions were examined with respect to cancer survival. The study showed a statistically significant correlation between propensity to investigate in a higher risk scenario for lung cancer and patient survival.(16) Sheringham et al. examined GPs' decision making around investigation with chest x-ray in vignettes which had varying degrees of risk for lung cancer. They found that increased risk did not increase the likelihood of decision to investigate, but that GPs who sought additional information that was not initially volunteered were more likely to request chest x-ray.(230) Kostopoulou et al. used vignettes, which allowed participants the option of requesting a chest x-ray, to explore referral decisions for cases in which lung cancer was possible. The study found evidence that that referrals are due to individuals' inclination to refer rather than GPs' ability to identify lung cancer symptoms.(231)

5.5.4 Implications for research and practice

Chest x-ray is a commonly requested investigation in general practice and is an important route to lung cancer diagnosis.(208) Since individual cancer diagnoses occur too infrequently at individual practice level to be a reliable comparator chest x-ray rates may have utility as a process measure in comparing general practices activity pertaining to lung cancer detection.(206)

The finding of substantial variation in chest x-ray rates not accounted for by population characteristics chimes with evidence of variations in individuals' investigation and referral behaviours from vignette studies. Since population characteristics exercise relatively little influence on variation in chest x-ray rates, practices may find if helpful to access the Diagnostic Imaging Dataset and reflect on their practice's utilisation of chest x-ray with respect to the median rate of 34 per year per 1,000 patients demonstrated in this study.

As discussed in ‘comparison with existing literature’ there is evidence from a symptom awareness campaign during which chest x-ray rates were increased suggested that higher volumes of imaging may contribute to a stage shift and improved survival.(45) This suggests that there is an opportunity to influence clinicians’ behaviour by encouraging investigation with chest x-ray in patients with symptoms suggestive of lung cancer. However no direct ecological evidence exists to demonstrate that patients diagnosed at practices with a greater propensity to investigate with chest x-ray benefit from earlier stage at diagnosis, as has been demonstrated for endoscopy and gastrointestinal cancer.(45, 232) Indeed O’Dowd et al. found no reduction in deaths within 90 days of diagnosis in practices which had higher utilisation of chest x-ray.(182) Further research exploring whether an association exists between practices with higher chest x-ray rates and earlier stage at diagnosis and improved survival could be undertaken using national cancer registry data, as has been performed in analyses exploring practice use of urgent suspected cancer pathways and cancer outcomes.(203, 204) If such an association were demonstrated, given the low cost and high accessibility of chest x-ray, reducing investigation thresholds for patients with symptoms in practices which currently have lower chest x-ray rates could be a cost effective way to improve outcomes. In chapter six a proposal for such a study is outlined.

This research follows previous work by reporting on associations between patient experience metrics and investigation rates.(215) Further research may be helpful both to clarify the reasons for these associations and to determine whether patient reported experience metrics accurately reflect objective comparisons of care between practices.

5.6 Ethical Approval

Ethical approval was granted by the University of Leeds School of Medicine Ethics Committee, reference 19-070.

5.7 Acknowledgements

Mr Kevin Doherty, Information Analyst at NHS Digital generously supplied guidance and support regarding the Diagnostic Imaging Dataset. Dr Mark Ashworth, King’s College London, provided advice on ethnicity and deprivation data.

6. Discussion

6.1 Overview

- Summary of findings
- Implications of findings for practice
- Implications of findings for policy
- Recommendations for further research
- Conclusions

6.2 Summary of findings

In chapter one the objectives for this programme of doctoral research were outlined, which were addressed in chapters two to five. The key findings of the research are briefly summarised below with respect to these objectives.

6.2.1 Objective 1: To determine the sensitivity and specificity of chest x-ray and LDCT for the detection of lung cancer in symptomatic patients in primary care

A systematic review on the sensitivity and specificity of low dose CT for detection of lung cancer in symptomatic patients identified no studies that met the inclusion criteria. In the corresponding systematic review for chest x-ray over 9,000 citations were screened, over 800 full texts were inspected and 21 studies were identified for inclusion in the review. Almost all of these studies had a high risk of bias and had not been conducted with the intention of determining sensitivity of chest x-ray for lung cancer. Three studies had a low risk of bias. Two of these studies, which were conducted in a primary care setting reported sensitivities of 76.8% (95% CI 64.5 to 84.2%) and 79.3% (95% CI 67.6 to 91.0%). One secondary care study reported a sensitivity of 79.7% (95% CI 72.7 to 86.8%). The total number of patients in these three studies was 380.

Chest x-ray is a very long established modality and its role in lung cancer detection became accepted through clinical practice long before rigorous evaluations of accuracy became expected for medical tests prior to their adoption. Despite this it is surprising that a test we depend upon to detect our leading cause of cancer death was so poorly understood prior to the research presented in this thesis, particularly as alternative modalities like computed tomography, have been available for decades.

In part because of the lack of evidence on sensitivity from studies involving large numbers of patients, I undertook a retrospective observational study which examined the results of chest

x-rays which had been requested by general practitioners in the year prior to diagnosis with lung cancer over a seven year period (n=2129). Based on the earliest chest x-ray in the year prior to diagnosis, sensitivity was 82% (95% CI 80.6% to 84.1%). This is the largest study population that has been examined to determine the sensitivity of chest x-ray in symptomatic patients and greatly exceeds the combined population of the three studies at low risk of bias identified in the systematic review in chapter two.

Determination of specificity was not possible from either the systematic review nor the observational study as these studies reported the chest x-ray results for patients who were known to have a diagnosis of lung cancer and did not include results for other patients who had the test, but who were not diagnosed with lung cancer. In the cohort study described in chapter four, which was based on routinely collected data from 8996 patients who accessed a service which allowed them to request their own chest x-ray because they had symptoms, specificity was 90.2% (95 CI = 89.6 to 90.9). The study included only patients aged 50 and over and it is possible that patients who accessed the service may differ from those who have a chest x-ray following a consultation with their GP, however this was the first study that has determined the specificity of chest x-ray for lung cancer for symptomatic patients from a large sample using a robust method.

6.2.2 Objective 2: To determine the risk of a diagnosis of lung cancer following a negative chest x-ray with respect to different symptoms

Risk of a lung cancer diagnosis within one and two years following negative chest x-ray was estimated as part of the cohort study mentioned in 6.2.1. The one and two year risk of lung cancer after haemoptysis was 2.9% (95% CI 0.6 to 5.3) and 3.9 (95% CI 1.3 to 6.6) respectively. Risks for all other individual symptoms were less than 1% at one year and two years, with the exception of weight loss which had a risk of 1.4% (95% CI 0.4 to 2.4) at two years. While the cohort numbered almost 9,000 patients, only a small proportion were diagnosed with lung cancer (n=154, 1.7%), which meant that there were wide confidence intervals and the interpretation of risk for several symptoms and symptom combinations is difficult to interpret.

For all symptoms, the study found that the negative predictive value for chest x-ray was 99.7 (95% CI 99.5 to 99.8), demonstrating that the chance of having lung cancer for any individual patient following a negative chest x-ray is very low. This means that although the sensitivity of chest x-ray is only around 80%, patients and clinicians can take reassurance from a negative chest x-ray result in most scenarios. Negative predictive value for chest x-ray in symptomatic patients has not previously been determined from a large sample using a

systematic method as in this study. While this study, along with the studies described in chapters two and three, has shown that sensitivity of chest x-ray is only around 80%, the high negative predictive value for chest x-ray demonstrated suggests that the test will remain valuable, particularly in low prevalence populations.

6.2.3 Objective 3: To determine if there are differences in outcomes between patients diagnosed with lung cancer who had a chest x-ray which identified their lung cancer and those who had a chest x-ray which did not identify the lung cancer

The retrospective observational study described in chapter three and already outlined in 6.2.1 included a comparison between patients diagnosed with lung cancer who had an initial chest x-ray that was positive to those who had an initial chest x-ray which was negative. The median time to diagnosis from chest x-ray was much longer for those who had a negative chest x-ray (204 days vs 43 days) but no evidence was found that survival or stage at diagnosis was worse for those in the negative chest x-ray group.

It is possible that delays in diagnosis caused by failure of chest x-ray to identify lung cancer does worsen outcomes but that such effects could not be detected given the observational design of the study. Alternatively it could be the case that tumours that were not identified on chest x-ray tend to be smaller or more slowly growing and therefore outcomes for these cancers may not be worse than that of cancers that are identified more easily on chest x-ray.

6.2.4 Objective 4: To quantify the volume of chest x-rays undertaken by English general practices and to determine the extent to which variation in numbers of these investigations are due to differences in patient populations and the practices themselves

A retrospective study was undertaken examining the number of chest x-rays arranged by English general practices in 2018 along with characteristics of the practices and their patients using a mixed effects Poisson model. After excluding practices with fewer than 1000 patients and those for which data was not available 6675 practices were included. The median number of chest x-rays requested was 34 per 1000 patients (IQR 26-43). Only 19% of the variation in number of chest x-rays performed was found to be attributable to recorded characteristics, of which 16% was attributable to differences in the patient populations and 3% was attributable to characteristics of the practices themselves. Higher practice scores for continuity and communication skills, and higher proportions of smokers, Asian and mixed ethnic groups, and patients aged 65 years and older were associated with higher numbers of

chest x-rays. Higher patient satisfaction scores for access and greater proportions of male patients and patients of black ethnicity were associated with lower numbers of chest x-rays.

While a previous study has determined a similar median chest x-ray rate using a different dataset, this study examined a larger number of general practices and is the only study in which the extent to which differences in chest x-ray rates between practices can be explained by differences between the practices and the populations they serve was examined.(182)

6.3 Implications of findings for practice

Prior to undertaking this thesis there was a dearth of evidence about the accuracy of chest x-ray for the detection of lung cancer in patients with symptoms. The three studies identified in the systematic review described in chapter two which were at low risk of bias comprised less than 400 patients and two of the three studies were more than fifteen years old. The studies described in chapters two and three have generated estimates for the performance of chest x-ray based on large populations that reflect 'real world' clinical practice.

These studies have provided much more evidence about the performance of chest x-ray for the detection of lung cancer in symptomatic patients. The findings can therefore inform decision making about both the interpretation of chest x-ray results when considering lung cancer and how this test should be utilised. However, important questions remain regarding the optimal investigation strategies for detection of symptomatic lung cancer, some of which are outlined in section 6.5.

With a sensitivity of around 80% it is important for clinicians to appreciate that chest x-ray will not identify around a fifth of patients who have lung cancer. This gives grounds for some caution in relying upon chest x-ray alone to exclude lung cancer where there are very strong grounds to suspect that the disease is present, known as a high 'pre-test probability'. One may expect that a more florid clinical presentation of lung cancer may be more detectable, if for example, the tumour itself is larger. But, the high level of suspicion prior to undertaking the test may not be satisfactorily assuaged solely by the test result. Considering a test with a sensitivity of 80%, a patient for whom a general practitioner estimates there is a 12% risk of lung cancer, that risk would remain about 3% following a negative result and thus reach the notional threshold for urgent referral for suspected cancer.(48) Such an example is highly theoretical – in terms of cancer risk 12% is so unusually high that it is greatly exceeds the levels of risk attributable to common symptom or risk parameters in large population

studies.(39, 51, 61) But, although such high levels of risk are not apparent from readily recordable characteristics, the example is not entirely outlandish. GPs may well recall cases in which they had a suspicion approaching or exceeding 12% that lung cancer was present, based on the totality of the clinical encounter, often termed ‘gut feeling’ or intuition.(233) In practical terms NICE has already recognised the importance of prioritising patients who have the classic ‘red flag’ symptom of haemoptysis for further testing even if chest x-ray is negative, not because the symptom is associated with negative chest x-ray results, but because the symptom is so strongly indicative of lung cancer that the diagnosis ought not to be dismissed on the basis of chest x-ray alone.(234) This guidance was issued before the research described in chapter three demonstrated that risk of lung cancer in patients with haemoptysis who had an unremarkable chest x-ray was almost 3%, but the study suggests that guidance was appropriate.

Aside from the specific example of haemoptysis, possibly the most important implication of this research for GP is that when they have a high level of suspicion that a serious illness such as lung cancer is present, though a negative chest x-ray means lung cancer is much less likely to be present, it does not eliminate that possibility. For such patients, it would be prudent for GPs to account for the possibility that chest x-ray may not identify lung cancer and plan further review or investigations even if the test is negative. A negative result will greatly reduce the likelihood that lung cancer is present, however it may not discount that possibility altogether. Nor does it provide any reassurance that other important illnesses, including cancers, which present with similar symptoms are not present. In England, GPs can refer patients who have non-specific symptoms to multidisciplinary diagnostic centres, which can undertake investigations to rule out several cancers.(235)

In particular GPs need to remember that the risk of lung cancer with unexplained haemoptysis greatly exceeds the risk of other symptoms and that such patients usually warrant referral for suspected cancer in accordance with NICE guidelines, regardless of chest x-ray result.

Although difficult to support with evidence, it is prudent to also consider persistent symptoms and concerns expressed by patients and families as indicators of higher risk that should also prompt GPs to consider whether their pre-test probability for lung cancer has changed, and if so, whether they need to re-evaluate the reassurance taken from a negative result. The best course of action in such cases may be unclear and it may be appropriate to share decision making with patients including agreeing upon an appropriate interval after which to arrange further review if symptoms persist and/or obtain advice from specialty colleagues.

Although it is important for clinicians to remain mindful of the limitations of chest x-ray, the studies in this thesis also support the continued role of the investigation in the detection of symptomatic lung cancer. Lung cancer presents most frequently with symptoms which are not at all specific for lung cancer and which are very common in the community, such as cough.(53) The risk of such symptoms is low and usually does not justify the inconvenience, health service cost and risks of computed tomography. Risks associated with computed tomography include iatrogenic harm from the radiation dose which greatly exceeds that of chest x-ray, although this has been mitigated by the development of 'low dose' imaging protocols.(110, 111) Other risks and costs include those resulting from identification of disease which may never have caused symptoms if left undiscovered ('overdiagnosis') and costs and complications resulting because of incidental findings. However much of our understanding regarding these problems is from the screening context and our knowledge of the trade offs of cost, harms and benefit that would result from using computed tomography to routinely investigate symptomatic patients is not sufficiently understood (section 6.5).

Given the imperative of early detection and the accessibility, relative convenience and low risks of chest x-ray the reasonable accuracy of the test makes it suitable to deploy for large volumes of patients who individually have a low risk of lung cancer. The finding that the utilisation of chest x-ray is highly variable and that such variation is only in small part attributable to differences in practice populations could help prompt GPs and managers to find out how many chest x-rays their practice performs and if this number is lower than peers to consider whether they need to use the test more frequently for patients who have symptoms.

In the studies described in this thesis chest x-ray results were considered to be negative based on their contemporaneous interpretation by a radiologist. Previous research has suggested that in a substantial proportion of chest x-rays in which the disease was not identified, the disease could be identified in retrospect, once the diagnosis was known.(160, 184) It may be possible to reduce some of this error using artificial intelligence, although rigorous validation for this technology specifically for the identification of lung cancer in symptomatic primary care patients remains outstanding (section 6.5).(236)

6.4 Implications of findings for policy

As noted in chapter one, the chest x-ray is still the first line test for lung cancer in patients with symptoms in the UK, in contrast to many comparable healthcare systems which make

greater use of computed tomography. During the course of this PhD there have been further calls to expand diagnostic capacity for radiological tests like computed tomography for diagnosing lung cancer as well as access to such testing for GPs.(237-239) Computed tomography images take considerably longer for radiologists to interpret than chest x-ray with the Royal College of Radiologists advising that three to six computed tomography examinations can be interpreted in an hour, compared to 30 to 60 chest x-rays.(240) The longstanding constraints particularly in the radiology workforce, but also shortages of equipment, means that substantial expansion of chest imaging with computed tomography for those with symptoms may remain an aspiration for the foreseeable future, particularly given the impact of the impact of the coronavirus pandemic on radiology services.(65, 93, 241)

Replacing chest x-ray with computed tomography as the first line investigation for lung cancer has been proposed as a means to improve early detection.(126, 242, 243) Denmark, which has a similar gatekeeping role for general practice as the UK, has transitioned to using computed tomography instead of chest x-ray and in some areas of England direct access to the investigation is being offered to GPs for suspected lung cancer.(86, 244) The roll out of lung cancer screening programmes using computed tomography for asymptomatic patients may contribute to the impetus to expand access to computed tomography for symptomatic patients, since it may be argued that it is illogical for patients without symptoms to be investigated with a superior modality than those who have symptoms and may who well have a higher risk of having the disease.(92)

Given that most symptomatic patients present with symptoms which are ubiquitous in the community, such as cough, transitioning to computed tomography to investigate such patients does not appear feasible at the present time. Aside from concerns about the risks of overdiagnosis and harms resulting from more widespread investigation using computed tomography, the critical obstacle is the opportunity cost that such a strategy would entail. Put simply, which other computed tomography scans should we not perform and which other parts of the NHS should lose out so that patients with low levels of risk are investigated with computed tomography? It is likely that performing more computed tomography scans on patients with symptoms would lead to early detection and prove clinically effective but there is little basis to assume that the scale of any benefits would prove cost effective, or that the clinical benefits of earlier diagnosis of lung cancer would offset the impact of diverting computed tomography resource from investigations for other types of disease, including other for types of cancers.

While uncertainties and barriers impede greater utilisation of computed tomography, chest x-ray is much more readily accessible. Experience has demonstrated that volume of testing can be increased in order to investigate patients who have common symptoms and there is evidence that this leads to earlier detection.(45, 245) In the case of gastro-oesophageal cancer it has previously been demonstrated that patients who have the disease who attend practices that request greater numbers of upper gastrointestinal endoscopies are diagnosed at earlier stages. The same could well be true of lung cancer and chest x-ray and whether this is the case constitutes an important outstanding question (section 6.5).

The evidence presented in this thesis supports the utilisation of chest x-ray for symptomatic patients who do not have haemoptysis, or are not otherwise felt to be at very high risk by clinicians. Chapter five of this thesis also demonstrated that there is a high degree of variation in the utilisation of chest x-ray by general practices. Therefore it is possible that there is scope to promote the utilisation of chest x-rays by general practices that currently use them infrequently and it may be reasonably hypothesised that such an approach could lead to earlier detection of lung cancers. The disruption caused by the coronavirus pandemic caused the numbers of chest x-rays performed and urgent referrals made for suspected cancer to fall precipitously (Figures 6.1 and 6.2) and is likely to adversely affect outcomes for many patients. In this context focusing on restoring chest x-ray for most symptomatic patients and preserving scarce computed tomography capacity for those who are most likely to have lung cancer could be the most efficacious strategy at least in the short term.

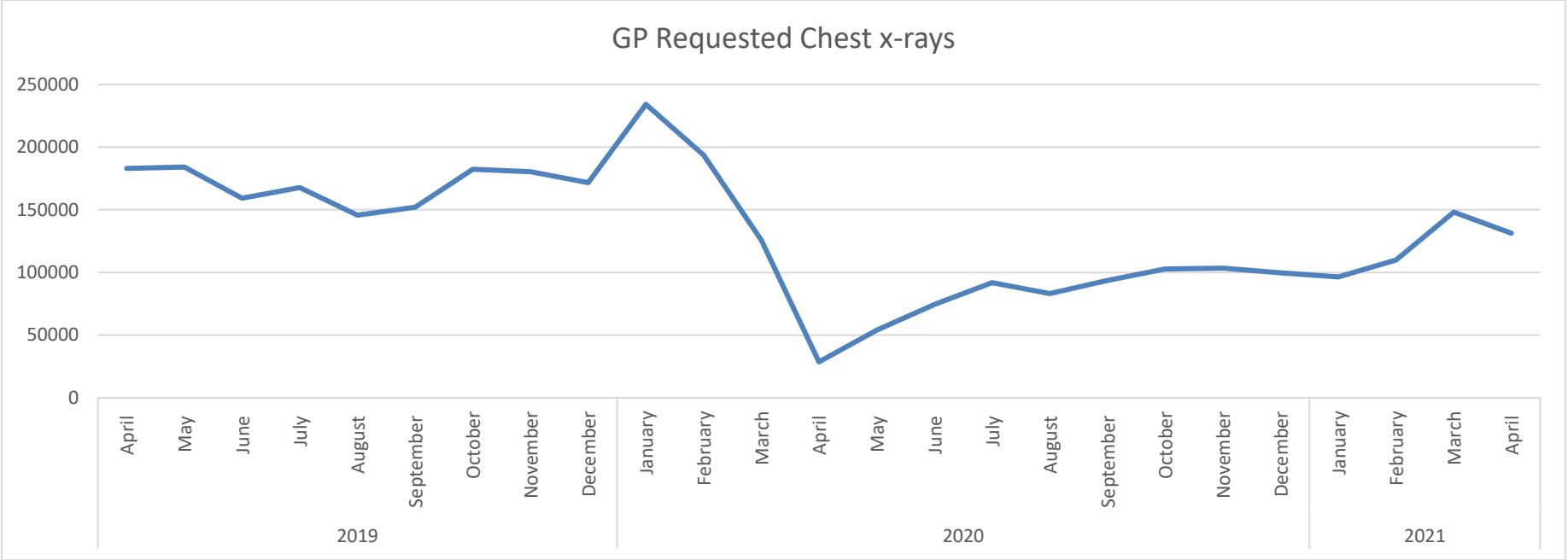


Figure 6.1 Number of GP requested chest x-rays in England April 2019 to April 2021.

The number of chest x-rays in April 2021 has recovered to 131,265 but remained 28% lower than the number performed in April 2019 (208, 246)

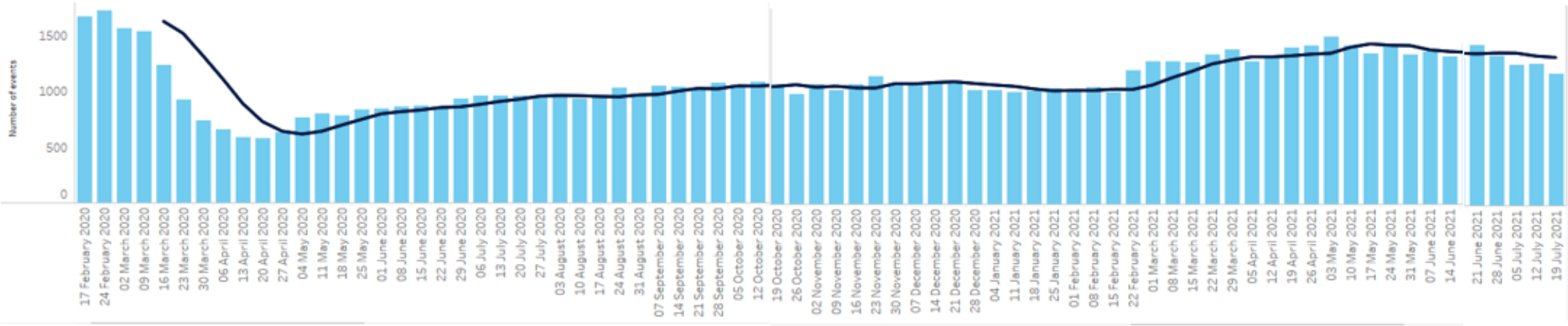


Figure 6.2 Number of lung cancer urgent referrals (two week wait) from February 2020 to July 2021

Weekly totals indicated by bars and four week rolling average is indicated by black line. The four week rolling average at the start of this period (17th February to 16th March) was 1,622 falling to a low of 638 (6th April to 27th April) and finishing on 1,324 (28th June to 19th July) which was 18% lower than the first four week period in this graph.(247)

As long as computed tomography capacity remains scarce, using the investigation for all those considered at risk (for example, smokers aged over 40) who have symptoms is unlikely to be proportionate. Based on the findings of this studies described in this thesis, we would need to perform around 300 computed tomography scans in patients who had a negative chest x-ray to detect one additional lung cancer.(192)

Identifying which patients are at highest risk and should be prioritised for computed tomography, or have additional investigations following negative chest x-ray remains challenging. The study described in chapter four vindicates existing guidance that unexplained haemoptysis warrants particular consideration but none of the other symptoms examined were found to have a substantially elevated risk.(234) Others have advocated incorporating demographic data along with symptoms in order to guide decision making.(231) An intervention based on this approach could involve making a bespoke risk score available through general practice systems based both on symptoms and prior cancer risk, which could be derived from models developed for lung cancer screening.(248) It seems likely however that the additional discrimination in terms of background risk beyond smoking status and age would be very low for most individuals, meaning the capacity of such an approach to influence decision making might be limited to a small proportion of 'borderline' cases. Even if decision aids providing quantifiable risk scores were widely used, harnessing doctors' intuition to select patients who elicit or express particular concern for further testing or referral remains a pragmatic strategy for the foreseeable future.(249) The studies detailed in this thesis provide little additional insights as to which patients should be considered high risk, but they do provide an evidence based rationale for continuing to use chest x-ray for those deemed to be at lower risk while recognising that further investigation may be necessary for some patients since it does not identify lung cancer in around a fifth of cases.

6.5 Recommendations for further research

A number of important research questions remain after, or lead from, the findings of this research, which are considered below.

6.5.1 What is the appropriate investigation strategy for patients with symptoms who have negative or inconclusive chest x-ray results?

As elucidated in chapters two and three chest x-ray does not identify a substantial proportion of lung cancer cases. However constraints in radiology capacity limit the prospect of investigating all patients with symptoms of possible lung cancer with computed tomography.

Other ways to detect cancer are under investigation including bio-markers and use of artificial intelligence to support interpretation of radiology images, but even if these are found to be cost effective, full evaluation may be some years off.(236, 250-253) Follow up chest x-rays are often arranged where symptoms persist or an initial chest x-ray is inconclusive.

The study detailed in chapter three demonstrated that 15% of those diagnosed with lung cancer had two or more chest x-rays in the year prior to diagnosis, but repeat chest x-rays remained negative in 16% of cases and 2% of patients had three or four chest x-rays before they were diagnosed. In addition a recent report which considered the problem of lung cancer which is not identified on chest x-ray called for more detailed safety netting advice to be formulated to help inform patients and their doctors under which circumstances further investigation or referral should be arranged.(92)

Research or guideline development which engaged key stakeholders to formulate consensus guidelines to support GPs in decision making for patients who have had a negative chest x-ray could help provide clarity as to a reasonable approach for clinicians and patients to take. Outcomes of such work could include guidance on which patients should have a repeat chest x-ray and after what duration and which patients should be prioritised for direct access investigations where these are available, or trigger discussion with specialty colleagues.

This could be produced through a Delphi study involving representatives of and key leaders in respiratory medicine, primary care, radiology and patients including those who are at risk of lung cancer but who have not been diagnosed with the disease. The study could be informed by considerations of possible resource implications by undertaking basic projections of the volume of additional investigations that might result under different scenarios, based on known cancer symptom epidemiology.

6.5.2 Are patients diagnosed with lung cancer who attend practices which request chest x-rays more frequently diagnosed with earlier stage disease?

Previous research from a single city has shown that increases in the volume of chest x-rays requested by GPs were associated with earlier stage disease at diagnosis but this was a temporal trend which could have been influenced by many other factors. The study described in chapter five showed that there is a great deal of variation in the number of chest x-rays performed by different general practices. Increasing the number of chest x-rays

performed by practices which currently test infrequently compared to other practices could be a highly cost effective means to improve outcomes but we currently lack direct evidence that increased rates of imaging with chest x-ray are linked to earlier detection. It is important to understand whether there is an association between frequency of investigation with chest x-ray between different General Practices and lung cancer stage at diagnosis and survival.

This could be determined through a study which used data on number of chest x-rays undertaken by English general practices over a specified period, e.g. 2014-18 from the Diagnostic Imaging Dataset. Practices could then be ranked into groups based on the number of chest x-rays performed and logistic regression analyses will be performed with respect to chest x-ray category and stage at diagnosis and survival.

6.5.3 Is using low dose CT as a first line test for lung cancer clinically and cost effective?

The research presented in chapters two and three have demonstrated that chest x-ray does not detect around a fifth of lung cancers. LDCT is known to be much more accurate in detection of lung cancer but due to the high prevalence of possible lung cancer symptoms such as cough it is not known whether the costs and harms that would result from using this modality instead of chest x-ray would be cost effective. There are calls to replace chest x-ray with LDCT as the first line investigation for lung cancer symptoms, but before such a profound change to the diagnostic pathway is made it is important to understand whether this would be clinically and cost effective.

To achieve this understanding it may be necessary to undertake a randomised trial control trial in which patients who attend their general practices who have a chest x-ray requested because of symptoms will offered enrolment in the study upon which they will either receive a chest x-ray only (usual care) or a LDCT. Alternatively a cluster randomised trial could be used, in which LDCT would be implemented across different general practices. Outcomes could include stage at diagnosis, survival and also any other resulting healthcare activity such as appointments, admissions and other investigations. It would be important to embed a robust health economic analysis within this research, to ensure adequate capture of the downstream consequences of routine implementation of LDCT in order to determine an accurate estimate of cost effectiveness. Undertaking such a study would necessitate overcoming significant obstacles including the recruitment of a large study population, since

as has been demonstrated in the study detailed in chapter three the prevalence of lung cancer in those who undergo chest imaging is just over 1%.

Given that computed tomography has been demonstrated to be a more sensitive modality for detecting lung cancer, at least in the screening context, undertaking a trial in which different patients had access to each modality, could be seen to disadvantage those investigated with chest x-ray alone and might be therefore be considered unethical. A pragmatic solution could be to offer all patients enrolled in a trial a chest x-ray as well as LDCT and to arrange for the results of each x-ray and LDCT to be interpreted by radiologists who were blinded to the other investigation, to ensure for example that the interpretation of a chest x-ray was not informed by the findings on LDCT. Such a trial could generate estimates as to the diagnostic accuracy of chest x-ray compared to LDCT but it would provide a much more limited capacity to compare the downstream consequences of health service utilisation of each modality.

6.5.4 Are lung cancers in never smokers as detectable by chest x-ray as those in smokers and do never smokers receive appropriate investigation with chest x-ray?

While tobacco exposure is the predominant cause of lung cancer it has been estimated that worldwide 10-25% of cases occur in never smokers.(254) Many of those who have been diagnosed with lung cancer who were not smokers have felt that their doctors did not adequately consider the possibility of the disease because they did not smoke.(92) NICE guidelines do recommend investigation of patients aged over 40 who have symptoms, although the threshold for investigations is lowered for those who are smokers.(234) It is possible that GPs may be inclined to restrict investigation to exclude lung cancer for those who are smokers, or may not be always be aware that guidelines do support investigation for symptoms in those who are not smokers.

Lung cancer screening may improve outcomes for some of those with lung cancer through detection before symptoms develop, but screening will be limited to those who are at high risk because of their smoking history. Some have worried that chest x-ray is not adequate to rule out lung cancer in never smokers because of cases in which the modality has failed to detect the disease in such patients.(92) There may be a case for expanding access to CT to investigate patients who are smokers who have common low risk symptoms such as cough, but investigation of such symptoms in low risk populations (i.e. never smokers) is probably not tenable. Instead it may be more fruitful to ensure that non-smokers who have symptoms are investigated with chest x-ray.

A study using primary care data, for example the primary care research datalink could establish the proportion of never smoker patients who have symptoms for which NICE recommend CXR should be arranged (Figure 1.2) have this investigation following consultation with a GP, using methodology employed in previous studies.(255, 256). In the studies described in chapters two and three chest x-ray results were not analysed with respect to smoking status. Another study using similar methodology, in which smoking status was recorded, which could be achieved by linking to general practice records, could examine whether the performance of chest x-ray in the detection of lung cancer was different in never smokers from smokers. If it was found that performance was comparable this finding could support greater utilisation of chest x-ray in low risk populations, rather than diverting further resource to computed tomography for individuals who are very unlikely to have lung cancer.

6.5.5 Can commercially available artificial intelligence systems identify lung cancer on chest x-ray in ways that can supplement conventional radiology interpretation?

While the studies described in chapters three and four detailed the performance of chest x-ray as a test, it was not explored whether lesions were evident in retrospect that were 'missed' or whether the cancer was not evident even if a radiologist was to re-evaluate the radiograph in retrospect with the knowledge of the diagnosis. Recently commercial systems have become available which aim to support radiology interpretation by highlighting abnormalities. However, these systems have generally been 'trained' on chest x-rays drawn from a diverse range of clinical diagnoses often from patients who were acutely unwell when the chest x-rays were obtained.

In the course of the studies described in chapters three and four, large numbers chest x-ray reports have been classified as positive or negative, including large numbers of patients who had a diagnosis of lung cancer (over 2,000) and patients who did not have lung cancer (almost 9,000). A study which set acceptable criteria of sensitivity and specificity for commercial systems in identifying lung cancer and which tested these systems using the images associated to the diagnostic codes generated for the above studies could help establish whether such systems could help radiologists improve detection of lung cancer. In particular it would be useful to ascertain if artificial intelligence systems had utility in identifying lesions which human radiographers tend to 'miss'.

6.6 Conclusions

In the course of this doctoral research I established that there was a dearth of evidence to support the role of chest x-ray in symptomatic detection of lung cancer in primary care and no studies reporting the diagnostic accuracy for LDCT in symptomatic patients. I undertook two studies which have substantially enhanced understanding of the performance of chest x-ray and have for the first time generated robust figures for sensitivity and specificity drawn from thousands, rather than hundreds, of patients. I established that lung cancer is not identified on chest x-ray in around 20% of cases but that because the prevalence of cancer among tested patients is low, the risk of cancer following a negative chest x-ray is very low, aside for patients with haemoptysis. Given the restrictions in capacity for more advanced imaging modalities such as computed tomography and because of the potential harms of using such modalities more widely, the performance of chest x-ray determined in this research suggests it continues to have an important role and should be utilised by GPs to investigate patients who have symptoms. However, I have demonstrated that there is wide variation in the frequency with which the investigation is actually being used, that isn't accounted for by recorded differences between practice populations. This suggests that practices which use chest x-ray less frequently could be supported to investigate more patients who have symptoms which could be a cost-effective way to diagnose lung cancer in some patients earlier and in turn to improve survival for these patients.

7. Appendices

Appendix 1: search strategies for systematic review

Sensitivity of chest x-ray for symptomatic lung cancer search strategy

CINAHL (EBSCO) 1981- present

S20 S4 AND S12 AND S19 (32)
S19 S16 OR S17 OR S18 (1,856)
S18 TX (LDCT? or MnDCT?) (3)
S17 TX ((tomograph* or CT?) and ((low* or minim* or ultralow* or "ultra low" or optim* or reduc*) and (dose? or dosage?))) (641)
S16 (S13 or S14) and S15 (1,387)
S15 (MH "Radiation Dosage+") (5,118)
S14 (MH "Tomography, X-Ray Computed+") (40,189)
S13 (MH "Tomography, X-Ray Computed+") (40,189)
S12 S9 OR S10 OR S11 (9,193)
S11 TX CXR? (107)
S10 TX ((chest or thora*) n4 (radiograph* or bronchograph* or "x ray*" or xray* or photoflurogra* or roentgenogram*)) (8,852)
S9 S6 and (S7 or S8) (591)
S8 (MH "Radiography+") (81,804)
S7 (MH "X-Rays") (1,270)
S6 (MH "Thorax+") (2,907)
S5 (MH "Radiography, Thoracic+") (4,851)
S4 S1 OR S2 OR S3 (21,878)
S3 TX (NSCLC or SCLC) (3,529)
S2 TX ((lung? or pulmon* or respirator* or bronchial) N1 (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)) (1,454)
S1 (MH "Respiratory Tract Neoplasms+") (20,382)

The Cochrane Library

#1 MeSH descriptor: [Respiratory Tract Neoplasms] explode all trees 6320
#2 ((lung? or pulmon* or respirator* or bronchial) and (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)):ti,ab,kw (Word variations have been searched) 5109
#3 (NSCLC or SCLC):ti,ab,kw (Word variations have been searched) 5089
#4 (145-#3) 13335
#5 MeSH descriptor: [Radiography, Thoracic] explode all trees396
#6 MeSH descriptor: [Thorax] explode all trees 536
#7 MeSH descriptor: [X-Rays] explode all trees 56
#8 MeSH descriptor: [Radiography] explode all trees 19856

#9 #6 and (#7 or #8) 44
#10 ((chest or thora*) and (radiograph* or bronchograph* or "x ray*" or xray* or photoflurogra* or roentgenogram*)):ti,ab,kw (Word variations have been searched) 3099
#11 CXR?:ti,ab,kw (Word variations have been searched) 46
#12 #5 or #9 or #10 or #11 3142
#13 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees 5226
#14 MeSH descriptor: [Tomography Scanners, X-Ray Computed] explode all trees 46
#15 MeSH descriptor: [Radiation Dosage] explode all trees 1356
#16 (#13 or #14) and #15 329
#17 ((tomograph* or CT?) and ((low* or minim* or ultralow* or "ultra low" or optim* or reduc*) and (dose? or dosage?))):ti,ab,kw (Word variations have been searched) 931
#18 (LDCT? or MnDCT?):ti,ab,kw (Word variations have been searched) 3
#19 #16 or #17 or #18 1223
#20 {and #4, #12, #19} 39

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(((ti((((tomograph* OR CT OR CTs) AND ((low* OR minim* OR ultralow* OR "ultra low" OR optim* OR reduc*) AND (dose? OR dosage?))))) OR ab((((tomograph* OR CT OR CTs) AND ((low* OR minim* OR ultralow* OR "ultra low" OR optim* OR reduc*) AND (dose? OR dosage?)))))) OR (ti(((LDCT? OR MnDCT?))) OR ab(((LDCT? OR MnDCT?))))) AND ((ti((((lung? OR pulmon* OR respirator* OR bronchial) AND (neoplas* OR cancer* OR tumo?r* OR metast* OR malignan* OR carcino* OR adenocarcinoma* OR angiosarcoma* OR chondrosarcoma* OR sarcoma* OR teratoma* OR lymphoma* OR blastoma* OR microcytic*)))) OR ab((((lung? OR pulmon* OR respirator* OR bronchial) AND (neoplas* OR cancer* OR tumo?r* OR metast* OR malignan* OR carcino* OR adenocarcinoma* OR angiosarcoma* OR chondrosarcoma* OR sarcoma* OR teratoma* OR lymphoma* OR blastoma* OR microcytic*))))) OR (ti(((NSCLC OR SCLC))) OR ab(((NSCLC OR SCLC)))))) AND ((ti((((chest OR thora*) AND (radiograph* OR bronchograph* OR "x ray*" OR xray* OR photoflu?rogra* OR roentgenogram*)))) OR ab((((chest OR thora*) AND (radiograph* OR bronchograph* OR "x ray*" OR xray* OR photoflu?rogra* OR roentgenogram*))))) OR (ti((CXR?)) OR ab((CXR?)))) found 6 results.

Embase Classic+Embase (Ovid) 1947 to 2018 September 14

1 exp respiratory tract tumor/ (427542)
2 ((lung? or pulmon* or respirator* or bronchial) adj (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)).ti,ab,kw. (297085)
3 (NSCLC or SCLC).ti,ab,kw. (72872)
4 or/1-3 (504278)
5 exp thorax radiography/ (170556)
6 exp thorax/ and (X ray/ or radiography/) (7212)

7 ((chest or thora*) adj4 (radiograph* or bronchograph* or "x ray*" or xray* or photoflurogra* or roentgenogram*)).ti,ab,kw. (77687)
8 CXR?.ti,ab,kw. (5453)
9 or/5-8 (202610)
10 exp x-ray computed tomography/ or exp computed tomography scanner/ (57970)
11 exp radiation dose/ (133521)
12 and/10-11 (4271)
13 ((tomograph* or CT?) adj4 ((low* or minim* or ultralow* or "ultra low" or optim* or reduc*) adj2 (dose? or dosage?))).ti,ab,kw. (8218)
14 (LDCT? or MnDCT?).ti,ab,kw. (1091)
15 or/12-14 (11881)
16 and/4,9,15 (657)
17 exp animal/ not (exp animal/ and exp human/) (5079306)
18 16 not 17 (657)

****

Ovid MEDLINE(R) 1946 to September Week 1 2018

1 exp Respiratory Tract Neoplasms/ (266351)
2 ((lung? or pulmon* or respirator* or bronchial) adj (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)).ti,ab,kf. (176108)
3 (NSCLC or SCLC).ti,ab,kf. (32510)
4 or/1-3 (302261)
5 exp radiography, thoracic/ (37096)
6 exp Thorax/ and (X-Rays/ or Radiography/) (1740)
7 ((chest or thora*) adj4 (radiograph* or bronchograph* or "x ray*" or xray* or photoflu?rogra* or roentgenogram*)).ti,ab,kf. (47418)
8 CXR?.ti,ab,kf. (1505)
9 or/5-8 (73494)
10 exp Tomography, X-Ray Computed/ or exp Tomography Scanners, X-Ray Computed/ (389396)
11 exp Radiation Dosage/ (79220)
12 and/10-11 (9120)
13 ((tomograph* or CT?) adj4 ((low* or minim* or ultralow* or "ultra low" or optim* or reduc*) adj2 (dose? or dosage?))).ti,ab,kf. (4050)
14 (LDCT? or MnDCT?).ti,ab,kf. (426)
15 or/12-14 (11325)
16 and/4,9,15 (348)
17 exp animals/ not (exp animals/ and humans/) (4492451)
18 16 not 17 (347)

****

Ovid MEDLINE(R) Epub Ahead of Print September 14, 2018

1 exp Respiratory Tract Neoplasms/ (0)
2 ((lung? or pulmon* or respirator* or bronchial) adj (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)).ti,ab,kf. (3826)
3 (NSCLC or SCLC).ti,ab,kf. (1125)
4 or/1-3 (3910)
5 exp radiography, thoracic/ (0)
6 exp Thorax/ and (X-Rays/ or Radiography/) (0)
7 ((chest or thora*) adj4 (radiograph* or bronchograph* or "x ray*" or xray* or photoflu?rogra* or roentgenogram*)).ti,ab,kf. (426)
8 CXR?.ti,ab,kf. (43)
9 or/5-8 (434)
10 exp Tomography, X-Ray Computed/ or exp Tomography Scanners, X-Ray Computed/ (0)
11 exp Radiation Dosage/ (0)
12 and/10-11 (0)
13 ((tomograph* or CT?) adj4 ((low* or minim* or ultralow* or "ultra low" or optim* or reduc*) adj2 (dose? or dosage?))).ti,ab,kf. (145)
14 (LDCT? or MnDCT?).ti,ab,kf. (23)
15 or/12-14 (145)
16 and/4,9,15 (6)
17 exp animals/ not (exp animals/ and humans/) (0)
18 16 not 17 (6)

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Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations - September 14, 2018

1 exp Respiratory Tract Neoplasms/ (0)
2 ((lung? or pulmon* or respirator* or bronchial) adj (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)).ti,ab,kf. (22943)
3 (NSCLC or SCLC).ti,ab,kf. (6672)
4 or/1-3 (23280)
5 exp radiography, thoracic/ (0)
6 exp Thorax/ and (X-Rays/ or Radiography/) (0)
7 ((chest or thora*) adj4 (radiograph* or bronchograph* or "x ray*" or xray* or photoflu?rogra* or roentgenogram*)).ti,ab,kf. (3894)
8 CXR?.ti,ab,kf. (274)
9 or/5-8 (3955)
10 exp Tomography, X-Ray Computed/ or exp Tomography Scanners, X-Ray Computed/ (0)
11 exp Radiation Dosage/ (0)
12 and/10-11 (0)
13 ((tomograph* or CT?) adj4 ((low* or minim* or ultralow* or "ultra low" or optim* or reduc*) adj2 (dose? or dosage?))).ti,ab,kf. (620)
14 (LDCT? or MnDCT?).ti,ab,kf. (123)
15 or/12-14 (626)

16 and/4,9,15 (28)
17 exp animals/ not (exp animals/ and humans/) (0)
18 16 not 17 (28)

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Web of Science Core Collection: Citation Indexes (Clarivate Analytics) 1900-present

9 #8 AND #3 37
8 (#4 or #5) and (#6 or #7) 260
7 TS= ((LDCT? or MnDCT?)) 19
6 TS=(((tomograph* or CT or CTs) and ((low* or minim* or ultralow* or "ultra low" or optim* or reduc*) and (dose? or dosage?)))) 7,636
5 TS=((CXR?)) 664
4 TS=(((chest or thora*) and (radiograph* or bronchograph* or "x ray*" or xray* or photoflu?rogra* or roentgenogram*))) 42,627
3 #2 OR #1 160,00
2 TS=((NSCLC or SCLC)) 51,374
1 TS=(((lung? or pulmon* or respirator* or bronchial) and (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*))) 113,125
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PROSPERO

#1 MeSH DESCRIPTOR Respiratory Tract Neoplasms EXPLODE ALL TREES 260
#2 ((lung? or pulmon* or respirator* or bronchial) and (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)) 1203
#3 (NSCLC or SCLC) 159
#4 #1 OR #2 OR #3 1225
#5 MeSH DESCRIPTOR Radiography, Thoracic EXPLODE ALL TREES 8
#6 MeSH DESCRIPTOR Thorax EXPLODE ALL TREES 31
#7 MeSH DESCRIPTOR X-Rays EXPLODE ALL TREES 11
#8 MeSH DESCRIPTOR Radiography EXPLODE ALL TREES 380
#9 #6 and (#7 or #8) 2
#10 ((chest or thora*) and (radiograph* or bronchograph* or "x ray*" or xray* or photoflu?rogra* or roentgenogram*)) 201
#11 CXR? 24
#12 #5 or #9 or #10 or #11 208
#13 MeSH DESCRIPTOR Tomography, X-Ray Computed EXPLODE ALL TREES 179
#14 Tomography, X-Ray Computed 0
#15 MeSH DESCRIPTOR Tomography Scanners, X-Ray Computed EXPLODE ALL TREES 0
#16 MeSH DESCRIPTOR Radiation Dosage EXPLODE ALL TREES 7
#17 (#14 or #15) and #16 2

#18 ((tomograph* or CT?) and ((low* or minim* or ultralow* or "ultra low" or optim* or reduc*) and (dose? or dosage?))) 399
#19 (LDCT? or MnDCT?) 6
#20 #17 OR #18 OR #19 400
#22 #20 AND #12 AND #4 8
****

ClinicalTrials.gov (U.S. NIH)

((tomography OR CT) AND (low OR minimum OR ultralow OR "ultra low" OR optimal OR reduced)) AND (lung OR lungs OR pulmon OR pulmons OR respiratory OR bronchial) AND (radiography OR bronchography OR "x ray" OR xray OR photoflurography) 216

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International Clinical Trials Registry Platform (WHO)

Search in title (tomography OR CT) AND (low OR minimum OR ultralow OR "ultra low" OR optimal OR reduced) AND (dose OR doses OR dosage OR dosages) AND (lung OR lungs OR pulmon OR pulmons OR respiratory OR bronchial) 166

****

Accuracy of low-dose CT versus chest x-ray for symptomatic lung cancer search strategy

CINAHL (EBSCO) 1981- present

S14	S5 AND S13	583
S13	S6 OR S10 OR S11 OR S12	8,890
S12	TX CXR?	105
S11	TX ((chest or thora*) N4 (radiograph* or bronchograph* or "x ray*" or xray* or photoflu?rogra* or roentgenogram*))	8,805
S10	S7 and (S8 or S9)	31
S9	(MH "Radiography")	5,027
S8	(MH "X-Rays")	1,250
S7	(MH "Thorax+")	2,874
S6	(MH "Radiography, Thoracic+")	4,812
S5	S1 OR S2 OR S3 OR S4	21,327
S4	TX (NSCLC? or SCLC?)	77
S3	AB ((lung? or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) N1 (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*))	1,303
S2	TI ((lung? or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) N4 (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*))	1,117
S1	(MH "Respiratory Tract Neoplasms+")	20,232

Cochrane Library

ID	Search	Hits
#1	MeSH descriptor: [Respiratory Tract Neoplasms] explode all trees	6356
#2	((lung? or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) N/4 (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)):ti,ab,kw (Word variations have been searched)	64
#3	(NSCLC? or SCLC?):ti,ab,kw (Word variations have been searched)	34
#4	(145-#3)	6438
#5	MeSH descriptor: [Radiography, Thoracic] explode all trees	401
#6	MeSH descriptor: [Thorax] explode all trees	536
#7	MeSH descriptor: [X-Rays] explode all trees	57
#8	MeSH descriptor: [Radiography] explode all trees	19939
#9	#6 and (#7 or #8)	44
#10	((chest or thora*) near/4 (radiograph* or bronchograph* or "x ray*" or xray* or photoflu?rogra* or roentgenogram*)):ti,ab,kw (Word variations have been searched)	2400

#11 CXR?:ti,ab,kw (Word variations have been searched) 48

#12 #5 or #9 or #10 or #11 2454

#13 #4 and #12 Publication Year from 1999 to 2017 143

Embase Classic+Embase (Ovid) 1947 - to 2018 July 27

Database: Embase Classic+Embase <1947 to 2018 July 27>
Search Strategy:
---
1 exp *respiratory tract tumor/ (250951)
2 ((lung? or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) adj4 (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)).ti,kw. (219233)
3 ((lung? or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) adj (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)).ab. (252172)
4 (NSCLC? or SCLC?).ti,ab,kw. (72580)
5 or/1-4 (410649)
6 exp *thorax radiography/ (23475)
7 exp *thorax/ and (*X ray/ or *radiography/) (381)
8 ((chest or thora*) adj4 (radiograph* or bronchograph* or "x ray*" or xray* or photoflu?rogra* or roentgenogram*)).ti,ab,kw. (77619)
9 CXR?.ti,ab,kw. (5446)
10 or/6-9 (95081)
11 and/5,10 (12170)
12 nonhuman/ not (nonhuman/ and human/) (4204014)
13 exp child/ not (exp child/ and (exp adult/ or juvenile/ or adolescent/)) (1699284)
14 or/12-13 (5830835)
15 11 not 14 (11733)
16 limit 15 to yr="1999 - 2018" (6773)

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Ovid MEDLINE(R) 1946 - to July Week 3 2018

Database: Ovid MEDLINE(R) <1946 to July Week 3 2018>
Search Strategy:
---
1 exp Respiratory Tract Neoplasms/ (264773)
2 ((lung? or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) adj4 (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)).ti,kf. (131762)
3 ((lung? or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) adj (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or

adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)).ab. (143075)
4 (NSCLC? or SCLC?).ti,ab,kf. (32289)
5 or/1-4 (304817)
6 exp radiography, thoracic/ (36965)
7 exp Thorax/ and (X-Rays/ or Radiography/) (1737)
8 ((chest or thora*) adj4 (radiograph* or bronchograph* or "x ray*" or xray* or photoflu?rogra* or roentgenogram*)).ti,ab,kf. (47260)
9 CXR?.ti,ab,kf. (1492)
10 or/6-9 (73236)
11 and/5,10 (9939)
12 exp animals/ not (exp animals/ and humans/) (4475707)
13 (exp child/ or exp infant/) not ((exp child/ or exp infant/) and (exp adult/ or adolescent/)) (1192712)
14 or/12-13 (5668121)
15 11 not 14 (9519)
16 limit 15 to yr="1999 - 2017" (4745)

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Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 27, 2018>

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1 ((lung? or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) adj4 (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)).ti,kf. (18094)
2 ((lung? or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) adj (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)).ab. (18944)
3 (NSCLC? or SCLC?).ti,ab,kf. (6605)
4 or/1-3 (24576)
5 ((chest or thora*) adj4 (radiograph* or bronchograph* or "x ray*" or xray* or photoflu?rogra* or roentgenogram*)).ti,ab,kf. (3835)
6 CXR?.ti,ab,kf. (265)
7 or/5-6 (3896)
8 and/4,7 (374)
9 limit 8 to yr="1999 - 2017" (307)

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Ovid MEDLINE(R) Epub Ahead of Print <July 27, 2018>

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1 ((lung? or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) adj4 (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)).ti,kf. (2631)

2 ((lung? or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) adj (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)).ab. (3423)

3 (NSCLC? or SCLC?).ti,ab,kf. (1129)

4 or/1-3 (4072)

5 ((chest or thora*) adj4 (radiograph* or bronchograph* or "x ray*" or xray* or photoflu?rogra* or roentgenogram*)).ti,ab,kf. (429)

6 CXR?.ti,ab,kf. (43)

7 or/5-6 (436)

8 and/4,7 (46)

9 limit 8 to yr="1999 - 2017" (30)

****

PubMed (NLM) 1946 – present

Search (((((("Radiography, Thoracic"[Mesh]) OR ((("Thorax"[Mesh]) AND ("X-Rays"[Mesh:NoExp]) OR "Radiography"[Mesh:NoExp])) OR ((((chest or thora*) and (radiograph* or bronchograph* or "x ray*" or xray* or photoflu?rogra* or roentgenogram*))))) OR CXR?)) AND ((("Respiratory Tract Neoplasms"[Mesh]) OR ((((lung* or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) AND (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*))))) OR (((NSCLC? or SCLC?)))))) AND (((pubstatusaheadofprint[sb] OR publisher[sb] OR pubmednotmedline[sb]))) 582

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Web of Science Core Collection: Citation Indexes (Thomson Reuters) 1900-present

9 Refined by: PUBLICATION YEARS: (2018 OR 2008 OR 2017 OR 2007 OR 2016 OR 2006 OR 2015 OR 2005 OR 2014 OR 2004 OR 2013 OR 2003 OR 2012 OR 2002 OR 2011 OR 2001 OR 2010 OR 2000 OR 2009 OR 1999) 853

8 #7 AND #4 1,146

7 #6 OR #5 32,496

6 TOPIC: ((CXR?)) 654

5 TOPIC: ((((chest or thora*) NEAR/4 (radiograph* or bronchograph* or "x ray*" or xray* or photoflu?rogra* or roentgenogram*)))) 32,216

4 #3 OR #2 OR #1 48,339

3 TOPIC: (((NSCLC? or SCLC?))) 1,990

2 TOPIC: ((((lung? or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) NEAR/1 (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)))) 41,435

1 TITLE: ((((lung? or pulmon* or respirator* or bronchi* or pancoast* or mesothelioma*) NEAR/4 (neoplas* or cancer* or tumo?r* or metast* or malignan* or carcino* or adenocarcinoma* or adenoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic*)))) 26,838

Appendix 2: Rationale for decisions about inclusion/exclusion which were not explicitly addressed in systematic review protocol

The following themes were identified by SB and the decisions were made agreed following discussion with RN.

Ambiguous Time Scales

Relevant text from study protocol:

“In determining a false negative rate for chest x-ray, we will consider any study which reported on the numbers of adult patients who had a chest x-ray which did not identify features suspicious of lung cancer and who subsequently received a diagnosis of lung cancer within one year.”

Problem identified:

Many papers report that patients had chest x-ray and then diagnosis but are not explicit about the duration between the chest x-ray being performed and the diagnosis with lung cancer.

Decision:

Studies will be included where on the balance of probability, it seems more likely that the duration of time between the chest x-ray being performed and the diagnosis of lung cancer is less than one year. It was agreed that this would be the case in cases in which the authors refer to the investigation and diagnosis occurring within a single episode of care, for example during a hospital admission.

In cases in which there is not sufficient information to make a judgement on the likelihood that the duration of time between the chest x-ray being performed and the diagnosis of lung cancer, these studies would be rejected.

Example 1 (included)

Hamanda, A clinicopathological study of lung cancer patients with occupational exposure to chrysotile asbestos fibers, Internal medicine, 1999(257).

Example 2 (excluded)

Murata, Two cases of multiple adenocarcinomas of lung including early bronchioalveolar carcinomas, Japanese Journal of Clinical Radiology(258).

Lung cancer revealed by Staging Imaging

Relevant text from study protocol:

“We will include studies relating to patients who had a chest X-ray after presenting to a clinician with symptoms…metastatic disease and post treatment or diagnostic surveillance of lung cancer will also be excluded.”

Problem identified:

This was not made sufficiently clear to exclude all staging imaging, for example, following diagnosis of head and neck cancer. Lung cancers picked up by staging CT could be metastatic or synchronous cancers and it is often impossible to differentiate these in the individual studies.

Decision:

To exclude studies which report on imaging performed for the purposes of staging. This was decided because

- The study protocol specifically excludes screening or incidentally discovered cancers, so it was not felt that it was consistent to include imaging performed for cancer staging
- it is not impossible to differentiate metastatic disease from synchronous tumours in several of the papers.

Example 3 (excluded):

Ong, The role of thorax imaging in staging head and neck squamous cell carcinoma, Journal of Cranio-Maxillo-Facial Surgery, 1999(259)

Retrospective Interpretation of films

Relevant text from study protocol:

“In determining a false negative rate for chest x-ray, we will consider any study which reported on the numbers of adult patients who had a chest x-ray which did not identify features suspicious of lung cancer and who subsequently received a diagnosis of lung cancer within one year”

The problem:

It is implicit in above text that we aimed to know the contemporaneous interpretation of the chest x-rays, not after diagnosis was known, as this would influence the interpretation of the chest x-ray. This is suggested strongly by the word 'subsequently'. A large number of studies were identified which examined chest x-rays retrospectively, in the knowledge of the final diagnosis. Some studies include retrospective reviews of imaging to glean the features that were present in chest x-rays, however since these images were examined in the knowledge of the diagnosis of lung cancer it is likely that the interpretation would have been influenced by this knowledge. In many cases the chest x-ray finding or what was visible is discussed but it is not made clear whether this was a contemporaneous report.

Decision:

We have excluded studies when it is not clear that the chest x-ray result reported is the result that was given at the time of the clinical episode and before the diagnosis was known or confirmed.

Date of Inclusion

Relevant text from study protocol:

"studies published before 1999 will be excluded"

The problem:

One paper includes reports results of previous studies that were published from before 1999.

Decision:

It was decided to include the data, if the data was reported in a paper which was published after 1999, as this was consistent with the protocol.

Example 4: (included)

Abraham, Facial pain as the presenting symptom of lung carcinoma with normal chest radiograph, Headache, 2003(260)

Appendix 3: data extracted from studies in systematic review

Hamada 1999 (257)

Authors: K. Hamada, T. Tokuyama, Y. Okamoto, S. Morikawa, Y. Konoike, H. Kasuga, H. Katada, K. Nishikawa, M. Tamura, R. Miyazaki and N. Narita

Title: A clinicopathological study of lung cancer patients with occupational exposure to chrysotile asbestos fibers

Journal, Volume (issue) and page number: Internal Medicine, 38(10), 780-4

Type of text: Journal article (full text obtained)

Number of eligible patients in study: 31

Total number of patients in study (including ineligible): 31

Presenting symptoms: not stated

Number who had positive CXR ('sensitivity' %): 22 (70.97%)

95% confidence intervals (%) for sensitivity: 52.00 to 89.94

Number who had negative CXR (%): 9 (29.03)

-Number who had a normal CXR (%): N/A. CXRs presented as either positive or negative

-Number who had abnormal but not suspicious CXR: N/A. CXRs presented as either positive or negative

Comparator to CXR ('gold standard'): unknown

Duration between CXR and diagnosis: not stated. The paper states that 'all patients were admitted to Nara Medical University Hospital' and suggests that investigations were undertaken in the course of an episode of care/admission.

Study design (quotation marks used where a design type stated): 'retrospective case study'

Histology, number (%): SCLC 8 (25%), adenocarcinoma 9 (28.1%), squamous cell carcinoma 11 (34.4%), combined 4 (12.5%)

Mean age: 60.6

Age range: 42-81

Male, number (%): 31 (100%)

Smoker or ex-smoker, number (%): 31 (96.88%)

Deprivation status: not stated

Setting/population: Nara Medical University Hospital. Patients admitted between September 1975 and August 1996 with history of occupational asbestos exposure Population with occupational exposure to asbestos who were diagnosed with lung cancer.

Country where study conducted: Japan

Language: English

Other notes: Includes some patients identified by routine check up CXR (i.e. screening) who could not be excluded

Tanaka 1999 (261)

Authors: M. Tanaka, M. Sawada, N. Inase, M. Ichioka, Y. Usui and Y. Yoshizawa

Title: Cases of gingival metastasis from lung cancer and a review of the literature.

Journal, Volume (issue) and page number: Japanese Journal of Lung Cancer, 39(3), 323-329

Type of text: Journal article (abstract only obtained)

Number of eligible patients in study: 3

Total number of patients in study (including ineligible): 3

Presenting symptoms, numbers (%): cough and bloody sputum 1 (33.33%), bloody sputum 1 (33.33%), gingival tumour 1 (33.33%)

Number who had positive CXR ('sensitivity' %): 3 (100%)

95% confidence intervals (%) for sensitivity: Unable to calculate as sensitivity 100%

Number who had negative CXR (%): 0

-Number who had a normal CXR (%): N/A

-Number who had abnormal but not suspicious CXR (%): N/A

Comparator to CXR ('gold standard'): not stated

Duration between CXR and diagnosis: not stated. Presents two case histories in which patients were admitted to hospital, with suggestion that CXR and diagnosis occurred within this episode of care.

Study design (quotation marks used where a design type stated): case series

Histology, number (%): adenocarcinoma 1 (33.33%), pleomorphic carcinoma 1 (33.33%), unknown 1 (33.33%)

Mean age: 72

Age range: 63-82

Male, number (%): 3 (100%)

Smoker or ex-smoker, number (%): not stated

Deprivation status: not stated

Setting/population: Hospital. Patients who had gingival metastasis from a lung primary.

Country where study conducted: Japan

Language: Japanese

Other notes:

Bini 2001 (262)

Authors: A. Bini, L. Ansaloni, G. Grani, M. Grazia, D. Pagani, F. Stella and R. Bazzocchi

Title: Pulmonary blastoma: report of two cases

Journal, Volume (issue) and page number: Surgery Today, 31(5), 438-42

Type of text: Journal article (full text obtained)

Number of eligible patients in study: 2

Total number of patients in study (including ineligible): 2

Presenting symptoms, numbers (%): chest pain 1 (50%), haemoptysis 1 (50%)

Number who had positive CXR ('sensitivity' %): 2 (100%)

95% confidence intervals (%) for sensitivity: Unable to calculate as sensitivity 100%

Number who had negative CXR (%): 0 (0%)

-Number who had normal CXR (%): N/A

-Number who had abnormal but not suspicious (%): N/A

Comparator to CXR ('gold standard'): bronchoscopy/CT/lobectomy

Duration between CXR and diagnosis: Case 1 suggests CXR performed on initial presentation and CT, bronchoscopy and lobectomy performed during that admission. Case 2 suggests that lobectomy and diagnosis achieved shortly after 3 months.

Study design (quotation marks used where a design type stated): case series

Histology, number (%): pulmonary blastoma 2 (100%)

Mean age: 62.5

Age range: 53-72

Male, number (%): 2 (100%)

Smoker or ex-smoker, number (%): 2 (100%)

Deprivation status: not stated

Setting/population: University affiliated hospital. Patients with diagnosis of pulmonary blastoma.

Country where study conducted: Italy

Language: English

Lee 2001 (263)

Authors: H. R. Lee, V. A. Lennon, M. Camilleri and C. M. Prather

Title: Paraneoplastic gastrointestinal motor dysfunction: clinical and laboratory characteristics

Journal, Volume (issue) and page number: American Journal of Gastroenterology

Type of text: Journal article (full text obtained)

Number of eligible patients in study: 6

Total number of patients in study (including ineligible): 12

Presenting symptoms, numbers (%)*: weight loss, nausea & vomiting 6 (50%), early satiety 5 (41.67%), abdominal pain 3 (25.00%), dysphagia 3 (25.00%), constipation 2 (16.67%) acute abdominal distention 1 (8.33%)

Number who had positive CXR ('sensitivity' %): 4 (66.67%)

95% confidence intervals (%) for sensitivity: 20.47 to 100.00

Number who had negative CXR (%): 2 (33.33%)

-Number who had normal CXR (%):

-Number who had abnormal but not suspicious (%):

Comparator to CXR ('gold standard'): not stated

Duration between CXR and diagnosis: less than 1 year (patients in which duration > 1 year excluded)

Study design (quotation marks used where a design type stated): case series

Histology, number (%): SCLC 6 (100%)

Mean age: 62.5

Age range: 52-79

Male, number (%): 3 (50%)

Smoker or ex-smoker, number (%): not reported

Deprivation status: not reported

Setting/population: Hospital. Patients with combined diagnosis of malignant neoplasm and GI dysmotility who attended Mayo Clinic 1985 to 1996.

Country where study conducted: United States

Language: English

Other Notes: Analysis for systematic review restricted to patients with lung cancer and for whom duration between CXR and diagnosis was less than 1 year.

Haro 2002 (264)

Authors: M. Haro, J. Jimenez, A. Tornero, M. Vizcaya, R. Tirado and T. Cros

Title: Usefulness of computerized tomography and bronchoscopy in patients with hemoptysis. Analysis of 482 cases

Journal, Volume (issue) and page number: Anales de Medicina Interna, 19(2), 59-65

Type of text: Journal article (full text obtained)

Number of eligible patients in study: 196. 208 patients with malignant disease, however this included oesophageal cancer (4) and pulmonary metastatic disease (8), neither of which could be excluded from this analysis.

Total number of patients in study (including ineligible): 482

Presenting symptoms, numbers (%): Haemoptysis, 196 (100%)

Number who had positive CXR ('sensitivity' %*): 185 (88.94%). These were infiltration 35 (16.83%), consolidation/atelectasis 39 (18.75%), mass or nodule 67 (32.21%), enlarged hilum 28 (13.46%), 'diffuse interstitial pattern' 2 (0.96%), 'scar lesions' 2 (0.96%), abscess/cavitation 7 (3.37%), pleural effusion 5 (2.40%)

95% confidence intervals (%) for sensitivity: 84.42 to 93.46

Number who had negative CXR (%): 23 (11.06%)

-Number who had normal CXR (%): 23 (11.06%)

-Number who had abnormal but not suspicious (%): N/A

Comparator to CXR ('gold standard'): bronchoscopy/CT

Duration between CXR and diagnosis: not stated. Participants were patients who had undergone bronchoscopy, having been referred because of haemoptysis. The CXR was undertaken as part of 'study protocol', therefore very likely this duration was much less than one year and was probably no more than days or weeks.

Study design (quotation marks used where a design type stated): prospective case review

Histology, number (%): unknown

Mean age*: 62

Age range*: 14-93

Male, number (%): 407* (84.43%)

Smoker or ex-smoker, number (%)*: 385 (79.88%)

Deprivation status: unknown

Setting/population: Hospital setting. Patients presenting with haemoptysis

Country where study conducted: Spain

Language: Spanish

Other notes: All findings on CXR have been categorised as positive CXR for this systematic review. In 66 patients (31.73%) the findings were termed ‘non-specific’ by the study authors, these were infiltration 35, enlarged hilum 28, diffuse interstitial pattern 2 and scar lesion 2. In each case the patient proceeded to further investigation (CT). These have not been categorised as ‘negative’ as they have not been categorised in this way by the authors it is not possible to speculate as to the degree of suspicion was attached to each of these findings in the clinical context.

The study group of those who had chest x-ray and who had lung cancer included 10 patients with pulmonary metastatic disease and 4 with oesophageal cancer, there was not sufficient data in the paper to exclude these patients.

Losa Gaspa 2002 (265)

Authors: F. Losa Gaspa, J. R. Germa, J. M. Albareda, A. Fernandez-Ortega, S. Sanjose and V. Fernandez Trigo

Title: Metastatic cancer presentation. Validation of a diagnostic algorithm with 221 consecutive patients

Journal, Volume (issue) and page number: Revista Clinica Espanola, 202(6), 313-9

Type of text: Journal article (full text obtained)

Number of eligible patients in study: 93

Total number of patients in study (including ineligible): 221

Presenting symptoms, numbers (%)*: Bone 66 (29.86%), neurological 54 (24.43%), respiratory 36 (16.29%), abdominal (16.29%), lymphadenopathy 17 (76.92%), other 12 (5.43%)

Number who had positive CXR ('sensitivity' %): 84 (90.32%)

95% confidence intervals (%) for sensitivity: 84.00 to 96.64

Number who had negative CXR (%): 9 (9.67%)

-Number who had normal CXR: N/A, dichotomous outcome

-Number who had abnormal but not suspicious CXR (%): N/A, dichotomous outcome

Comparator to CXR ('gold standard'): bronchoscopy/CT

Duration between CXR and diagnosis: Not stated. All participants were patients who had been admitted and all had CXR as part of investigative work up.

Study design (quotation marks used where a design type stated): case series

Histology, number (%): Histology of lung cancer cases not detailed

Mean age*: 63

Age range*: 18-88

Male, number (%): 160* (72.40%)

Smoker or ex-smoker, number (%): not stated

Deprivation status: not stated

Setting/population: Hospital Princeps, Spain. All patients admitted who had a diagnosis of metastatic cancer from January 1992 to April 1997.

Country where study conducted: Spain

Language: Spanish

Other notes:

Abraham 2003 (260)

Authors: P. J. Abraham, D. J. Capobianco and W. P. Cheshire

Title: Facial pain as the presenting symptom of lung carcinoma with normal chest radiograph

Journal, Volume (issue) and page number: Headache,

Type of text: Journal article (full text obtained)

Number of eligible patients in study: 23

Total number of patients in study (including ineligible): 33

Presenting symptoms, numbers (%): head and/or facial pain 23 (100%)

Number who had positive CXR ('sensitivity' %): 19 (82.61%). Results are dichotomised as normal/abnormal

95% confidence intervals (%) for sensitivity: 65.57 to 99.65

Number who had negative CXR (%): 4 (17.39%)

-Number who had normal CXR (%):4 (17.39%)

-Number who had abnormal but not suspicious CXR (%): not stated

Comparator to CXR ('gold standard'): not stated

Duration between CXR and diagnosis: Less than 1 year (studies in which duration of symptoms > 1 year excluded)

Study design (quotation marks used where a design type stated): case series and literature review

Histology, number (%): not stated

Mean age: 53.4

Age range: 34-72

Male, number (%): 11 (47.83%)

Smoker or ex-smoker, number (%): 21 (100%)

Deprivation status: unknown

Setting/population: Patients who presented with facial or head pain as a presenting symptom for lung cancer

Country where study conducted: United States

Language: English

Other notes: Two cases are presented, both which had no lesion visible on CXR. In addition 31 other cases are described. 23 cases included for analysis in review (the two case novel case reports in this study are amongst those excluded, since they are presented because the CXR was negative).

Results of initial chest x-ray are dichotomised as 'abnormal' or 'normal' only, therefore 'abnormal' has been interpreted as a positive result. Most of the studies referenced precede 1999, however decision

has been made to include as this publication was after 1999, which is consistent with the criteria stated in the protocol.

Gomez 2004 (266)

Authors: A. Gomez, R. Zalacain, V. Cabriada, L. Lopez, L. Cancelo and C. Jaca

Title: Bronchial carcinoid tumors. Analysis of 41 cases

Journal, Volume (issue) and page number: Revista Clinica Espanola, 204(4), 202-5

Full text obtained (yes/no): yes

Number of eligible patients in study: 41

Total number of patients in study (including ineligible): 41

Presenting symptoms, numbers (%): Described for 23 cases (56.10%) as including dry or productive cough, haemoptysis, dyspnoea or pleuritic pain. No patients presented with endocrinological symptoms.

Number who had positive CXR ('sensitivity' %): 36 (87.80%). Termed as 'pathological' by authors, these included pulmonary mass 5 (12.20%), pulmonary nodule 8 (19.51%), alveolar infiltration 13 (31.71%), atelectasis 7 (17.07%), enlarged hilum 3 (7.32%)

95% confidence intervals (%) for sensitivity: 77.11 to 98.45

Number who had negative CXR (%): 5 (12.20%)
-Number who had normal CXR (%): 5 (12.20%)

-Number who had abnormal but not suspicious CXR: none reported

Comparator to CXR ('gold standard'): bronchoscopy/CT

Duration between CXR and diagnosis: Not reported, however medium diagnostic time was 67 days, suggesting that the majority and perhaps all durations were less than one year.

Study design (quotation marks used where a design type stated): case series

Histology, number (%): carcinoid (100%)

Mean age: 50

Age range: 19-84

Male, number (%): 66% reported, precise number not reported.

Smoker or ex-smoker, number (%): 61% reported, precise number not reported

Deprivation status: unknown

Setting/population: Hospital de Cruces. Patients presenting to a respiratory service 1 January 1987 to 31 December 2001 who were diagnosed with bronchial carcinoid .

Country where study conducted: Spain

Language: Spanish

Other notes:

Kitazaki 2005 (267)

Authors: T. Kitazaki, M. Fukuda, H. Soda and S. Kohno

Title: Novel effects of gefitinib on mucin production in bronchioloalveolar carcinoma; two case reports

Journal, Volume (issue) and page number: Lung Cancer, 49(1), 125-8

Type of text: Journal article (full text obtained)

Number of eligible patients in study: 2

Total number of patients in study (including ineligible): 2

Presenting symptoms: cough with sputum (patient 1), dysponea, cough, sputum (patient2)

Number who had positive CXR ('sensitivity' %): 2 (100%)

95% confidence intervals (%) for sensitivity: unable to calculate as sensitivity reported as 100%

Number who had negative CXR (%): 0%

-Number who had normal CXR (%): N/A

-Number who had indeterminate findings on CXR (%): N/A

Comparator to CXR ('gold standard'): CT/transbronchial biopsy

Duration between CXR and diagnosis: Not stated. In both cases CXR performed during single episode of care, CXR performed following admission, therefore very likely to have been within one year.

Study design (quotation marks used where a design type stated): 'two case reports'

Histology, number (%): NSCLC (bronchioloalveolar carcinoma) 2 (100%)

Mean age: 71.5 years

Age range: 67-76

Male, number (%): 0 (0%)

Smoker or ex-smoker, number (%): 0(0%)

Deprivation status: unknown

Setting/population: Hospital setting. Patients with bronchioloalveolar carcinoma treated with gefitinib

Country where study conducted: Japan

Language: English

Other notes: Infiltrate present on both chest x-rays, this led to further investigation and thus we have considered to be a positive finding.

Bando 2006 (268)

Authors: H. Bando, T. Nishio, H. Bamba, T. Uno and Y. Hisa

Title: Vocal fold paralysis as a sign of chest diseases: a 15-year retrospective study

Journal, Volume (issue) and page number: World Journal of Surgery, 30(3), 293-8

Full text obtained (yes/no): yes

Number of eligible patients in study: 15

Total number of patients in study (including ineligible): 42

Presenting symptoms, numbers (%): vocal cord paralysis (100%)

Number who had positive CXR ('sensitivity' %): 12 (80.00%). These were stated as 'abnormal'.

95% confidence intervals (%) for sensitivity: 57.37 to 100.00

Number who had negative CXR (%): 3 (20.00%)

-Number who had normal CXR: 3 (20.00%)

-Number who had indeterminate findings on CXR (%):

Comparator to CXR ('gold standard'): CT

Duration between CXR and diagnosis: Lesion was detected in all cases within 2 months. CXR appears to have taken place as part of diagnostic work up.

Study design (quotation marks used where a design type stated): case series

Histology, number (%): SCLC 5 (33.33%), adenocarcinoma 3 (20.00%), squamous cell carcinoma 1 (6.67%), other 2 (13.33%), unknown 4 (26.67%)

Mean age*: 68.3

Age range: 51-88

Male, number (%): 11 (73.33%)

Smoker or ex-smoker, number (%): not stated

Deprivation status: not stated

Setting/population: Kyoto Prefectural University of Medicine Hospital. Patients with vocal cord paralysis.

Country where study conducted: Japan

Language: English

Other notes: 'Abnormal' CXR is understood to be 'positive' given context of vocal cord paralysis.

Bjerager 2006 (269)

Authors: M. Bjerager, T. Palshof, R. Dahl, P. Vedsted and F. Olesen

Title: Delay in diagnosis of lung cancer in general practice

Journal, Volume (issue) and page number: British Journal of General Practice, 56(532), 863-8

Full text obtained (yes/no): yes

Number of eligible patients in study: 58

Total number of patients in study (including ineligible): 84

Presenting symptoms: Cough, dysponea, fatigue, fever, weight loss, thoracic pain, haemoptysis, shoulder pain, other MSK pain. Paper quantifies the numbers of symptoms presented rather than the numbers of patients with each.

Number who had positive CXR ('sensitivity' %): 46 (79.31%)

95% confidence intervals (%) for sensitivity: 67.60 to 91.02

Total number who had negative CXR (%): 12 (20.69%) 'result raised no suspicion of cancer'

-number who had normal chest x-ray (%) :not stated

-number who had indeterminate findings on CXR (%):not stated

Comparator to CXR ('gold standard'): not stated

Duration between CXR and diagnosis: not stated. Median delay in primary care 32.5 days (IQI 12-68 days). False negative CXR cases the median delay was 161 days (IQI 128-203). Likely that for almost all, or all cases the duration was under one year.

Study design (quotation marks used where a design type stated): retrospective case note review

Histology, number (%): not stated

Mean age*: unknown. Median age 66 years

Age range: 34-83

Male, number (%)*: 54 (64.29%)

Smoker or ex-smoker, number (%): unknown

Deprivation status: unknown

Setting/population: Primary care. Patients diagnosed with lung cancer in Aarhus, Denmark during a 6 month period in 2003.

Country where study conducted: Denmark

Language: English

Other notes:

Brock 2006(270)

Authors: M. V. Brock, C. M. Hooker, E. A. Engels, R. D. Moore, M. L. Gillison, A. J. Alberg, J. C. Keruly, S. C. Yang, R. F. Heitmiller, S. B. Baylin, J. G. Herman and J. R. Brahmer

Title: Delayed diagnosis and elevated mortality in an urban population with HIV and lung cancer: implications for patient care

Journal, Volume (issue) and page number: Journal of Acquired Immune Deficiency Syndromes, 43(1), 47-55

Type of text: Journal article (full text obtained)

Number of eligible patients in study: 30

Total number of patients in study (including ineligible): 92

Presenting symptoms, numbers (%): not stated

Number who had positive CXR ('sensitivity' %): 12 (40.00%)

95% confidence intervals (%) for sensitivity: 12.28 to 67.72

Number who had negative CXR (%): 18 (60.00%)

-Number who had normal CXR: 9 (30.00%)

-Number who had abnormal but not suspicious findings on CXR (%): 9 (30.00%). Described as 'non specific infiltrates'

Comparator to CXR ('gold standard'): CT

Duration between CXR and diagnosis: within 1 year

Study design (quotation marks used where a design type stated): case series

Histology, number (%)*:Adenocarcinoma 44 (47.83), squamous cell 16 (17.39%), NSCLC 14 (15.22%), SCLC 8 (8.70%), Large cell 5 (5.43%), other 5 (5.43%)

Mean age: unknown. Median age 46

Age range: unknown

Male, number (%): 62 (67.39%)*

Smoker or ex-smoker, number (%): 91 (98.91)*

Deprivation status: unknown

Setting/population: Hospital setting. Lung cancer in HIV infected patients attending Johns Hopkin's 1986 to 2004

Country where study conducted: United States

Language: English

Other notes: 9 with non-specific infiltrates. These have been included as negative chest x-ray, this is consistent with authors categorisation, as they assert that ‘60% of chest radiographs had no evidence of neoplasm within 1 year of diagnosis’.

Stapley 2006 (70)

Authors: S. Stapley, D. Sharp and W. Hamilton

Title: Negative chest X-rays in primary care patients with lung cancer

Journal, Volume (issue) and page number: British Journal of General Practice 56(529, 570-3)

Full text obtained (yes/no): yes

Number of eligible patients in study: 164

Total number of patients in study (including ineligible): 260, of whom 247 were studied

Presenting symptoms, numbers (%): Haemoptysis 41 (16.60%) , weight loss 47 (19.03%), loss of appetite 32 (12.96%), SOB 94 (38.06%), Chest or rib pain 68 (27.53%), Fatigue 50 (20.24%), cough 120 (48.58%), hoarseness 15 (6.07%)*

Number who had positive CXR ('sensitivity' %): 126 (76.83%)

95% confidence intervals: 69.46-84.20 (CI for false negatives stated as 16-32% in paper)

Number who had negative CXR (%): 38 (23.17%)

-Number with a normal CXR (%): 17 (10.37%)

-Number who had abnormal but not suspicious CXR (%): 21 (12.80%)

Comparator to CXR ('gold standard'): not stated

Duration between CXR and diagnosis: within 1 year

Study design (quotation marks used where a design type stated): 'retrospective cohort study'

Histology, number (%)*: squamous 80 (32.39%), adenocarcinoma 57 (23.08%), SCLC 52 (21.05%), large cell 21 (8.50%), unspecified carcinomas 27 (10.93%), histology not known 10 (4.05%)

Mean age*: 70.8 years

Age range: not stated

Male, number (%)*: 170 (68.8%)

Smoker or ex-smoker, number (%): not stated

Deprivation status: not stated

Setting/population: general practices in Exeter Primary Care Trust, diagnosed between 1998-2002.

Country where study conducted: England

Language: English

Other notes: X-ray results were categorised into three groups:

- normal;
- abnormal but no malignancy suspected; and

- abnormal with possible malignancy.

Patients with indefinite abnormalities (such as ill-defined shadowing) were classified into group 2 or group 3 depending on the action suggested by the reporting radiologist. If any further investigation, such as a repeat chest X-ray or referral, was recommended (even if possible malignancy was not explicitly stated), or if malignancy was mentioned as a possibility, then the report was classified as group 3. For simplicity, groups 1 and 2 can be described as negative X-rays, and group 3 positive X-rays. The radiologists' reports were used as the only method of categorisation, as they would be all that the GPs would have available to make their decisions about the need for further investigation.

Results were presented as false negative rate. The confidence intervals differ slightly from those calculated in this review.

Fernandez 2007 (71)

Authors: V. Fernandez, J. L. Alonso, L. Munuera, J. L. Moya, B. Lasa, A. Suarez and J. Gutierrez

Title: Analysis of lung cancer cases diagnosed in an internal medicine department: from January 2001 to September 2006

Journal, Volume (issue) and page number: Anales del Sistema Sanitario de Navarra 30(3), 353-62

Full text obtained (yes/no): yes

Number of eligible patients in study: 102

Total number of patients in study (including ineligible): 124

Presenting symptoms, numbers (%): haemoptysis & pain 40 (32.26%), SVCO 2 (1.61%). Presentation by body system was as follows, respiratory symptoms 37, neurological 29, musculoskeletal 27, general 22, cutaneous 10, gastrointestinal 7, miscellaneous 5

Number who had positive CXR ('sensitivity' %): 97 (95.10%), these were nodules or masses 53 (51.96%), pleural effusions 16 (15.69%), enlarged hilum 16 (15.69%), multiple pulmonary metastasis 6 (5.88%), widened mediastinum 4 (3.92%), interstitial infiltration 2 (1.96%)

95% confidence intervals (%) for sensitivity: 90.80 to 99.40

Number who had negative CXR (%): 5 (4.90%)

-Number who had normal CXR (%): 5 (4.90%)

-Number who had abnormal but not suspicious CXR (%): 0

Comparator to CXR ('gold standard'): CT, bronchoscopy, mediastinoscopy, surgery

Duration between CXR and diagnosis: not stated precisely, but appears to have been within one hospital episode. Mean symptomatic time before hospitalisation was 74.5 +/- 7 days, suggesting that the duration for all or nearly all was likely to have been within one year.

Study design (quotation marks used where a design type stated): case series

Histology, number (%)*: SCLC 28 (22.59%), NSCLC 77 (62.10%). Anaplastic 10 (8.06%), no histology available 9 (7.26%)*

NSCLC: large cell 18 (14.52%), epidermoid 22 (17.74%), well differentiated adenocarcinoma 2 (1.61%), bronchoalveolar 7 (5.65%),

Mean age*: 68

Age range*: 35-98

Male, number (%)*: 105 (85.37%)

Smoker or ex-smoker, number (%): 85%. Number not stated, though 85% of group is 105.

Deprivation status: not stated.

Setting/population: Hospital setting. Patients diagnosed from January 2001 to September 2006

Country where study conducted: Spain

Language: Spanish

Other notes: Total number in study stated as 136, of whom 12 excluded. However numbers of patients when added by presenting body system is 137. Of the 124 studied states that 105 were men and 18 women (which totals 123). Positive CXR findings in the paper included 6 ‘multiple pulmonary metastases’, the definition of lung cancer conforms to a recognised diagnosis of lung cancer (GDR 082) so it is likely that these were secondary to a pulmonary primary so we have not excluded them from the analysis. Fernandez has confirmed via email that the interpretations of the CXR were contemporaneous (prior to diagnosis known).

The authors have not discriminated between ‘positive’ and ‘negative’ chest x-rays but have reported all abnormalities. In this analysis we have considered all reported abnormalities as ‘positive’

Kato 2010 (271)

Authors: T. Kato, K. Narita and K. Ohara

Title: Three cases of squamous cell carcinomas which enlarged rapidly with necrotic cavities after bronchoscopy

Journal, Volume (issue) and page number: Japanese Journal of Lung Cancer, 50(6), 822-7

Type of article: journal article (full text obtained)

Number of eligible patients in study: 3

Total number of patients in study (including ineligible): 3

Presenting symptoms, numbers (%): cough 1 (33.33%); symptoms not reported in other cases

Number who had positive CXR ('sensitivity' %): 3 (100%)

95% confidence intervals (%) for sensitivity: unable to calculate as sensitive calculated at 100%

Number who had negative CXR (%): 0 (0%)

-Number who had normal CXR(%): 0 (0%)

-Number who had abnormal but not suspicious CXR (%): 0 (0%)

Comparator to CXR ('gold standard'): bronchoscopy/CT

Duration between CXR and diagnosis: less than 3 months

Study design (quotation marks used where a design type stated): case series

Histology, number (%): squamous cell 3 (100%)

Mean age: 64.67

Age range: 60-70

Male, number (%): 3 (100%)

Smoker or ex-smoker, number (%): 2 (66.67%)

Deprivation status: unknown

Setting/population: Hospital. Patients with squamous cell carcinoma with necrotic cavities

Country where study conducted: Japan

Language: Japanese

Other notes: Cases were selected and presented together due to presence of necrotic cavities, not generalisable.

Kikuchi 2010 (272)

Authors: R. Kikuchi, N. Isowa, H. Tokuyasu, Y. Kawasaki, H. Onuma and H. Miura

Title: Three cases of resected pleomorphic carcinoma

Journal, Volume (issue) and page number: Annals of Thoracic & Cardiovascular Surgery, 16(4), 264-9

Full text obtained (yes/no): yes

Number of eligible patients in study: 2

Total number of patients in study (including ineligible): 3 (one patient excluded from this analysis as had CT as well as CXR and not clear that CXR interpretation was performed in isolation)

Presenting symptoms, numbers (%): sleep apnoea 1 (50%) & back pain 1 (50%)

Number who had positive CXR ('sensitivity' %): 2 (100%)

95% confidence intervals (%) for sensitivity: unable to calculate as sensitivity calculated as 100%

Number who had negative CXR (%): 0 (100%)

Number who had indeterminate findings on CXR (%):

Comparator to CXR ('gold standard'): CT/biopsy

Duration between CXR and diagnosis: not stated. CXR performed on presentation to hospital for investigation of symptoms and narrative suggests that diagnosis occurred within that episode of care, therefore almost certainly this occurred with one year.

Study design (quotation marks used where a design type stated): case series ('case report')

Histology, number (%): pleomorphic carcinoma 3 (100%)

Mean age: 71.00

Age range: 60-78

Male, number (%): 2 (100%)

Smoker or ex-smoker, number (%): smoking status stated for one patient only (who was a smoker)

Deprivation status: unknown

Setting/population: Hospital. Patients with pleomorphic carcinoma.

Country where study conducted: Japan

Language: English

Other notes:

Uzun 2010 (273)

Authors: O. Uzun, Y. Atasoy, S. Findik, A. G. Atici and L. Erkan

Title: A prospective evaluation of hemoptysis cases in a tertiary referral hospital

Journal, Volume (issue) and page number: The Clinical Respiratory Journal 4(3), 131-8

Type of text: journal article (full text obtained)

Number of eligible patients in study: 51

Total number of patients in study (including ineligible): 178

Presenting symptoms, numbers (%): haemoptysis 51 (100%)

Number who had positive CXR ('sensitivity' %): 50 (98.04%) had an 'abnormal' chest x-ray

95% confidence intervals (%) for sensitivity: 94.20 to 100

Number who had negative CXR (%): 1 (1.96%)

-Number who had normal CXR (%): 1 (1.96%)

-Number who had indeterminate findings on CXR (%): 0 (%)

Comparator to CXR ('gold standard'): CT/bronchoscopy

Duration between CXR and diagnosis: unknown. Maximum duration of haemoptysis was 90 days (mean 12.1 days), therefore seems likely was within one year. In addition, the cases were recruited upon presentation with haemoptysis and chest x-ray was performed as an initial investigation on all.

Study design (quotation marks used where a design type stated): case series

Histology, number (%): SCLC 3 (5.88%), squamous cell 41 (80.39%), adenocarcinoma 5 (9.80%)

Mean age*: 54.3

Age range*: 16-85

Male, number (%)*: 136 (76.40%)

Smoker or ex-smoker, number (%)*: 119 (66.85%)

Deprivation status: unknown

Setting/population: Hospital. Consecutive patients presenting with haemoptysis

Country where study conducted: Turkey

Language: English

Other notes: Reports CXR as normal or abnormal, authors have not stated whether these constituted 'positive' or 'negative' chest x-rays. This may not correspond to positive/negative, as abnormal may include CXR with indeterminate abnormality. For this analysis we have considered all reported abnormities as 'positive'

Mao 2011 {Mao, 2011 #460}

Authors: Mao, J. F. Zhang, J. L. Nie, M. Lu, S. H. Wu, X. Y.

Title: Diabetes insipidus as the first symptom caused by lung cancer metastasis to the pituitary glands: Clinical presentations, diagnosis, and management

Journal, Volume (issue) and page number: Journal of Postgraduate Medicine, 57 (4) 302-6

Type of text: journal article (full text obtained)

Number of eligible patients in study: 10

Total number of patients in study (including ineligible): 10

Presenting symptoms, numbers (%): polyuria 9 (90%), hyperosmotic coma 1 (10%),

Number who had positive CXR ('sensitivity' %): 6 (60%)

95% confidence intervals (%) for sensitivity: 20.8 to 99.2

Number who had negative CXR (%): 4

-Number who had normal CXR (%): unknown

-Number who had indeterminate findings on CXR (%): unknown

Comparator to CXR ('gold standard'): CT

Study design (quotation marks used where a design type stated): 'retrospective analysis'

Histology, number (%): adenocarcinoma 7 (70%), small cell 3 (30%)

Mean age: 58.7

Age range: 37-71

Male, number (%): 5 (50%)

Smoker or ex-smoker, number (%): unknown

Deprivation status: unknown

Setting/population: Patients who presented with diabetes insipidus because of pituitary metastasis from a lung cancer. Hospital.

Country where study conducted: China

Language: English

Other notes: Study states: 'Lung cancers were diagnosed by chest imaging and pathological biopsy. The masses could be readily seen in chest CT images in all patients, whereas in four patients, no abnormalities could be found in their chest X-ray plain films.' For the eight patients for whom sudden onset polyuria and polydipsia was the cause of presentation, the duration of symptoms ranged from 2 weeks to 6 months. One patient presented with coma. One patient had symptoms of diabetes insipidus for 4 years but was diagnosed following referral. It is possible that the patient who had long standing symptoms (4 years) did not have a chest x-ray in the year prior to diagnosis, however seems likely would have had radiological assessment on referral to centre in the study.

Okazaki 2012(274)

Authors: A. Okazaki, T. Araya, A. Sakai, T. Sone, K. Kasahara and M. Fujimura

Title: Two cases of small cell lung cancer with metastasis to the stomach at initial diagnosis.

Journal, Volume (issue) and page number: Japanese Journal of Lung Cancer, 52(2), 220-5

Full text obtained (yes/no): yes

Number of eligible patients in study: 2

Total number of patients in study (including ineligible): 2

Presenting symptoms, numbers (%): anorexia 1 (50%), malaise & epigastric pain 1 (50%)

Number who had positive CXR ('sensitivity' %): 2 (100%)

95% confidence intervals (%) for sensitivity: unable to calculate as sensitivity reported as 100%

Number who had negative CXR (%): 0 (0%)

Number who had indeterminate findings on CXR (%):

Comparator to CXR ('gold standard'): CT/bronchoscopy

Duration between CXR and diagnosis: not stated. In both cases CXR performed for investigation of symptoms and further diagnostic activity resulted from the positive findings, so the duration almost certainly less than one year.

Study design (quotation marks used where a design type stated): case series

Histology, number (%): SCLC 2 (100%)

Mean age: 75.0

Age range: 74-76

Male, number (%): 1 (50%)

Smoker or ex-smoker, number (%): 2 (100%)

Deprivation status: unknown

Setting/population: Hospital. Patients with gastric metastasis from lung cancer.

Country where study conducted: Japan

Language: Japanese

Other notes:

Barry 2015(150)

Authors: C. Barry and D. Bergin

Title: Non-detected primary lung cancers on chest x-ray: 3 year retrospective review in university hospital

Journal, Volume (issue) and page number: Irish Journal of Medical Science, 1, S262

Type of text: conference abstract

Number of eligible patients in study: 158

Total number of patients in study (including ineligible): 158

Presenting symptoms, numbers (%): not stated

Number who had positive CXR ('sensitivity' %): 52 identified as 'malignant' and further 74 advised to have follow up, total = 126 (79.75%)

95% confidence intervals (%) for sensitivity: 72.73 to 86.77

Number who had negative CXR (%): 32 (20.25%)

-Number with normal CXR (%): 'lesion not identified' in 23 (14.56%)

-Number who had abnormal but not suspicious CXR (%): abnormal but no follow up recommended 9 (5.70%)

Comparator to CXR ('gold standard'): not stated. Retrospectively identified from a database.

Duration between CXR and diagnosis: Within 1 year

Study design (quotation marks used where a design type stated): audit ('retrospective review')

Histology, number (%): not stated

Mean age: not stated

Age range: not stated

Male, number (%): not stated

Smoker or ex-smoker, number (%): not stated

Deprivation status: not stated

Setting/population: University hospital. Patients with lung cancer.

Country where study conducted: Republic of Ireland

Language: English

Other notes: Does not state if population includes patients who were referred from primary care or if drawn from patients who presented to secondary care only.

Ghimire 2016(275)

Authors: R. H. Ghimire, N. Bhatta, P. Koirala, B. Bista, D. R. Misra and B. Shah

Title: Outcomes bronchoscopic evaluation in a university hospital

Journal, Volume (issue) and page number: Journal of the Nepal Medical Association, 55(204), 51-4

Type of text: Journal article (full text obtained)

Number of eligible patients in study: 7

Total number of patients in study (including ineligible): 100

Presenting symptoms, numbers (%)*: haemoptoysis 58 (58%), chronic cough 30 (30%), not resolving pneumonia 12 (12%)

Number who had positive CXR ('sensitivity' %): 7 (100%)

95% confidence intervals (%) for sensitivity: unable to calculate as sensitivity reported as 100%

Number who had negative CXR (%): 0 (0%)

-Number with normal CXR (%): 0 (0%)

-Number who had abnormal but not suspicious CXR (%): 0 (0%)

Comparator to CXR ('gold standard'): Bronchoscopy

Duration between CXR and diagnosis: unknown. Underwent assessment including CXR on presentation to clinic and then proceed to bronchoscopy so very likely to be within 1 year.

Study design (quotation marks used where a design type stated): 'cross sectional study' case series

Histology, number (%): NSCLC 7 (100%); squamous cell 6 (85.71%), 1 (14.29%)

Mean age*: 54.71

Age range*: 18-85

Male, number (%)*: 76 (76%)

Smoker or ex-smoker, number (%): unknown

Deprivation status: unknown

Setting/population: Hospital. Consecutive patients who underwent bronchoscopy from 1st May 2013 to 30th April 2015

Country where study conducted: Nepal

Language: English

Other notes:

Appendix 4: Assessment of risk of bias for studies included in systematic review

Modified QUADAS-2 tool used for assessment of risk of bias:

Domain	**Patient Selection**	**CXR**
Risk of bias (high, low or unclear)	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?
Concerns about applicability (high, low, or unclear)	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct or interpretation differ from the index question?

Quality assessment of studies agreed by SB and AG:

	Patient selection		**CXR**	
	Risk of bias	Applicability concerns	Risk of bias	Applicability concerns
Hamada 1999	High	High	Unclear	Unclear
Tanaka 1999	High	High	Unclear	Unclear
Bini 2001	High	High	Unclear	Unclear
Lee 2001	High	High	Unclear	Unclear
Haro 2002	Low	High	Unclear	High
Losa Gaspa 2002	Low	High	Unclear	Unclear
Abraham 2003	High	High	Unclear	High
Gomez 2004	High	High	High	High
Kitazaki 2005	High	High	Unclear	Unclear
Bando 2006	High	High	High	High
Bjerager 2006	Low	Low	Low	Low
Brock 2006	High	High	Low	Unclear
Stapley 2006	Low	Low	Low	Low
Fernandez 2007	Low	Low	Unclear	High
Kato 2010	High	High	Unclear	Unclear
Kikuchi 2010	High	High	High	Unclear
Uzun 2010	Low	High	Unclear	High
Ozaki 2012	High	High	Unclear	Unclear
Barry 2015	Low	Low	Low	Low
Ghimire 2016	Low	High	Unclear	Unclear
Mao	High	High	Unclear	Unclear

Appendix 5: protocol for validation of chest x-ray coding

Protocol for adding diagnostic codes to chest x-ray reports in patients who were investigated for lung cancer.

Leeds Teaching Hospitals NHS Trust, 9th October 2018

(Revised June 2019 & January 2020)

Dr Mat Callister, Consultant Respiratory Physician, LTHT

Dr Bobby Bhartia, Consultant Thoracic and Oncological Radiologist, LTHT

Dr Stephen Bradley, Clinical Research Fellow, University of Leeds

Dr Luke Hatton, Academic Foundation Doctor, University of Leeds & Leeds Teaching Hospitals NHS Trust

Professor Richard Neal, Professor of Primary Care Oncology, University of Leeds

Background

Chest x-rays are a frequently requested investigation for suspected lung cancer. In many cases the chest x-rays are reported by radiologists however as a descriptive text entry which is recorded on the PPM+. PPM+ contains a field in which to enter a numeric code for each chest x-ray report which is not currently being used.

The Royal College of Radiologists clinical audit ‘missed lung cancers on chest radiographs’ (see appendix) proposes retrospective categorisation of chest x-rays be undertaken as follows:

• Appropriate reports: Lesion identified

• Appropriate reports: Lesion identified as indeterminate (not as malignant). Appropriate further investigation or follow up suggested

• Non-specific reports: Lesion identified as indeterminate (not as malignant). No follow up suggested

• Missed cancers: Lesion not identified

• Examination not reported by Radiology Department

Benefits of coding chest x-ray reports

Approximately 580 lung cancers are diagnosed in Leeds per year. Chest x-ray is frequently the first investigation undertaken. The ability to rapidly retrieve the diagnostic category of chest x-rays for several thousand patients will enhance the capacity of departments in LTHT including radiology and respiratory medicine to evaluate the performance of current diagnostic pathways.

The experience of coding of investigation results in the United States suggests this practice may support improved safety and also the development of novel systems to ensure that abnormal results are acted upon(276, 277).

Method

Diagnostic categories

The 5 available diagnostic codes will be allocated as follows:

1-suspicion of lung cancer identified/urgent investigation indicated

2- abnormality identified/non urgent investigation indicated

3- Non-specific reports, abnormality identified but no further investigation/assessment indicated

4- normal chest x-ray

5- examination not reported by Radiology Department

These categories are aligned to the categories used in the Royal College of Radiologists audit. However these codes will be applied to a range of chest x-ray reports, not only those in whom a diagnosis of lung cancer was subsequently confirmed, as was the case in the RCR audit. Therefore category 3 has been amended to include any abnormality, rather than a lesion retrospectively considered consistent with a subsequent diagnosis of lung cancer.

Principles on categorising chest x-rays

- Reports which suggest repeat chest x-ray, without a delay, e.g. to obtain a lateral view, will be coded as 1

- Reports which specify or suggest reimaging or clinical reassessment, after an intervening period, even without specific reference to the possibility of lung cancer will be categorised as 2 (e.g. suspicion of heart failure with suggestion of repeat chest x-ray after treatment with diuretics)
- Reports which specify *any* time interval before repeating a chest x-ray will be categorised as 2 (even if less than two weeks)
- Reports which identify consolidation or pneumonia will be categorised as 2, even if the report does not specify the recommendation to repeat the chest x-ray after a period of (e.g. 6-8 weeks), since it is widely accepted clinical practice to repeat the chest x-ray to ensure resolution.
- Reports which state only that there is no change since the last chest x-ray and with no further remarks on the interpretation of the film or the context of the request, will be categorised as 3 as it is likely in this context that the previous films did have an abnormality.

The categorisers will not check the report of the previous chest x-ray, unless required to do so to clarify the category of a report (e.g. 'no change from previous film'). In some cases, the text of the chest x-ray request, which is presented along with the chest x-ray report, may confirm that the previous chest x-ray did have an abnormality.

- Where the chest x-ray report notes, for example, 'no change from previous study':
    - if the previous chest x-ray was known to have consolidation or another feature which required follow up will be categorised as 1.
    - if the previous x-ray was noted to have abnormalities (for example evidence of COPD) which did not require active follow up then this will be categorised as 3
    - if the report lists other findings that indicate that the x-ray is normal, with no abnormalities noted then the report will be categorised as 4.

Addendums to chest x-ray reports

In the case of addendums which have been subsequently added to a chest x-ray report and which would alter the diagnostic category, if the addendum was added within 28 days of the date of the study then the information contained in the addendum report, rather than the original report, will be used to inform the diagnostic code.

Validation of diagnostic categories

A group of 100 chest x-rays will be categorised into one of 5 categories (see above) by both Dr Stephen Bradley (clinical research fellow at the University of Leeds) and Dr Luke Hatton, an academic foundation doctor employed by LTHT. If either clinician is uncertain as to the

appropriate diagnostic category they will consult with Dr Callister or Dr Bhartia who will advise upon the category to allocate. The designated categories (and the patients for whom either doctor sought clarification from Dr Callister and/or Dr Bhartia) along with an NHS number or LTHT number will be recorded by both clinicians on separate password protected excel spreadsheets, and saved on a server in Leeds Teaching Hospitals NHS trust.

The allocated categories will be compared with a Cohen's Kappa score generated to determine the level of agreement between Dr Bradley and Dr Hatton. A score of greater than >=0.61 is used to as a threshold of 'substantial' agreement(278) and this will be accepted as satisfactory agreement between categorisation by Dr Bradley and Dr Hatton.

Following generation of the Kappa score there will be a discussion amongst the team as to the clinical significance of a score that deviates either in excess, or below 0.61.

If a Kappa score of at least 0.61 is not achieved, a sample of 20 of the reports will be categorised together by Dr Bradley, Dr Callister and the other clinician in order to determine any cause of disparity. A further sample of 50 chest x-rays reports will be then be categorised by Dr Bradley and Dr Hatton and the Kappa score will be recalculated.

Coding of chest x-rays

Following achievement of a satisfactory level of concordance in chest x-ray report categorisation, Dr Bradley and Dr Hatton will undertake the coding of chest x-rays for patients who were diagnosed with lung cancer in selected years (2008-2017) and also all of the chest x-rays for which are known to have been were performed as part of the self request chest x-ray service between 2011 and 2016.

Information governance and data protection

This programme of data enhancement will be undertaken on LTHT computer systems only and no information will be extracted from LTHT systems without separate ethical and governance approval. Dr Bradley has an honorary contract with LTHT status in order to contribute to this work and Dr Hatton is a current employee of LTHT.

In collecting data to determine the agreement between the categorisers (Dr Bradley and Dr Hatton) it will be necessary to create two excel spreadsheets which will contain the NHS number or LTHT number and the date of chest x-ray for each of 100 patients. Alongside each of these will be added a numbered category as described in this document. The excel files will be held on an LTHT server, they will be password protected and they will not be removed from LTHT or copied and sent elsewhere.

In order to determine Cohen's Kappa score the two ordered lists of categories 1-5 (see page 2, diagnostic categories) will be extracted into a separate excel file. This file will not contain the NHS numbers or any other identifiers of the patients. Dr Bradley will transfer this file to his personal storage space on the University of Leeds M: drive, in order to facilitate the

generation of the Kappa score. This file will consist only of two lists of 100 numbers (1-5) and will not be able to be used to identify any patients. Following generation of a satisfactory Kappa score all files created which contain patient identifiers will be deleted. The excel file containing the two lists of categories allocated by Dr Bradley and Dr Hatton but with no other identifying information will be retained by Dr Bradley as evidence that a satisfactory Kapa score was obtained.

Other considerations

Duty of candour

It will be assumed that imaging reports have been inspected by the clinical teams who requested the investigation and that appropriate action was taken. This programme of data enhancement is intended to support future audit and service evaluation but does not itself constitute an audit exercise and it will not include correlating the results of imaging to care that the patient received. In categorising the chest x-rays only the chest x-ray report and no other element of the electronic patient record will be deliberately inspected.

It is thought unlikely that this work will lead to the discovery of clinical management that patient's received or of any aspect of clinical care other than the chest x-ray report. However if the team undertaking this data enhancement discover evidence of harm that has resulted to (a) patient(s) due to clinical error then they will proceed in accordance with the principles and obligations set out in the duty of candour and will abide by LTHT governance protocols in respect to escalating such issues to the clinical team and/or to other members of the trust management.

It is well understood that a significant proportion of patients who have significant pathology, such as lung cancer, that is not identified on initial chest x-ray(70). The inability of plain radiography to detect all serious intrathoracic pathology is an expected performance characteristic of the investigation and does not in itself represent diagnostic error.

Addendum 1

Validation of chest x-ray coding-October 2018

SB and LH undertook the coding of 100 chest x-ray reports in Leeds Chest Clinic on 27th October 2018. This was conducted independently in two separate clinic rooms. There was disagreement between SB and LH on 14 chest x-ray reports, although this disagreement constituted a difference between the assignment to the overall categories of positive or negative only on four occasions. This corresponded to a Cohen's Kappa score of 0.80, indicating a high degree of consistency between reviewers. In only 4 cases were there

differences in the positive or negative designation of the chest x-ray reports between reviewers. When analysing the coding decisions of SB and LH for categorisation into positive (code 1 or 2) or negative (codes 3 or 4) alone, the Cohen's Kappa score was 0.92, indicating a very high degree of consistency between SB and LH.

Chest x-ray reports for which there were divergences between LH and SB were discussed and the following themes were discussed. Decisions were made by agreement between SB and LH and where this was not possible an adjudication was made by MC. The outcomes of these discussions are listed below.

Presence of additional features described on CXR report

Chest x-rays reports in which there were features such as the presence of a pacemaker, a median sternotomy or a nipple shadow but no other abnormality, should be coded as 4.

Repeat CXR advised but with no timescale suggested

Instances in which repeat CXR is advised to reassess for a finding that is thought to be likely to be artefactual, such as 'composite shadow', to be coded as 2.

Report advises referral for CT imaging with no timescale suggested

A case in which the report suggested the possibility of bronchiectasis and advised follow up with high resolution CT but with no suggestion of what urgency was required. It was decided that such cases should be coded as 2.

Synonyms for pneumonia/consolidation

Reports with reference to radiological evidence of lower respiratory tract infection, such as 'superimposed infection' to be coded as 2.

Comment on report suggesting 'referral if remains symptomatic'

Statements such as 'suggest referral to chest clinic if remains symptomatic' should be disregarded and coding to rely on what is in the report which refers to the interpretation of the image.

Addendum 2

Clarification on codes 1 & 2 –June 2019

SB and LH noted a disparity of coding in chest x-rays in which an interval had been suggested on Wednesday 19th June. SB had understood that chest x-ray reports which suggested repeat imaging immediately (typically lateral view) or within two weeks would be

considered code ‘1’, whereas LH had considered any request for repeat imaging to be considered code ‘2’.

SB acknowledged that the protocol document ‘principles for coding’ had been worded ambiguously in that respect, such that the advice that reports which suggested non-lung cancer pathology but did suggest repeat imaging should be categorised as positive (2), was interpreted by LH to mean that any repeat imaging with chest x-ray should be deemed 2, irrespective of the immediacy.

This was discussed with Dr Mat Callister on 20th June 2019 and resolved as follows:

- Reports which suggest immediate repeat imaging, without stipulation of a delay (e.g. obtain lateral view), will be coded ‘1’
- Reports which stipulate, or suggest any delay to assess after a period of time or following a treatment, to be coded ‘2’, even if the stipulated period of time is less than two weeks
- SB to review all reports so far coded by him as ‘1’ and LH to review all reports so far coded by him as ‘2’ in the light of the above.

Addendum 3

Adjudication on coding decisions by Dr M. Callister, Jan 2020

Following completion of coding, Dr Callister was asked to adjudicate on how to code 94 chest x-ray reports for which it had been uncertain which code should be allocated.

Dr Callister determined the following further principles:

- Where options for management are presented (e.g. consider antibiotics and repeat CXR or referral for CT now) I have opted for the more aggressive of these. The former would be a 2, the latter a 1, so the 1 trumps the 2.
- I have generally interpreted “Referral to a chest physician” as code for a CT and therefore coded as 1. This was the pathway then (now I think they’d just recommend CT directly). I think in this context (i.e. abnormal CXR) they mean cancer most of the time. The exceptions to this are when they specifically reference an alternative cause (e.g. reactivation of TB, progression of pulmonary fibrosis) in which case I’ve classed it as 2
- Similarly, where CT is suggested due to suspicions about specific non-malignant aetiologies (usually pulmonary fibrosis) I’ve classed it as 2.
- There are some cases where action is contingent on other clinical features. Some of these have CXRs that on their own would be 3 or 4 (i.e. are specifically referenced as reassuring) but action is either mandated or offered depending on other bits of information (e.g. compression through oesophageal wall at OGD, low sodium, chest wall pain). Where specific comment is made about the CXR being 3 or 4, I have categorised it thus. Where some possible new change is referenced on the CXR and

CT is listed as an option (even is symptoms are mentioned in this decision tree) I've classed as 1. I found it very difficult to decide for some of these.

- Where "new pleural effusion" is commented without any other recommendation, I've classed as 2. They generally want us to act on these, but in most cases they're benign.

Appendix 6: Analysis plan for study 'what is the sensitivity of primary care chest x-ray for lung cancer and what are the differences in time to diagnosis and outcomes between patients who have a true positive and those who have a false negative chest x-ray?'

Final plan agreed with PhD supervisors on 14th January 2020.

Study Design

This is an observational study using routinely collected patient data. The population are people diagnosed with a primary lung cancer in the years 2008 to 2015 (inclusive) in Leeds Teaching Hospitals Trust who had a chest x-ray which was requested from primary care in the year prior to diagnosis. The study population will be grouped according to the diagnostic code of the first primary care chest x-ray (index chest x-ray) in the year prior to diagnosis.

Analysis will consist of comparison between groups including proportion of patients diagnosed accurately with lung cancer, healthcare activity and stage of lung cancer at diagnosis and survival.

Study Objectives

- To determine the sensitivity of chest x-ray for lung cancer
- To compare outcomes (stage at diagnosis) and survival between those who had a true positive chest x-ray and a false negative chest x-ray

Data Available

Domain	**Variable**	**Variable type**	**Timepoint (0= at diagnosis,** **-1 to 0 = 1 year prior to diagnosis,** **CXR = time of index CXR**
Demographic	Age (5 yr age bands 20-90, then > 90)	Ordinal categorical (5 yrs age bands 20-90, then > 90) 1 = 20>= - <= 25 2 = 26>= - <=30 3 = 31>= - <=35	0

		4 = 36>= - <=40 5 = 41>= - <=45 5 = 46>= - <=50 6 = 50>= - <= 55 3 = 56>= - <=60 4 = 61>= - <=65 5 = 66>= - <=70 6 = 71>= - <=75 7 = 76>= - <=80 6 = 71>= - <=75 7 = 76>= - <=80 8 = 81>= - <=85 9 = 86>= - <=90 10 = >91	
	Gender	Categorical Male = 1 Female = 0	0
	Ethnicity	not stated = 0 white = 1 mixed = 2 Asian or Asian British = 3 Black or Black British = 4 Chinese = 5 any other ethnic group = 6	
	Smoking status	Categorical (never, ex-smoker, smoker unknown 0 = Unknown 1 = Never 2 = Ex-smoker 3 = Current smoker	0

	Index of Multiple Deprivation decile (Generated from http://imd-by-postcode.opendatacommunities.org/imd/2019)	Ordinal categorical, 1-10	0
	World Health Organization performance status	Ordinal categorical 0=not recorded 1= WHO category 0, able to carry out all normal activity without restriction 2= WHO category 1, restricted in strenuous activity but ambulatory and able to carry out light work 3= WHO category 2, ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours 4= WHO category 3, symptomatic and in a chair or in bed for greater than 50% of the day but not bedridden 5=WHO category 4, completely disabled; cannot carry out any self-care; totally confined to bed or chair	0
Cancer History	Previous cancer diagnosis on referral (see appendix for	0=not known 1= none 2=breast	0

	corresponding ICD 10 codes)	3=renal & urological 4=gastrointestinal 5=malignant neoplasm of bronchus or lung (if present, to also include number of episodes and number of months each episode occurred prior to this diagnosis) 6= other respiratory and intrathoracic (excluding neoplasm of bronchus or lung) 7=gynaecological & testicular 8=dermatological 9=neurological 10=haematological 11=other	
Cancer Stage	Tumour (6th edition 2008-9, 7th edition 2010-15)	Ordinal categorical 0=Tx 1= T1 2= T2 3= T3 4 = T4	0
	Nodes (6th edition 2008-9, 7th edition 2010-15)	Ordinal categorical 0=Nx 1=N1 2=N2 3=N3	0
	Metastases (6th edition 2008-9, 7th edition 2010-15)	Ordinal categorical 0=no distant metastasis 1=metastasis to distant organs	0
	Histology	Categorical 0=Unknown 1=Adenocarcinoma 2= Large cell	

		3= Squamous 4=Small cell 5=Typical carcinoid 6=Atypical carcinoid 7=NSCLC NOS	
	Overall stage (7th edition)	0=unknown 1= Stage I 2= Stage II 3= Stage III 4= Stage IV	
CXR	Number of reported primary care chest x-rays in year prior to diagnosis	Integer	-1 to 0
	Category of earliest chest x-ray (index chest x-ray or CXR1) in year prior to diagnosis	Categorical 1=suspicious for lung cancer, urgent action required 2=abnormal, routine follow up (or after a defined interval) required 3=abnormal, no follow up required 4=normal	-1 to 0
	Number of days prior to diagnosis which earliest chest x-ray (index chest x-ray or CXR1) in year prior to diagnosis was performed	Integer 0 to 365	-1 to 0
	Category of second earliest chest x-ray (CXR2) in year prior to diagnosis	Categorical 1=suspicious for lung cancer, urgent action required 2=abnormal, routine follow up (or after a defined interval) required 3=abnormal, no follow up required 4=normal	-1 to 0

	Number of days prior to diagnosis which second earliest chest x-ray (CXR2) in year prior to diagnosis was performed	Integer 0 to 365	-1 to 0
	Category of third earliest chest x-ray (CXR3) in year prior to diagnosis	Categorical 1=suspicious for lung cancer, urgent action required 2=abnormal, routine follow up (or after a defined interval) required 3=abnormal, no follow up required 4=normal	-1 to 0
	Number of days prior to diagnosis which third earliest chest x-ray (CXR3) in year prior to diagnosis was performed	Integer 0 to 365	-1 to 0
	Category of fourth earliest chest x-ray (CXR4) in year prior to diagnosis	Categorical 1=suspicious for lung cancer, urgent action required 2=abnormal, routine follow up (or after a defined interval) required 3=abnormal, no follow up required 4=normal	-1 to 0
	Number of days prior to diagnosis which fourth earliest chest x-ray (CXR4) in year prior to diagnosis was performed	Integer 0 to 365	-1 to 0
	Category of fifth earliest chest x-ray (CXR4) in year prior to diagnosis	Categorical 1=suspicious for lung cancer, urgent action required 2=abnormal, routine follow up (or after a defined interval) required 3=abnormal, no follow up required	-1 to 0

		4=normal	
	Number of days prior to diagnosis which fourth earliest chest x-ray (CXR4) in year prior to diagnosis was performed	Integer 0 to 365	-1 to 0
Survival	Number of days from index chest x-ray to death	Integer 0 to 1825 or >1825	
	1, 2 and 5 year survival	Ordinal categorical Survival 1 year	

Data Analysis

1) To determine the sensitivity of chest x-ray for lung cancer

The proportion of patients who had a positive index chest x-ray (categories 1 or 2) will be determined, which will be equivalent to the sensitivity of chest x-ray. This will be expressed on a simple table. Confidence intervals for the sensitivity estimate will also be determined.

2) To compare outcomes (stage at diagnosis) and survival between those who had a true positive chest x-ray and a false negative chest x-ray

Analysis of stage at diagnosis

The stage and histology of the entire population and each group 1-4 and groups 1&2 and 3&4 will be presented descriptively on a table.

A 2x2 chi squared test will be used to determine if there is a statistically significant association between early and late stage and positive and negative chest x-ray results. In order to ensure reporting mirrors the clinical context we will also perform a 2x3 chi squared of group 1, group 2 and group 3 & 4 combined. (279) Group 2 will serve as an 'intermediate' group.

Analysis of time to diagnosis from index chest x-ray and survival from index chest x-ray

Descriptive statistics will be used to summarise the time to diagnosis and survival from index chest x-ray. Given that both of these variables are likely to be heavily skewed, the median and interquartile range will be reported. Histograms will be generated to illustrate the distribution of this data. These analyses will reported for the total sample, and then broken down by those with a positive index chest x-ray (groups 1&2) and those with a negative index chest x-ray (groups 3 & 4).

We will also chart the variation in duration (days) prior to diagnosis of lung cancer at which chest x-ray was obtained in the year prior to diagnosis for patients who had a positive index chest x-ray. For patients who had a negative index chest x-ray, to chart variation in the number of subsequent chest x-rays and the duration (days) between which these occurred prior to diagnosis Poisson regression (with robust errors) will be used to model the count of days between index chest x-ray and diagnosis. Assessment of the validity of the model will be undertaken with regards to goodness of fit, omnibus test, test of model effects and parameter estimates.

It is likely that the survival data will include some censoring i.e. there will be individuals for which we know their last follow-up date, but we do not know whether or when they have died since this time point. Kaplan-Meier survival curves will therefore be used to visualise and compare survival from the index chest x-ray for those with a 'true positive' and 'false negative' x-ray result. These curves show the probability of survival across at different time intervals. The numbers at risk and the numbers censored will be reported alongside these plots. The Log rank test will be used to test the null hypothesis that there is no difference in survival between these two groups.

To explore whether the chest x-ray test result is an independent predictor of survival a cox proportional hazards model will be fitted to allow adjustment for other factors of potential importance. Independent variables included in the model will include: time for index chest x-ray to diagnosis, chest x-ray test result, age, gender, deprivation and lung cancer stage.

<u>Exploratory analysis comparing of stage at diagnosis and survival between cases diagnosed earlier and later than 42 days following chest x-ray</u>

It is possible that cancers which are more readily detected on lung cancer may be at a more advanced stage of disease which could represent an intrinsic confounder to this work. In order to generate further insight into the scale of such confounding, we will compare the stage of disease in patients with a negative chest x-ray who are diagnosed within 6 weeks (42 days) with those who have a positive chest x-ray and are diagnosed in 6 weeks (42 days). This will be presented descriptively on a table.

Since the behavior of tumour development is likely to be linked to their detectability on chest x-ray and also with the likelihood of early detection (as more advanced tumours may be more likely to cause symptoms which lead to detection) it will not be possible to definitively state if false negative chest x-rays contribute to later stage at diagnosis.

<u>Exploratory Analysis to determine if index chest x-ray group affects outcome, other than through diagnostic interval and stage at diagnosis</u>

There are three key hypotheses we would like to explore with this data: 1) whether a delay in diagnosis is likely to result in a later stage of diagnosis and 2) whether a 'false negative' result is likely to result in a longer delay to diagnosis compared to a 'true positive' result, and 3) whether a 'true positive' test result is likely to be a more advanced cancer stage compared to a 'false negative' test result (more advanced stage disease

may be easier to detect on a chest x-ray). However, it is also possible that there is an interactive effect these variables. For example, it may that some 'false negatives' may result in a long delay in diagnosis but, if the disease is at a very early stage, this has minimal impact on stage at diagnosis. In contrast, there may be some 'true positive' cases for whom the disease is more aggressive, which this could have a significant impact on stage at diagnosis.

To explore these hypotheses, we will conduct a secondary exploratory analysis in order to determine if the patient group ('false negative' or 'true positive') influences outcomes in addition to any effect this has on delay to diagnosis and stage. In this analysis the outcome variable will be stage at diagnosis, time to diagnosis will be the explanatory variable and time to diagnosis*group) will be the interaction variables.

A Priori Sample Size Justification

The number of lung cancers diagnosed in each year in Leeds has been estimated as approximately 580. The study population will be restricted to those patients with lung cancer who have had a chest x-ray, requested by their General Practitioner in the year prior to diagnosis. A 2006 study of chest x-ray indicated that of patients who were diagnosed with lung cancer 66% had a chest x-ray arranged by their GP in the year prior to diagnosis (70).

It is possible that fewer patients are now receiving a chest x-ray prior to diagnosis as the proportion who are referred directly under a two week wait protocol is likely to have increased. However, a more recent study suggested that the majority of patients still have a chest x-ray in the year prior to diagnosis (280). It therefore still seems reasonable to assume that at least 50% of patients will have had a chest x-ray in this timeframe, equating to approximately 300 per year or 2400 over an 8 year period.

Findings from a systematic review suggest that approximately 80% of patients who had a chest x-ray in the year prior to diagnosis have a 'positive' chest x-ray (70-73), corresponding to groups 1 & 2 in this study. Applying this to our sample (n=~2400) this would yield around 1900 patients in groups 1 & 2 ('true positives') and around 450 patients in groups 2 & 3 ('false negatives').

It is anticipated that the sample size will be sufficient to undertake all the analyses which have been outlined. However sample size calculation will be undertaken prior to regression analyses to ensure that each subgroup, for example age category and gender is sufficiently large, using either the Sidak correction or Bonferroni correction.

Addendum to analysis plan

The above analysis plan which was prepared prior to conducting analyses stated the intention of using Poisson regression to model the count of days between index chest x-ray and diagnosis. This was an error as Poisson regression is used typically to count events rather than days. The analysis plan also anticipated using Sidak correction or Bonferroni correction prior to undertaking regression analyses calculation prior to undertaking regression analyses to ensure that each subgroup, for example age category and gender was sufficiently large to support analyses. It was subsequently decided that these techniques could not be used to

determine sample size. It was also initially planned that previous cancer diagnoses would be obtained, however it was later decided that there was not sufficient confidence in how well the data was recorded.

In addition the secondary exploratory analysis to determine if index chest x-ray group affects outcome, other than through diagnostic interval and stage at diagnosis was not carried out. This exploratory analysis was included in the analysis plan in response to a comment received on peer review of the study proposal, however on carrying out the study it was not possible to satisfactorily ascertain how to interpret this exploratory analysis.

Appendix 7: Self-request chest x-ray service data collection form

NHS Leeds

The Leeds Teaching Hospitals NHS Trust

Self-referral Chest X-ray Form

Please fill in this form so that we can check that you need an X-ray.

Name _____

Address _____

Date of Birth _____ Patient contact phone _____

GP name and practice _____

Have you had any of these symptoms for more than three weeks (please tick box and say how long you have had these symptoms)

Cough	☐	How long? _____
Coughing up blood	☐	How long? _____
Feeling short of breath	☐	How long? _____
Chest pain	☐	How long? _____
Weight loss	☐	How long? _____
Change in voice	☐	How long? _____

Have you ever smoked?

Never ☐ Given up ☐ Still smoking ☐

By completing and signing this form, you are consenting to having a chest X-ray taken. You should read the patient information leaflet you have been given before signing this form. You do not have to have this investigation performed, and it you have any concerns about having it done, you should see your GP who will be able to refer you for a chest X-ray if he/she thinks you need one. If you are happy to proceed with the chest X-ray, please sign and date below.

Signature _____ Print name _____ Date _____

Staff use only Date _____ Radiographer _____ Signature _____

St George's Centre ☐
Seacroft ☐

Age≥50yrs ☐
Symptoms≥3/52 ☐
No CXR in last 3/12 ☐
Not pregnant ☐

CXR performed ☐
CXR not performed ☐ (please give reason overleaf)
Patient information leaflet given ☐
Stop smoking info given (if smoker) ☐

CXR questionnaire/consent form - Version 1.9 produced 15.11.11

Appendix 8: analysis plan for study 'What is the risk of lung cancer in people who have symptoms but who have who have had a negative chest x-ray result?'

Study Design

This is a prospective cohort study based on routinely collected data from patients who attended a self-request chest x-ray (SRCXR) service because of symptoms that warrant a chest x-ray to exclude lung cancer, according to NICE guidelines.

The study database contains the recorded symptoms, their smoking status at presentation for chest x-ray, the presence or absence of thrombocytosis on any full blood count in the one or two years prior to presentation (if a full blood count had been obtained), the age category of each patient (to 5 years), the result of the chest x-ray at the time of reporting (positive or negative for lung cancer), whether or not lung cancer was diagnosed at one or two years from the time of the SRCXR.

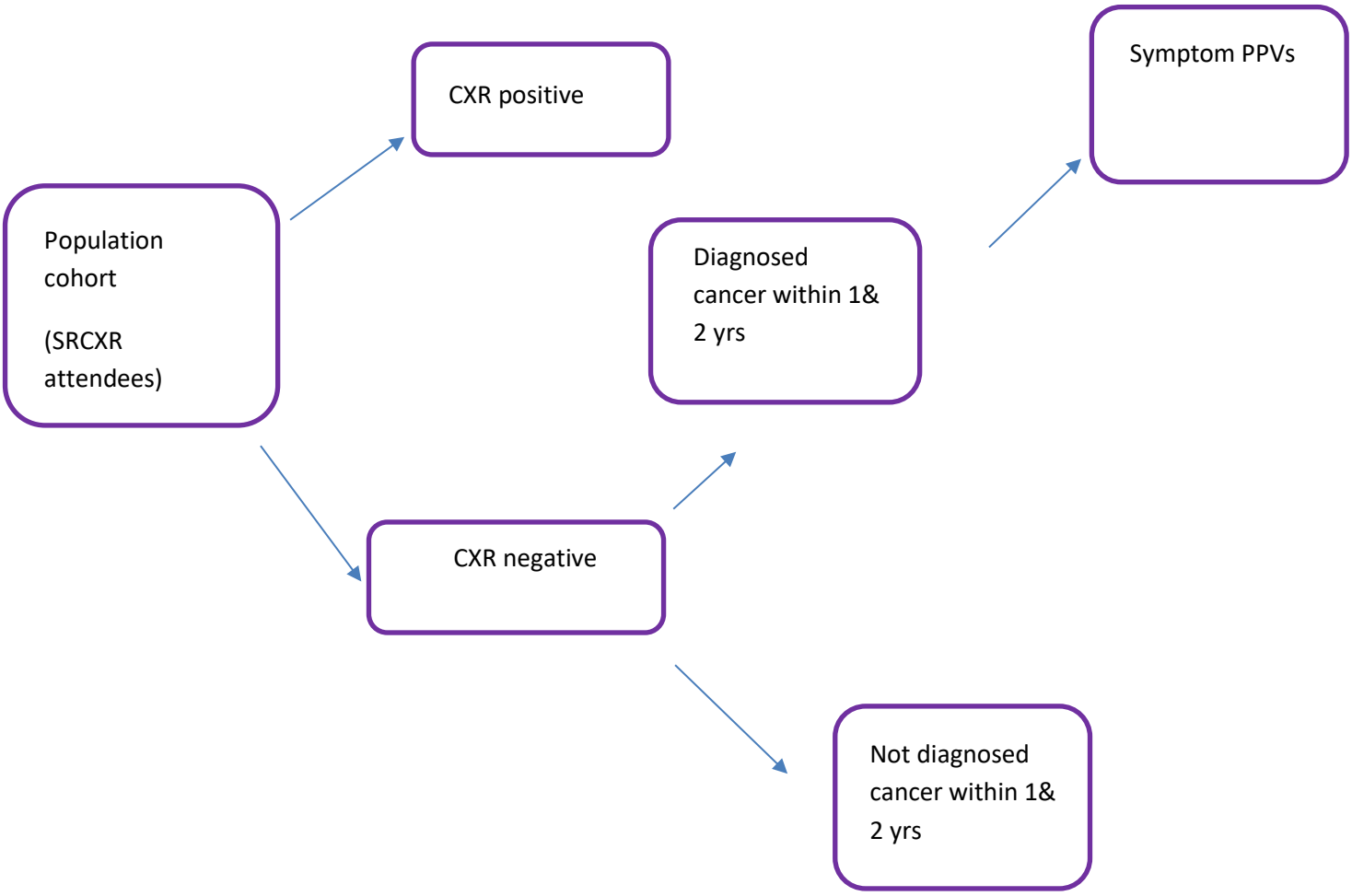
Study Objectives

Primary Objectives:

1. To estimate the risk of being diagnosed with lung cancer within one year and two years following a negative chest x-ray result in patients with relevant symptoms who requested a chest x-ray. This is equivalent to the false negative rate of chest x-ray
2. To estimate the risk of lung cancer associated with specific symptoms/symptom combinations in people who have had a negative chest x-ray result

Secondary Objectives:

1. To determine the sensitivity, specificity, PPV and NPV of chest x-ray in those over >50 for lung cancer
2. To determine whether the symptoms associated with lung cancer are different in those who had a positive chest x-ray result compared to those who had a negative chest x-ray result



Primary analysis for prospective cohort study

Study variables

Domain	Variable	Variable type	Time point with respect to SRCXR in yrs (- indicates yrs prior to SRCXR)	Measure of data Type of data for SPSS
	ID study number	1-10000	0	Nominal String
Demographic	Age (5 yr age bands 50-80, then > 80)	Ordinal categorical (5 yrs age bands 50-80, then > 80) 2 = 50>= - <= 55 3 = 56>= - <=60 4 = 61>= - <=65 5 = 66>= - <=70 6 = 71>= - <=75 7 = 76>= - <=80 8 = >=81	0	Ordinal Numeric
	Gender	Categorical Male = 1 Female = 0	0	Nominal Numeric
	Smoking status	Categorical (never, ex-smoker, smoker unknown 0 = Unknown 1 = Never 2 = Ex-smoker 3 = Current smoker	0	Nominal Numeric
Clinical data	Symptoms	Categorical (present/absent of 6 symptoms) Present = 1 Absent = 0	0	Nominal Numeric
	Length of symptom	Raw data as per original data entry sheets		Ordinal Numeric
	Length of symptoms	For all symptoms excepted haemoptysis 1 = 0-3 months 2 = 3-6 months 3 = 6-9 months 4 = 9-12 months	0	Ordinal Numeric

		5 = >12months 6 = Symptom absent 7 = Symptom present unknown time For Haemoptysis 1 = 1-7 days 2 = 8-14 days 3 = 15-21 days 4 = 22-28 days 5 = >28 days 6 = Symptom absent 7 = Symptom present but unknown time		
	Thrombocytosis	Categorical (present/absent/missing) 0 = Not available 1 = Not thrombocytosis 2 = Thrombocytosis	- 1, -2	Nominal Numeric
	Date of SRCXR	Numerical	0	Scale Numeric
	Code of X-ray	Categorical 1. Urgent referral suspected cancer 2. Non urgent follow up required 3. Abnormal no follow up required 4. Normal	0	Ordinal Numeric
	Lung cancer	Categorical (yes, no Yes = 1 No = 0	1, 2	Nominal Numeric
	Lung cancer diagnosis duration category from SRCXR to lung cancer diagnosis	a. 1 = 1 to 90 days b. 2 = 91 to 180 days c. 3 = 181 to 270 days d. 4 = 271 to 365 days e. 5 = 366 to 720 days f. 8 = 721 to 20000 days g. 0 no lung cancer diagnosis	1, 2	Ordinal Numeric
	Cancer within 1 year of SRCXR	0 = No cancer within 1 year 1 = Cancer within 1 year of SRCXR	1	Nominal Numeric
	Cancer 2 years (if we decide to use it)	0 = No cancer within 1-2 years	1-2	Nominal Numeric

		1 = Cancer within 1-2 years		
	Cancer at all	0 = No cancer diagnosed 1 = Cancer diagnosed with study time frame	Length of study	Nominal Numeric
	Duration following SRCXR that lung cancer diagnosed	Discrete (number of days)	N/A	Scale Numeric
	Histology	Adenocarcinoma Squamous NSCLC Small cell lung cancer Other Unknown	N/A	Nominal Numeric
	Index of multiple deprivation	1-10	N/A	Ordinal Numeric

Data Analysis

Analysis will begin with basic descriptive statistics. Simple counts including demographics, cancer stage and frequency of symptoms will be determined and presented as histograms for continuous measures, and pie/bar charts for proportions/counts with mean, median and interquartile range determined as appropriate. For variables that contain ordinal data including age bands, symptom duration and duration from chest x-ray to lung cancer diagnosis ('lung cancer duration category' in above table) we will also determine the means and standard deviations for grouped data as appropriate.

Primary Objective 1: To estimate the risk of being diagnosed with lung cancer within one year and two years following a negative chest x-ray result in patients self-referring with relevant symptoms

Unadjusted 1-year and 2-year cancer incidences following a negative chest x-ray will be derived as the percentage of patients with a negative chest x-ray who received a lung cancer diagnosis within each timescale, with 95% confidence intervals (CIs). Separate logistic regressions predicting lung cancer diagnosis within 1 year and 2 years following a negative chest x-ray will provide incidence estimates adjusted for patients' age, gender, and smoking status.

For nominal variables and ordinal variables in which there may be a threshold effect, we will derive indicator variables (i.e. binary variables for each level of the variable) and enter these into models, excluding one indicator to be the reference (which we will specify). This only applies for inferential analyses.

Since having undergone testing with a full blood count will itself represent selection of a higher risk group, caution will be required around interpretation of thrombocytosis. To allow

for this patients without a platelet count will also be compared to those with a normal platelet count.

Primary Objective 2. To estimate the risk of lung cancer associated with specific symptoms/symptom combinations in people who have had a negative chest x-ray result.

For patients with a negative chest x-ray, the percentage of patients with each symptom/symptom combination who were diagnosed with lung cancer within 1 year and 2 years will provide unadjusted estimates of the positive predictive value of that symptom/combination. Estimates adjusted for patient characteristics as above will be obtained using the marginal distributions of logistic regressions for each outcome, with separate models for each symptom/combination as a predictor.

A risk assessment table will be constructed, for both patients who had a positive and negative SRCXR as follows, including 95% confidence intervals:

Cough	Haemoptysis	Breathless	Chest pain	Weight loss	Change in voice	PPV
						As single symptom
						Haemoptysis
						Breathless
						Chest Pain
						Weight loss
						Change Voice
						Thrombocytosis 1 yr
						Thrombocytosis 2 yr

Secondary Objective 1: To determine the sensitivity, specificity, PPV and NPV of chest x-ray in those over >50 for lung cancer

The sensitivity, specificity, positive and negative predictive values of chest x-ray for lung cancer (diagnosed within 1 and 2 years) will be determined through the construction of 2x2

tables. Sensitivity will be calculated by dividing the number of cases diagnosed with lung cancer by the number of SRCXRs which were positive. The specificity will be calculated by dividing the number of cases which did not have lung cancer by the number of SRCXRs which were negative. The positive predictive value of chest x-ray for lung cancer (1 and 2 years) will be determined by calculating the proportion of patients with a positive chest x-ray who were diagnosed with lung cancer, and the negative predictive value will be calculated as the proportion of patients with a negative chest x-ray who were not diagnosed with lung cancer.

Secondary Objective 2: To determine whether the symptoms associated with lung cancer are different in those who had a positive chest x-ray result compared to those who had a negative chest x-ray result

For each symptom/combination, we will construct a logistic regression model predicting lung cancer diagnosis with that symptom/combination and chest x-ray result as the predictors, and including an interaction between the two. This interaction will estimate the relative association of presence of the symptom/combination with lung cancer diagnosis between patients with a positive chest x-ray and those with a negative x-ray.

Appendix 9: Patients who received more than one self-request chest x-ray

Patient records for those who had more than one chest x-ray were included in the study as long as they had not had a chest x-ray within three months. The numbers of subsequent chest x-rays which occurred in the study population are outlined below.

Number of chest x-rays	Number of Patients
2	662
3	86
4	19
5	3
6	1

Out of these 771 patients, 20 were had a diagnosis of lung cancer within 1 year and 11 by two years.

Appendix 10: Analysis plan for 'associations between general practice characteristics with rate of investigation using chest x-ray: an observational study'

09/11/20

Objective

To examine the associations between characteristics of general practices and their populations and the rate of investigation with chest x-ray

Data

Data on numbers of chest x-rays per general practice will be obtained for 2018 from the diagnostic imaging dataset (DID). Due to data suppression rules, counts of chest x-rays are rounded to the nearest five, with counts of three or less indicated separately. NHS digital estimate that approximately 2% of chest x-rays are not associated with a patient NHS number, therefore it is not possible to obtain a precise count of individual patients who had chest x-rays.

For practices with counts of less than three we will substitute '2', on the assumption that it seems more likely that practices will have performed two chest x-rays rather than one, since it is a common type of examination. Only chest x-rays requested by GPs were included. No data is available on the indication for the chest x-ray or the result of the chest x-ray.

Data on general practice populations will be obtained for 2018 from Public Health England (PHE) practice profiles (https://fingertips.phe.org.uk/profile/general-practice). PHE uses NHS General and Personal Medical Services Dataset (GPMS) and the Quality Outcomes Framework (QOF) register in addition to other sources to maintain its GP practice profiles. Practices with list sizes of < 1,000 will be excluded as data for these practices is not made available on practice profiles.

Data on general practice staffing will be obtained from https://digital.nhs.uk/data-and-information/publications/statistical/general-and-personal-medical-services)

Analysis

The following population variables will be included in analyses:

- % of practice population who are male
- % of practice population who are aged > 65
- Index of multiple deprivation (2015) quintile for practice
- % of practice population who are smokers
- % of practice population who are on QOF registers for COPD and heart failure
- Population ethnicity estimate (% of practice patients who are white, mixed ethnic group, Asian, black or other ethnicity). These were not directly measured but were population weighted averages derived from 2011 census and applied to the practice populations in 2015.

Index of multiple deprivation quintiles will be allocated based on the IMD scores of all the practices (i.e. calculated prior to excluding practices with < 1000 patients).

The following practices variables will be included in analyses:

- Number of patients per full time equivalent (FTE) GP
- % of GPs who are male
- % of GPs who are UK qualified
- Mean GP age
- Practice list size
- Singlehanded practice (yes/no).
- GP training practice (yes/no). Training practices are defined as those which host GP trainees.
- Practice rurality binary category (rural or urban)(2).
- % of patients who gave the most positive response to questions in the General Practice survey relating to access, continuity and communication

Singlehanded practices are defined as those for which 'all Qualified Permanent GPs (excludes Registrars & Locums) headcount' ≤ 1

GP age is recorded in age categories (total GP headcount < age 30, then 5 year age bands to age 69, then age>70. The mid point in each age band will be substituted for each category (e.g. 32.5 for age 30-34), 27.5 will be substituted for age <30 and 72.5 for age >70.

Patient ratings of satisfaction and access will be obtained from the General Practice patient survey for 2018. We will include the following question items:

- question 2 helpfulness of receptionist
- question 10 ability to see preferred doctor (continuity)
- question 17 ability to book appointment
- question 26 health care professional communication skills.

For each questionnaire item we will include the % of patients who answered the question and gave the highest rating (e.g. 'very good' or 'all the time'). These scores will be adjusted for patient sex, age, ethnicity, deprivation and the presence of a long term condition.

Analysis will be modelled on a similar study which examined investigations for gastrointestinal cancers(4, 6). Crude chest x-ray rates will be determined for each practice for the period 2018-19. Practices for which data is not available from Public Health England's practice profiles or for which a count of chest x-rays is not available from Diagnostic Imaging Dataset will be omitted. The number of exclusions will be reported.

To determine the relative importance of the practice population compared with practice characteristics, we will firstly compare the between-practice variance in chest x-ray rates (total number of individuals who had chest x-rays) explained by 2 broad factors: 1) population characteristics, and 2) practice characteristics. This will be done using a mixed-effects Poisson regression model, including a random effect for general practice. An offset variable will be included which will be the log of the general practice size, with the regression co-efficient constrained to 1. This model will capture the overall underlying variation between practices after removing the role of chance due to small numbers (7).

We will then run three further versions of the model, adding: 1) the practice population variables examined; 2) practice characteristics variables, and (3) both groups of variables combined. We will determine the median incidence rate ratio (MIRR)(8) for each version of the model and we will determine the proportion by which the MIRR is reduced in each version

of the model compared to the model with no population or practice characteristics to provide an estimate of the proportion of the overall between-practice variance in rates of chest x-ray that is explained by either set of characteristics. We will extract adjusted estimates of association from a model which includes all exposure variables.

Because continuous exposure variables have different distributions across practices, and to facilitate comparisons of their effect sizes, we will standardized their practice values by subtracting the mean value across all practices from actual value then dividing by 1.35 standard deviations. One unit difference in these standardized scores corresponds to a change between the 25th and 75th centile of normally distributed continuous variables. When using these standardised scores in regression, for either rate or proportion indicators, the resulting rate or odds ratios correspond to the change (in the rate or the odds) resulting from moving from the 25th to the 75th centile of the exposure variable (practice team or practice population characteristic) of interest, if it is normally distributed.
We will use an effect size cut-off of rate ratio values equal or greater to a 4% difference from parity (i.e. 0.96 or smaller or 1.04 or greater) and with $P < 0.01$ (4).

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