EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Sequential screening for lung cancer in a high-risk group: randomised controlled trial

Stephen G. Spiro, Pallav L. Shah, Robert C. Rintoul, Jeremy George, Samuel Janes, Matthew Callister, Marco Novelli, Penny Shaw, Gabrijela Kocjan, Chris Griffiths, Mary Falzon, Richard Booton, Nicholas Magee, Michael Peake, Paul Dhillon, Kishore Sridharan, Andrew G. Nicholson, Simon Padley, Magali N. Taylor, Asia Ahmed, Jack Allen, Yenting Ngai, Nyasha Chinyanganya, Victoria Ashford-Turner, Sarah Lewis, Dahmane Oukrif, Pamela Rabbitts, Nicholas Counsell, Allan Hackshaw

Please cite this article as: Spiro SG, Shah PL, Rintoul RC, *et al*. Sequential screening for lung cancer in a high-risk group: randomised controlled trial. *Eur Respir J* 2019; in press (https://doi.org/10.1183/13993003.00581-2019).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Copyright ©ERS 2019

Sequential screening for lung cancer in a high-risk group: randomised controlled trial

LungSEARCH: A randomised controlled trial of Surveillance using sputum and imaging for the EARly detection of lung Cancer in a High-risk group

Stephen G Spiro,[1] Pallav L. Shah,[2] Robert C Rintoul,[3] Jeremy George,[4] Samuel Janes,[4] Matthew Callister,[5] Marco Novelli,[1] Penny Shaw,[1] Gabrijela Kocjan,[1] Chris Griffiths,[6] Mary Falzon,[1] Richard Booton,[7] Nicholas Magee,[8] Michael Peake,[9] Paul Dhillon,[10] Kishore Sridharan,[11] Andrew G Nicholson,[12] Simon Padley,[2] Magali N. Taylor,[1] Asia Ahmed,[1] Jack Allen,[13] Yenting Ngai,[13] Nyasha Chinyanganya,[13] Victoria Ashford-Turner,[5] Sarah Lewis,[14] Dahmane Oukrif,[1] Pamela Rabbitts,[5] Nicholas Counsell,[13] Allan Hackshaw[13]

Lead investigator: Stephen Spiro

Correspondence:
Allan Hackshaw
a.hackshaw@ucl.ac.uk
Cancer Research UK & UCL Cancer Trials Centre
90 Tottenham Court Road
London W1T 4TJ
UK

1. University College Hospital, London
2. Royal Brompton Hospital, Chelsea & Westminster Hospital and Imperial College, London
3. Royal Papworth Hospital, and University of Cambridge
4. UCL Respiratory, Department of Medicine, University College London
5. University of Leeds
6. St Bartholomew's Hospital, London
7. Manchester University NHS Trust & University of Manchester
8. Belfast City Hospital
9. University of Leicester; University College London Hospitals
10. University Hospital Coventry
11. Sunderland Royal Hospital
12. Royal Brompton Hospital and Harefield NHS Foundation Trust and National Heart and Lung Institute
13. Cancer Research UK & UCL Cancer Trials Centre, London
14. Royal Papworth Hospital

Funding: LungSEARCH was funded by Cancer Research UK (C5784/A17168)

Trial registration number ISRCTN 80745975

ABSTRACT

Background

Low-dose CT (LDCT) screening detects early stage lung cancer and reduces mortality. We proposed a sequential approach targeted to a high-risk group as a potentially efficient screening strategy.

Methods

LungSEARCH was a national multicentre randomised trial. Current/former smokers with mild/moderate COPD were allocated (1:1) to have 5 years surveillance or not. Screened participants provided annual sputum samples for cytology and cytometry, and if abnormal were offered annual LDCT and autofluorescence bronchoscopy (AFB). Those with normal sputum provided annual samples. Primary endpoint was the percentage of lung cancers diagnosed at stage I/II (non-small cell) or limited disease (small cell).

Results

1568 individuals were randomised 2007-2011, from 10 UK centres. 85.2% of those screened provided an adequate baseline sputum sample. There were 42 lung cancers among 785 screened and 36 among 783 controls. 54.8% (23/42) screened versus 45.2% (14/31) controls with known staging were diagnosed with early stage disease (one-sided p=0.24). Relative risk 1.21 (95%CI 0.75-1.95) or 0.82 (95%CI 0.52-1.31) for early stage or advanced cancers respectively. Overall sensitivity for sputum (in those randomised to surveillance) was low (40.5%) and cumulative false-positive rate (FPR) 32.8%. 55% of cancers had normal sputum results throughout. Among sputum-positive individuals who had AFB, sensitivity was 45.5% and cumulative FPR 39.5%; the corresponding measures for those who had LDCT were 100% and 16.1%.

Conclusions

Our sequential strategy, using sputum cytology/cytometry to select high-risk individuals for AFB and LDCT, did not lead to a clear stage shift, and did not improve the efficiency of lung cancer screening.

Introduction

Lung cancer is associated with poor survival because most cases are diagnosed at a late stage. However, early detection with intended curative treatments can have an 80% one-year survival rate for stage I disease.[1]

During the 2000s, several randomised trials were developed to evaluate low dose CT (LDCT).[2] Expected major issues with LDCT screening included affordability and high false-positive rates (which can be reduced through improved management of pulmonary nodules).[3] Furthermore, LDCT might miss early squamous cell tumours located in the central airways.[4]

Two major LDCT trials (US National Lung Screening Trial [NLST] and the NELSON study) now show a clear reduction in lung cancer mortality among current/former smokers who had annual LDCT compared to either chest radiograph or no screening.[5,6] LDCT screening is recommended in the US,[7] and suggested for Europe.[8] However, uptake in the US is low (<5% of those eligible).[9,10] Our LungSEARCH study was developed in 2006, long before those two trials were published. We proposed a different strategy to make screening more efficient. Instead of offering a single screening test, we created a novel approach of sequential screening (using sputum and imaging), and in a particularly high-risk group, i.e. current/former smokers with chronic obstructive pulmonary disease (COPD), based on promising evidence for the component tests.

COPD is correlated with lung cancer risk, and is an independent risk factor to smoking and other characteristics.[11-12] Decreasing lung function (using GOLD criteria) is associated with increasingly worse survival.[13-14] Therefore, targeted lung cancer screening among people with COPD is appealing.[11,15-17]

Sputum cytology is a non-invasive and non-radiological test for lung disease, especially central airway tumours. Sample procurement can be done at home without specialist equipment. Many smokers (particularly those with COPD) produce more sputum, containing exfoliated cells from the bronchial tree. There is an established association

between having abnormal sputum cytology and lung cancer,[18-19] although randomised trials of cytology failed to reduce lung cancer mortality.[20] However, modern cytology methods have better sensitivity. Another sputum test involves computer assisted image analysis (automated image cytometry), which quantitatively analyses the nuclear structure and DNA content of individual cells, distinguishing normal from suspicious cells.[21-23] In a large study of smokers, 80% of lung cancers with sputum samples had abnormal cytometry, compared to only 4% who had abnormal cytology.[21] We hypothesized that the high performance sensitivities expected using modern cytology/cytometry would miss few cancers as a first screening test.

Autofluorescence bronchoscopy (AFB) is an optical imaging technique which compares fluorescence properties between normal and malignant/pre-malignant bronchial mucosa.[24-26] AFB has a sensitivity for early stage lung cancer of 44-82% compared with 9-58% using conventional white light bronchoscopy.[26] The sensitivity for detecting abnormal lesions could be twice greater using AFB with white light than white light alone.[27] In a prior study of individuals with pre-invasive lesions, 73% had ≥1 high-grade lesion, and 1 in 6 of these lesions progressed to invasive carcinoma.[28,29]

LungSEARCH evaluated sequential testing for detecting lung cancer in a high-risk group, in which a cheap first screen is used to select who is offered LDCT and AFB. To date, it is the only randomised lung cancer screening study to triage participants.

Methods

Design and participants

LungSEARCH was a national multi-centre randomised trial. The objective was to examine whether annual surveillance of individuals at high-risk of lung cancer (current/ex-smokers with COPD) can lead to a shift in cancer stage at diagnosis.

Participants were identified primarily from general practice. A research nurse visited each practice to perform an electronic search of their COPD register, and those potentially eligible were invited by telephone to attend for baseline assessments. We also approached participants within outpatient COPD or pulmonary rehabilitation hospital clinics in which the trial investigators worked.

Baseline COPD (by spirometry) was classified according to GOLD criteria as mild (FEV1/FVC <70%; FEV1≥80% predicted) or moderate (FEV1/FVC <70%; FEV1 50-80% predicted).[30,31] Those with mild-moderate COPD were eligible for the trial if they currently smoked, or were former smokers who had quit within 8 years (agreed by the investigators to still have a high risk of lung cancer), and both groups had ≥20 pack-years and/or have smoked for ≥20 years (thresholds often used in studies at the time); no history of malignant disease during the previous 5 years; and without serious co-morbidities. The trial had multi-centre ethics approval and participants gave written informed consent. Trial number:ISRCTN 80745975.

Randomisation

Participants were randomised (1:1) to have annual screening/surveillance or not (controls). Research nurses telephoned the Cancer Trials Centre, where the random allocation (minimisation) was performed by computer, stratified by location,10-year age bands, sex, smoking status (former or current), and mild or moderate COPD.

Procedures

Individuals in the control arm had no trial-specific procedures, but to encourage study continuation they were offered an exit chest radiography 5 years post-randomisation (or

sooner if they withdrew earlier) if they had not developed lung cancer. This was also offered to the screened group.

Individuals in the screened group had sputum cytology and cytometry as initial tests, and only those with abnormal findings were offered LDCT and AFB, expecting that these in combination would be better than either alone at finding cancer in the central (by AFB) and peripheral (by LDCT) airways (Appendix Figure 1). Appendix Texts 1-3 describes the three component tests. Screened individuals posted sputum samples to the central laboratory for assessment, annually. Those with normal cytology/cytometry provided sputum samples the following year. Unless participants formally withdrew from the trial, they were asked to provide sputum annually even if they had not done so previously.

Specimens obtained via AFB were categorized as positive/abnormal if the cells exhibited squamous metaplasia, mild to severe dysplasia, carcinoma *in situ* or carcinoma. LDCT (target radiation dose <2mSv) was conducted without contrast. A positive/abnormal LDCT (nodule size ≥9mm) could initiate cancer investigations according to local practice. People with both normal AFB and LDCT continued to have these tests annually. Individuals with abnormal AFB or LDCT, not indicative of invasive cancer, could be seen 4-6 months later, depending on nodule size. Neither group provided further sputum samples.

All participants were flagged with established cancer registries (Health & Social Care Information Centre in England, and the Northern Ireland Cancer Registry); notifications received until April 2018. Research nurses also periodically checked patient records for cancer diagnoses. These two sources provided the cancer notifications; stage and histology at diagnosis were then manually retrieved from medical records.

Outcomes

The primary outcome was the proportion of lung cancers diagnosed at an early stage, an endpoint used previously:[32,33] stage I/II for non-small cell lung cancer, or limited disease for small cell lung cancer. For completeness, we also examined the proportion with advanced lung cancer (post hoc), which might be less influenced by over-diagnosis. Other endpoints included: uptake of sputum sampling, AFB and LDCT;

proportion of participants in the surveillance arm with abnormal sputum cytology and/or cytometry; number of failed/inadequate sputum samples; and prevalence of pre-invasive disease among participants with abnormal cytometry/cytology.

The proportion of people with lung cancer who were diagnosed at an early (or advanced) stage was compared between the trial arms (relative risk), and also rate ratio using person-years. Additional analyses were performed to check consistency in the findings. Estimates of screening performance for each test separately were: (i) sensitivity (proportion of all lung cancers with positive test results) and (ii) false-positive rate (FPR: proportion of all those without lung cancer with positive test results).

Statistical methods

15% of controls were expected to be diagnosed at an early stage.[32] From prior LDCT studies and our pilot study of pre-invasive disease, 80% of cancers were stage I/II,[29] so we conservatively used 50%. To detect a difference of 15 vs. 50% required a target sample size of at least 37 lung cancers per arm (95% power, and 5% one-sided significance test pre-specified for this preliminary study). The expected total proportion of prevalent and incident lung cancers was ~6%[9] so to obtain 74 cancers required about 1700 people.

Results

1568 participants (785 screened, 783 controls) were recruited from 10 UK centres between August 2007 and March 2011 (Figure 1, Appendix Table 1). Baseline characteristics were balanced (Table 1).

Seven centres routinely collected screening logs of people approached: 38.7% of all those contacted by telephone after the initial search accepted the invitation to attend the pre-trial assessment, of which 42.4% were randomised (Appendix Table 2). The initial uptake (38.7%) is high compared to LDCT screening trials, and probably due to our focus on COPD patients who might be more aware of smoking-related risks and their chronic symptoms influenced their decision to enroll, compared to a more general population. Older people were more likely to decline to participate in the trial (odds ratio

1.92 for ≥70 versus <50 years, p<0.0001). There was no association with gender, but there were geographical differences (Appendix Table 3).

Provision of sputum samples

In the first year (baseline), 89.8% provided sputum samples, but 36 were inadequate for assessment (so 85.2% provided an evaluable sample). Of those with adequate samples, 19.0% were abnormal for either cytology or cytometry, and the rate was lower in subsequent years (Table 2). The percentage not providing an adequate sputum sample increased from 14.8% at baseline up to 46.1% by year 5.

33.2% of all individuals in the screened arm had an abnormal sputum result at any time, of which 22.5% had abnormal cytology, and 12.6% had abnormal cytometry (1.9% [15/785] had both abnormal cytology and cytometry, 20.6% [162/785] had abnormal cytology only, and 10.7% [84/785] had abnormal cytometry only). 82.4% (14/17) of the sputum-positive cancers were detected at an early stage compared to 38.1% (8/21) of sputum-negative cancers (p=0.01). Cytology which used morphological criteria alone, identified more cancers than image cytometry (12 vs. 5), among those with abnormal sputum, so they appeared to be complementary. No cancer had both abnormal cytology and cytometry. There was no discernable association between type of sputum test and histology, particularly with having only few cases.

Primary endpoint

78 lung cancers were identified (36 and 42 in the control and screened groups respectively); Kaplan-Meier plot in Appendix Figure 2. The median follow-up was 5 years, matching the planned duration in the protocol for each participant.

Table 3 shows histology and cancer staging. Overall, 54.8% screened versus 45.2% controls, with known staging, were diagnosed at an early stage (similar to 59.4% versus 48.1% for non-small cell lung cancer alone). Table 4 compares stage at diagnosis between the trial arms. The relative risk for early stage cancer detection was 1.21 (95% CI 0.75-1.95, one-sided exact p=0.24); or 0.82 (95%CI 0.52-1.31) for advanced cancers. Hence there was no clear stage shift. In the sensitivity analyses, the rate ratio was a secondary analysis (not pre-specified in the trial protocol), and although the estimate for early stage disease made screening appear favorable (1.83, 95%CI 0.94-

3.54), there was no corresponding reduction in advanced cancers (1.24, 95%CI 0.65-2.39).

Screening performance

Table 5 summarizes the findings of all three tests among the lung cancers in the screened group: 44.7% had an abnormal sputum sample, but 55.3% (21 cases) had normal results for all samples.

Figure 2 summarizes sensitivity and FPR for all three tests, estimated only among individuals who actually had the tests (labelled 'direct'), and among all 785 randomised to surveillance (labelled 'overall'); further description in Appendix Text 4. The measures for LDCT and AFB can only be interpreted in the context of being second-stage tests, and do not represent performance for population screening where everyone has the test(s).

In the screened group, the overall sensitivity for sputum was 40.5% and FPR 32.8%. When examining only those who had sputum results, the direct sensitivity for cytology/cytometry was 44.7%, and corresponding FPR 38.7% (Figure 2). Hence, sputum testing did not detect many cases. The direct FPR at baseline only was 18.7%, and lower in the subsequent year 13.2%. Sputum testing had insufficient screening performance.

188 individuals had an AFB at any time during the trial (an additional 73 declined or did not attend; uptake 72.0%). Only 11 sputum-positive cancer cases had AFB, and the direct sensitivity was 45.5%, with high FPR 39.5% (Figure 2). Among participants with abnormal sputum, 38% had pre-invasive disease (72/188 mild to severe dysplasia or metaplasia); only 3 of these (2 moderate dysplasia and 1 squamous metaplasia), later developed lung cancer.

239 individuals had a LDCT at any time during the trial (an additional 22 declined or did not attend; uptake 91.6%). Sixteen sputum-positive cancer cases had LDCT, and the direct sensitivity (nodule size ≥9mm) was 100%, with FPR 16.1% (Figure 2).

Other cancers, mortality and smoking status

Appendix Table 4 summarizes the end of trial status, including the number who had an exit chest radiography (430 screened and 486 controls, so unlikely to have biased the cancers found). Other cancer types were balanced between the two groups. Lung cancer mortality (16 screened vs. 21 controls, hazard ratio 0.86, p=0.65), and all-cause mortality (hazard ratio 0.87, p=0.39) were similar; Appendix Figure 3. Among those who were current smokers at baseline (with known smoking status at 5 years), 15.0% controls and 17.7% screened individuals had stopped completely during the trial.

Adverse events

In the surveillance group, one person had a COPD exacerbation possibly linked to AFB, and another committed suicide unrelated to study participation.

Discussion

We examined a sequential approach to only offer LDCT and AFB as second screening tests among particularly high-risk individuals with abnormal sputum cytology/cytometry. Had we found a substantial stage shift a larger randomised trial of lung cancer mortality would overcome lead-time bias and over-diagnosis. LungSEARCH complements LDCT trials,[2,6] including the only other randomised trial of lung cancer screening conducted in the UK (UKLS).[33]

Although LungSEARCH preceded NLST and NELSON,[5,6] the concept that an effective, cheap and easy initial test (sputum) could be considered for a wider group of smokers than is currently eligible for LDCT remains valid. This is because current criteria excludes many high-risk people. Applying USPSTF criteria,[7] 25% of the LungSEARCH participants would be ineligible for LDCT. We hoped, therefore, that our sequential approach could find many cancers without offering many more LDCT scans.

We exceeded the target of 50% of lung cancers diagnosed at an early stage using our surveillance strategy (observed 55%), but the lack of effect was driven by the high percentage of unscreened participants diagnosed at early stage (45% observed instead of 15% expected when LungSEARCH was designed in 2006). Prominent health campaigns encourage people with persistent cough to seek medical attention sooner,

explaining why more lung cancers are now diagnosed earlier, as seen in UK audit data.[34] Although we reached the target sample size and hence had power for the expected primary outcome (50 vs 15% early stage cancers), the observed small stage shift of 55 versus 45% is not worthwhile clinically.

In LungSEARCH, 90% of those who attempted a sputum sample did so successfully. However, an increasing number of people did not provide sputum over time, and 4 lung cancers were among participants who provided no samples. Hence, 60% of all lung cancers in the screened group did not have the opportunity for earlier detection by LDCT. Furthermore, of the cancers with sputum samples, only 45% had abnormal results (referred for LDCT and AFB). This is lower than the expected 80% from a study that had more males than LungSEARCH and 59% had moderate/severe cough, though in that study the sensitivity of sputum decreased to 21% for stage I adenocarcinoma.[21] It is unclear why sputum was not effective. Unlike cervical cancer screening which involves active removal of cells in the cervix, detecting lung cancer in sputum depends on cells naturally shed into the bronchi, which is influenced by tumour location and histology. It could be that malignant cells in the early stages of lung cancer are still anchored to the basement membrane and each other, so that not enough travel into the lumen. Although sputum testing has the appeal of being conducted at home, avoiding travel to screening clinics which is required by LDCT (especially from rural areas), the lower number of individuals who provided samples from year 2 plus the fact that several samples are inadequate together makes sputum testing less useful than LDCT in which a result could be obtained in almost all cases who are scanned.

AFB uptake was not high (72%), because several participants informed us that they found AFB off-putting or uncomfortable.[35] Systematic reviews of AFB show heterogeneous study designs and variable sensitivities (67-100%),[37-39] Whilst AFB has value for people presenting with symptomatic lung problems, LungSEARCH suggests a limited role in screening. Improvements in the optics in videobronchoscopes have reduced the need for the fluorescence mode, and the shift in the natural history of lung cancer from central to more peripheral tumours further limits the utility of AFB.

Very few reports have examined lung cancer screening in COPD. The NLST sub-study (ACRIN) indicated a shift towards early stage cancer among COPD participants who had LDCT compared to those who had chest radiography,[40] but no reduction in lung

cancer deaths.[41] The Danish Lung Cancer Screening Trial hinted that COPD participants with >35 pack-years might benefit from LDCT.[42] Whereas in a non-randomised matched cohort study of mild to moderate COPD, 80% of lung cancers in those who had LDCT were diagnosed at stage I versus 0% among those without LDCT; corresponding lung cancer deaths of 1 vs. 12 (p=0.002).[43]

Our trial had limitations. As in all cancer screening trials, participants cannot be blinded, hence the potential for bias (e.g. controls were aware of the trial objectives possibly making them more alert to symptoms and seeking medical advice sooner) which might contribute to the higher than expected proportion of early stage cancers. Similarly, participants who stopped having the screening tests earlier might lead to a lower percentage diagnosed with early stage cancer. We had no data on cancer treatments nor retrieved histological specimens for central pathology review, as these required additional local resources. Over-diagnosis bias is an established issue in studies examining stage shift. We found slightly more lung cancers in the screened group (42) than controls (36), and the different denominators (expected in screening studies) can influence the comparison of stage shift. Therefore, we allowed longer time for cancer notifications from the registries and to arrange the exit chest radiographs in the controls. Although we did not find a material difference in cancer stage in LungSEARCH, there is some evidence that people with COPD tend to develop more aggressive lung cancers,[44-45] and the NLST suggests that over-diagnosis from LDCT screening is only seen in people with normal lung function, not in COPD, though this should be confirmed in other studies.[40] Finally, we did not know whether some of the control group participants had LDCT during the trial, which might have reduced the effect of our screening policy, though we expect this to be very few because LDCT is not recommended routinely.

LDCT screening can be made more efficient using risk algorithms (including age and smoking intensity), where only those with a risk exceeding a specified cut-off are offered LDCT. Such models detect more lung cancers with fewer false-positives than current criteria.[7] Several risk calculators contain COPD as a factor,[46-48], and demonstration/pilot studies in the UK conclude that the Liverpool Lung Project risk model and/or the $PLCO_{2012}$ model should be used to identify high-risk population in screening programmes.[49-52] These recommendations are supported by LungSEARCH in which LDCT detected all lung cancers among sputum-positives

(though we cannot tell how well LDCT would have performed in the sputum-negative cases, and our trial did not include people without COPD).

In conclusion, our sequential screening strategy did not show a stage shift in cancer diagnosis. Our trial has implications for future research and practice. First, it provides evidence from a large randomised trial that it is difficult to find ways of targeting LDCT screening to make it more efficient (other than risk-based algorithms). LDCT should therefore be offered to all eligible individuals within planned screening programmes. Second, our study was based on particularly high-risk individuals (smokers with COPD) and many unscreened individuals (controls) were diagnosed at an early cancer stage, indicative of them seeking medical attention sooner, in line with UK audit data. This probably means that this group are more receptive to screening and early detection, such that the uptake of LDCT within organised programmes could be high among them. Third, LDCT detected all lung cancers among COPD patients in our trial who were sputum-positive, which is suggestive evidence that planned screening programmes should consider sufficient inclusion of COPD.

Contributors

The original study conception came from SGS, and developed with JG, PLS, RCR, MN, PS, GK, CG, MF, PR and AH. Clinical leads at each recruiting centre were PLS, RCR, JG, SJ, MC, RB, NM, MP, PD and KS. Central sputum testing was led by MN, GK and MF. Radiology oversight came from PS and SP. MT and AA performed the central radiology audit. Expertise in general practice was led by CG. Senior research nurses involved in recruitment and management were NC, VAT, AM and SL. NC did the statistical analyses with AH. Study co-ordination and data management were done by YN and JA. SGS had oversight of the study organisation. All authors were involved in commenting on the manuscript and have approved the submitted version. We also acknowledge Alison Mitchell, who was the research nurse in Cambridge/Papworth Hospital for several years. The lead author had full access to the data and final responsibility to submit for publication.

Declaration of interests

No author has any conflict of interest associated with this study.

Auto-florescence bronchoscopy (D-light) systems in some centres were kindly provided by Karl Storz Gmbh, Germany

Acknowledgments

We are indebted to all of the trial participants who kindly agreed to take part and be followed up. We also thank all of the supporting staff in radiology, pathology and data management at each of the recruiting sites. Also the independent data monitoring committee: Marc Lipman, Angshu Bhowmik and Stephen Duffy. Finally, we are grateful to all of the general practitioners who participated.

RCR was part funded by the NIHR Cambridge BRC and CRUK Cambridge Centre. SMJ is a Wellcome Trust Senior Fellow in Clinical Science (WT107963AIA). This work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centre's funding scheme (AH and SMJ).

Role of the funding source

Cancer Research UK (and its external expert review panel) reviewed and approved the trial and its design before funding the study, after which it was not involved in the conduct, analysis, or report writing.

References

1. Cancer survival in England: adult, stage at diagnosis and childhood – patients followed up to 2016. Cancer survival in England for specific cancer sites by age, sex and stage at diagnosis. Statistical Bulletin. Office for National Statistics. Public Health England 2017

2. Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, Byers T, Colditz GA, Gould MK, Jett JR, Sabichi AL, Smith-Bindman R, Wood DE, Qaseem A, Detterbeck FC. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA. 2012;307(22):2418-29.

3. van Klaveren RJ, Oudkerk M, Prokop M, Scholten ET, Nackaerts K, Vernhout R, van Iersel CA, van den Bergh KA, van 't Westeinde S, van der Aalst C, Thunnissen E, Xu DM, Wang Y, Zhao Y, Gietema HA, de Hoop BJ, Groen HJ, de Bock GH, van Ooijen P, Weenink C, Verschakelen J, Lammers JW, Timens W, Willebrand D, Vink A, Mali W, de Koning HJ. Management of lung nodules detected by volume CT scanning. N Engl J Med. 2009;361(23):2221-9

4. Bepler G, Carney DG, Djulbegovic B, Clark RA, Trockman M. A systematic review and lessons learned from early lung cancer detection trials using low-dose computed tomography of the chest. Cancer Control. 2003;10:306-314.

5. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, Gareen IF, Gatsonis C, Marcus PM, Sicks JD. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409

6. NELSON trial: presented at the International Association for the Study of Lung Cancer conference (IASLC) September 2018. https://wclc2018.iaslc.org/media/2018%20WCLC%20Press%20Program%20Press%20Release%20De%20Koning%209.25%20FINAL%20.pdf [This is the only publically available reference to the results; the journal paper is expected shortly]

7. US Preventive Services Task Force. https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/lung-cancer-screening

8. Kauczor HU, Bonomo L, Gaga M, Nackaerts K, Peled N, Prokop M, Remy-Jardin M, von Stackelberg O, Sculier JP; European Society of Radiology (ESR); European Respiratory Society (ERS). ESR/ERS white paper on lung cancer screening. Eur Respir J. 2015;46(1):28-39

9. Pham D, Bhandari S, Oechsli M, Pinkston CM, Kloecker GH, Brown JG. Lung cancer screening rates: Data from the lung cancer screening registry. J Clin Oncol 2018; 36 suppl; abstr 6504

10. Jemal A, Fedewa SA. Lung cancer screening with low-dose computed tomography in the United States—2010 to 2015. JAMA Oncol. 2017;3(9):1278-1281

11. Mannino DM, Aguayo SM, Petty TL, Redd SC. Low lung function and incident lung cancer in the United States: data From the First National Health and Nutrition Examination Survey follow-up. Arch Intern Med. 2003;163(12):1475-80

12. Huang R, Wei Y, Hung RJ, Liu G, Su L, Zhang R, Zong X, Zhang ZF, Morgenstern H, Brüske I, Heinrich J, Hong YC, Kim JH, Cote M, Wenzlaff A, Schwartz AG, Stucker I, Mclaughlin J, Marcus MW, Davies MP, Liloglou T, Field JK, Matsuo K, Barnett M, Thornquist M, Goodman G, Wang Y, Chen S, Yang P, Duell EJ, Andrew AS, Lazarus P, Muscat J, Woll P, Horsman J, Teare MD, Flugelman A, Rennert G, Zhang Y, Brenner H, Stegmaier C, van der Heijden EH, Aben K, Kiemeney L, Barros-Dios J, Pérez-Ríos M, Ruano-Ravina A, Caporaso NE, Bertazzi PA, Landi MT, Dai J, Hongbing Shen H, Fernandez-Tardon G, Rodriguez-Suarez M, Tardon A, Christiani DC.
Associated Links Among Smoking, Chronic Obstructive Pulmonary Disease, and Small Cell Lung Cancer: A Pooled Analysis in the International Lung Cancer Consortium. EBioMedicine. 2015;2(11):1677-85

13. Carr LL, Jacobson S, Lynch DA, Foreman MG, Flenaugh EL, Hersh CP, Sciurba FC, Wilson DO, Sieren JC, Mulhall P, Kim V, Kinsey CM, Bowler RP. Features of COPD as Predictors of Lung Cancer. Chest. 2018;153(6):1326-1335

14. Mattila T, Vasankari T, Kanervisto M, Laitinen T, Impivaara O, Rissanen H, Knekt P, Jousilahti P, Saarelainen S, Puukka P, Heliövaara M. Association between all-cause and cause-specific mortality and the GOLD stages 1-4: A 30-year follow-up among Finnish adults. Respir Med. 2015;109(8):1012-8

15. Sekine Y, Fujisawa T, Suzuki K, Tsutatani S, Kubota K, Ikegami H, Isobe Y, Nakamura M, Takiguchi Y, Tatsumi K. Detection of chronic obstructive pulmonary disease in community-based annual lung cancer screening: Chiba Chronic Obstructive Pulmonary Disease Lung Cancer Screening Study Group. Respirology. 2014;19(1):98-104

16. Young RP, Hopkins RJ. Diagnosing COPD and targeted lung cancer screening. Eur Respir J. 2012; 40(4):1063-4

17. Wilson DO, Weissfeld JL, Balkan A, Schragin JG, Fuhrman
CR, Fisher SN, Wilson J, Leader JK, Siegfried JM, Shapiro SD, Sciurba FC. Association of radiographic emphysema and airflow obstruction with lung cancer. Am J Respir Crit Care Med. 2008;178(7):738-44

18. Prindiville SA, Byers T, Hirsch FR, Franklin WA, Miller YE, Vu KO, Wolf HJ, Baro´n AE, Shroyer KR, Zeng C, Kennedy TC, and Bunn PA. Sputum Cytological Atypia as a Predictor of Incident Lung Cancer in a Cohort of Heavy Smokers with Airflow Obstruction. Cancer Epidemiology, Biomarkers & Prevention. 2003;12:987–993.

19. Tockman MS, Gupta PK, Myers JD, Frost JK, Baylin SB, Gold EB, Chase AM, Wilkinson PH, Mulshine JL. Sensitive and Specific Monoclonal-Antibody Recognition of Human-Lung Cancer Antigen on Preserved Sputum Cells - a New Approach to Early Lung-Cancer Detection. J Clin Oncol. 1988;6(11):1685-93.

20. Manser R, Lethaby A, Irving LB, Stone C, Byrnes G, Abramson MJ, Campbell D. Screening for lung cancer. Cochrane Database Syst Rev. 2013 Jun 21;(6):CD001991

21. Xing S, Khanavkar B, Nakhosteen JA, Atay Z, Jockel K-H, and Merek W. Predictive value of image cytometry for diagnosis of lung cancer in heavy smokers. Eur Respir J. 2005;25:956-963.

22. Li G, Guillaud M, LeRiche J, McWilliams A, Gazdar A, Lam S, MacAulay C. Automated sputum cytometry for detection of intraepithelial neoplasias in the lung. Anal Cell Pathol (Amst). 2012;35(3):187-201

23. Kemp RA, Reinders DM, Turic B. Detection of lung cancer by automated sputum cytometry. J Thorac Oncol. 2007;2(11):993-1000

24. Palcic B, Lam S, Hung J, MacAulay C. Detection and localization of early lung cancer by imaging techniques. Chest. 1991;99(3):742-3

25. Lam S, MacAulay C, Hung J, LeRiche J, Profio AE, Palcic B. Detection of dysplasia and carcinoma in situ with a lung imaging fluorescence endoscope device. J Thorac Cardiovasc Surg. 1993;105(6):1035-40.

26. Inage T, Nakajima T, Yoshino I, Yasufuku K. Early Lung Cancer Detection. Clin Chest Med. 2018;39(1):45-55

27. Lam S, MacAulay C, leRiche JC, Palcic B. Detection and localization of early lung cancer by fluorescence bronchoscopy. Cancer. 2000;89(11 Suppl):2468-73.

28. Banerjee AK, Rabbitts, Pamela H and George, PJ. Pre-invasive bronchial lesions: surveillance or intervention? Chest. 2005; 125:95S–96S.

29. George PJ, Banerjee AK, Read CA, O'Sullivan C, Falzon M Pezzella, Francesco, Nicholson AG, Shaw P, Laurent G, Rabbitts HP. Surveillance for the detection of early lung cancer in patients with bronchial dysplasia, Thorax, 2007; 62;43-50.

30. National Institutes of Health, National Heart, Lung and Blood Institute Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Workshop Report. Update 2003. www.goldcopd.org [accessed 2011 for the LungSEARCH protocol]

31. Sterk PJ. Let's not forget: the GOLD criteria for COPD are based on post-bronchodilator FEV1. Eur Respir J. 2004;23(4):497-8.])

32. Aberle DR, DeMello S, Berg CD, Black WC, Brewer B, Church TR, Clingan KL, Duan F, Fagerstrom RM, Gareen IF, Gatsonis CA, Gierada DS, Jain A, Jones GC, Mahon I, Marcus PM, Rathmell JM, Sicks J. National Lung Screening Trial Research Team. Results of the two incidence screenings in the National Lung Screening Trial. New Engl J Med. 2013;369(10):920-31

33. Field JK, Duffy SW, Baldwin DR, Brain KE, Devaraj A, Eisen T, Green BA, Holemans JA, Kavanagh T, Kerr KM, Ledson M, Lifford KJ, McRonald FE, Nair A, Page RD, Parmar MK, Rintoul RC, Screaton N, Wald NJ, Weller D, Whynes DK, Williamson

PR, Yadegarfar G, Hansell DM. The UK Lung Cancer Screening Trial: a pilot randomised controlled trial of low-dose computed tomography screening for the early detection of lung cancer. Health Technol Assess. 2016;20(40):1-146

34. National Lung Cancer Audit 2015. www.nlcaudit.co.uk

35. Bulzebruck H, Bopp R, Drings P, Bauer E, Krysa S, Probst G, van Kaick G, Muller KM, Vogt-Moykopf I. New aspects in the staging of lung cancer. Prospective validation of the International Union Against Cancer TNM classification. Cancer. 1992;70(5):1102-10.

36. Patel D, Akporobaro A, Chinyanganya N, Hackshaw A, Seale C, Spiro S, Griffiths C. Attitudes to participation in a lung cancer screening trial: a qualitative study. Thorax 2012; 67:5 418-425

37. Chen W, Gao X, Tian Q, Chen L. A comparison of autofluorescence bronchoscopy and white light bronchoscopy in detection oflung cancer and preneoplastic lesions: a meta-analysis. Lung Cancer. 2011;73(2):183-8

38. Sun J, Garfield DH, Lam B, Yan J, Gu A, Shen J, Han B. The value of autofluorescence bronchoscopy combined with white light bronchoscopy compared with white light alone in the diagnosis of intraepithelial neoplasia and invasive lung cancer: a meta-analysis. J Thorac Oncol. 2011;6(8):1336-44.

39. Thakur A, Gao L, Ren H, Yang T, Chen T, Chen M. Descriptive data on cancerous lung lesions detected by auto-fluorescence bronchoscope: A five-year study. Ann Thorac Med. 2012;7(1):21-5.

40. Young RP, Duan F, Chiles C, Hopkins RJ, Gamble GD, Greco EM, Gatsonis C, Aberle D. Airflow Limitation and Histology Shift in the National Lung Screening Trial. The NLST-ACRIN Cohort Substudy. Am J Respir Crit Care Med. 2015;192(9):1060-7

41. Young RP, Duan F, Greco E, Hopkins RJ, Chiles C, Gamble GD , Aberle D Lung Cancer-Specific Mortality Reduction With CT Screening: Outcomes According to Airflow Limitation in the ACRIN NLST Sub-Study (N=18,475). Am J Respir Crit Care Med 2016;193:A6166

42. Wille MM, Dirksen A, Ashraf H, Saghir Z, Bach KS, Brodersen J, Clementsen PF, Hansen H, Larsen KR, Mortensen J, Rasmussen JF, Seersholm N, Skov BG, Thomsen LH, Tønnesen P, Pedersen JH. Results of the Randomized Danish Lung Cancer Screening Trial with Focus on High-Risk Profiling. Am J Respir Crit Care Med. 2016;193(5):542-51

43. de-Torres JP, Casanova C, Marín JM, Zagaceta J, Alcaide AB, Seijo LM, Campo A, Carrizo S, Montes U, Cordoba-Lanus E, Baz-Dávila R, Aguirre-Jaime A, Celli BR, Zulueta JJ. Exploring the impact of screening with low-dose CT on lung cancer mortality in mild to moderate COPD patients: a pilot study. Respir Med. 2013;107(5):702-7

44. Wilson DO, Ryan A, Fuhrman C, Schuchert M, Shapiro S, Siegfried JM, Weissfeld J. Doubling times and CT screen–detected lung cancers in the Pittsburgh Lung Screening Study. Am J Respir Crit Care Med 2012;185:85–89.

45. Young RP, Hopkins RJ. Estimating overdiagnosis of lung cancer. Ann Intern Med 2013;158:635–636.

46. Tammemägi MC, Church TR, Hocking WG, Silvestri GA, Kvale PA, Riley TL, Commins J, Berg CD. Evaluation of the lung cancer risks at which to screen ever- and never-smokers: screening rules applied to the PLCO and NLST cohorts. PLoS Med. 2014;11(12):e1001764

47. Raji OY, Duffy SW, Agbaje OF, Baker SG, Christiani DC, Cassidy A, Field JK. Predictive accuracy of the Liverpool Lung Project risk model for stratifying patients for computed tomography screening for lung cancer: a case-control and cohort validation study. Ann Intern Med. 2012;157(4):242-50

48. Muller DC, Johansson M, Brennan P. Lung Cancer Risk Prediction Model Incorporating Lung Function: Development and Validation in the UK Biobank Prospective Cohort Study. J Clin Oncol. 2017;35(8):861-869

49. Duffy SW, Maroni R, Vulkan D, Shah Z, Timoney M, Jones L, Arvanitis R, Ledson M, Lukehirst L, Rutherford P, Clarke F, Gardner K, Smith SG, Quaife S, Marcus M, Hill S, Fideo D, Mason S, Field JK. Liverpool Healthy Lung Programme – Second year Evaluation Report. [serial online] 2018 [cited 12-01-2018]. https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.liverpoolccg.nhs.uk%2Fmedia%2F3245%2Ffinal-lhlp-2nd-year-report-10-july-2018-with-logos.pdf&data=02%7C01%7Cnicholas.counsell%40ucl.ac.uk%7C9b4d5d9275be44c984a908d6f0373dea%7C1faf88fea9984c5b93c9210a11d9a5c2%7C0%7C0%7C636960517381434374&sdata=%2FDgBto2ORtW%2BXtZdJi8zXowvOe1i5axzIjhoLs3xZ5s%3D&reserved=0

50. Crosbie PA, Balata H, Evison M, Atack M, Bayliss-Brideaux V, Colligan D, Duerden R, Eaglesfield J, Edwards T, Elton P, Foster J, Greaves M, Hayler G, Higgins C, Howells J, Irion K, Karunaratne D, Kelly J, King Z, Manson S, Mellor S, Miller D, Myerscough A, Newton T, O'Leary M, Pearson R, Pickford J, Sawyer R, Screaton NJ, Sharman A, Simmons M, Smith E, Taylor B, Taylor S, Walsham A, Watts A, Whittaker J, Yarnell L, Threlfall A, Barber PV, Tonge J, Booton R. Implementing lung cancer screening: baseline results from a community-based 'Lung Health Check' pilot in deprived areas of Manchester. Thorax. 2019;74(4):405-409

51. ISRCTNRegistry. The Yorkshire Lung Screening Trial- ISRCTN42704678. 2019. Available from: https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fdoi.org%2F10.1186%2FISRCTN42704678&data=02%7C01%7Cnicholas.counsell%40ucl.ac.uk%7C9b4d5d9275be44c984a908d6f0373dea%7C1faf88fea9984c5b93c9210a11d9a5c2%7C0%7C0%7C636960517381434374&sdata=5%2B6H7PJTbw6Cqi6wtAEMkZ5t9vlyH%2BMldNs2UGMiWP8%3D&reserved=0.

52. NHS England National Cancer Programme. Targeted Screening for Lung Cancer with Low Radiation Dose Computed Tomography; Standard Protocol prepared for the Targeted Lung Health Checks Programme. 2019 16/04/2019]. https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.england.nhs.uk%2Fwp-content%2Fuploads%2F2019%2F02%2Ftargeted-lung-health-checks-standard-protocol v1.pdf&data=02%7C01%7Cnicholas.counsell%40ucl.ac.uk%7C9b4d5d9275be44c984a908d6f0373dea%7C1faf88fea9984c5b93c9210a11d9a5c2%7C0%7C0%7C636960517381434374&sdata=7zOpZYjQg3IHIeGKiiGezFq9TT6L8boPFEU9q7fy5Dw%3D&reserved=0

Table 1. Baseline characteristics of the randomised individuals

	Control group N=783	Screened group N=785
Sex:		
Female	373 (48%)	377 (48%)
Male	410 (52%)	408 (52%)
Smoking status:		
Current	435 (56%)	439 (56%)
Former	348 (44%)	346 (44%)
COPD severity:		
Mild	195 (25%)	196 (25%)
Moderate	588 (75%)	588 (75%)
missing/unknown	*0*	*1*
Source of participants:		
General practice	622 (79%)	619 (79%)
Pulmonary rehabilitation program	95 (12%)	94 (12%)
Hospital outpatients	35 (4%)	42 (5%)
Lung function laboratory	31 (4%)	30 (4%)
	Mean	Mean
Age at randomisation (years)	63	63
Age when started smoking	16	16
Age when stopped smoking	61 (n=348)	62 (n=346)
Number of cigarettes smoked per day	24	24
Number of years of smoking	45	45
Pack years	53	54

Table 2. Sputum results in the screened group in each year

	Baseline	Year 2	Year 3	Year 4	Year 5
Cytology or cytometry result[1]	**N=785***	**N=639***	**N=560***	**N=516***	**N=447***
Normal	542 (81%)	398 (87%)	343 (94%)	300 (89%)	221 (92%)
Abnormal - low grade	111 (17%)	51 (11%)	18 (5%)	33 (10%)	17 (7%)
Abnormal - high grade	16 (2%)	6 (1%)	2 (1%)	4 (1%)	3 (1%)
Died or cancer diagnosed since last visit	N/A	19	22	24	32
No sputum result	116 (15%)#	184 (29%)#	197 (35%)#	179 (35%)#	206 (46%)#
Did not provide sample	68	131	155	157	195
Tried but unable to provide sample	12	10	3	8	5
Provided spontaneous sample[2]	33	43	38	14	6
Provided induced sample[2]	3	0	1	0	0
Cytology result (where available)	**N=604**	**N=400**	**N=301**	**N=285**	**N=198**
Normal	503 (83%)	358 (90%)	289 (96%)	269 (94%)	191 (96%)
Abnormal - low grade	86 (14%)	36 (9%)	11 (4%)	13 (5%)	5 (3%)
Abnormal - high grade	15 (2%)	6 (2%)	1 (<1%)	3 (1%)	2 (1%)
Cytometry result (where available)	**N=603**	**N=418**	**N=350**	**N=323**	**N=237**
Normal	570 (95%)	400 (96%)	342 (98%)	298 (92%)	221 (93%)
Abnormal - low grade	32 (5%)	18 (4%)	7 (2%)	22 (7%)	15 (6%)
Abnormal - high grade	1 (<1%)	0	1 (<1%)	3 (1%)	1 (<1%)

The percentages in brackets for normal or abnormal sputum are based on the total number who had a sputum result as the denominators.

* These are the total number of people expected to provide sputum samples in each year (i.e. excluding those who had an abnormal sputum result, died or were diagnosed with cancer who were no longer expected to provide sputum samples)

#These represent the percentage who did not provide a sputum sample, out of the total expected

1. In some cases only cytology or cytometry results were available (not both), and so the result classification was based on the known result if a repeat sputum sample was not done.
2. But sample was inadequate for cytology and cytometry assessment

Table 3. Histology and stage of the lung cancers

	Control group N=36	Screened group N=42
Small cell	5 (14%)	10 (24%)
Adenocarcinoma	8 (22%)	11 (26%)
Squamous	9 (25%)	14 (33%)
Large cell	0	1 (2%)
Other histology	9 (25%)	5 (12%)
Unknown	*5 (14%)*[2]	*1 (2%)*
Non-small cell lung cancer:	N=27[1]	N=32[1]
Stage I	11	16
Stage II	2	3
Stage III	6	4
Stage IV	7	9
Unknown	*1*	
Small cell lung cancer:	N=5	N=10
Limited disease	1	4
Extensive disease	4	6

1. Includes 1 patient in each trial group where histology was unknown but stage was available

2. Diagnosed at non-trial sites (unknown, or not set up for the trial so no access to medical records). These cancers were notified through registries, and we found staging for one of the 5 cases.

The exit chest radiography found 5 cancers in the screened group (these had no sputum samples or their sputum tests were normal throughout the trial: cancer stage was I [n=2], II [n=1], IV [n=1]) and limited disease [n=1]); and 6 cancers in the control group (stage was I [n=3], III [n=1], IV [n=1] and missing [n=1]).

Table 4. Comparison of stage at diagnosis among those with lung cancer (in total there were 42 and 36 lung cancers in the screened and control arms respectively)

	Primary outcome measure Early stage disease (I/II for non-small cell and limited disease for small cell cancer)		Advanced disease (III/IV for non-small cell and extensive disease for small cell cancer)	
	Screened	Controls	Screened	Controls
Main analysis *(cancer cases with known stage)*	54.8% (23/42) Relative risk 1.21 (95%CI 0.75-1.95, p=0.24)	45.2% (14/31)	45.2% (19/42) Relative risk 0.82 (95%CI 0.52-1.31, p=0.24)	54.8% (17/31)
Sensitivity analyses: All cancers included in the denominators	54.8% (23/42) Relative risk 1.41 (95%CI 0.86-2.30, p=0.09)	38.9% (14/36)	45.2% (19/42) Relative risk 0.96 (95%CI 0.59-1.55, p=0.50)	47.2% (17/36)
Excluding cancers found by the exit chest x-ray (5 screened; 6 controls)	51.3% (19/37) Relative risk 1.21 (95%CI 0.70-2.09, p=0.30)	42.3% (11/26)	48.9% (18/37) Relative risk 0.84 (95%CI 0.53-1.35, p=0.30)	57.8% (15/26)
Cancer incidence expressed as person years**	6.8 per 1000 Rate ratio 1.83 (95%CI 0.94-3.54, p=0.049)	3.7 per 1000	5.6 per 1000 Rate ratio 1.24 (95%CI 0.65-2.39, p=0.31)	4.5 per 1000
Cancer incidence expressed as person years, & excluding cancers found by the exit chest x-ray	5.7 per 1000 Rate ratio 1.92 (95%CI 0.91-4.03, p=0.049)	3.0 per 1000	5.4 per 1000 Rate ratio 1.33 (95%CI 0.67-2.64, p=0.24)	4.0 per 1000

*P-values are one-sided (specified in the protocol) because of interest only in finding more early stage cancers in the screened arm. LungSEARCH is not a definitive assessment of a screening policy, so it is analogous to phase II treatment trials which commonly use one-sided statistical tests.

Rate ratio, which uses person-years, might be less affected by overdiagnosis and unknown disease stage in the denominators
Relative risk or rate ratio of >1 for early stage indicates that screening was effective (more early stage disease found in the screened group).
Relative risk or rate ratio of <1 for advanced stage indicates that screening was effective (less advanced stage disease found in the screened group).

Table 5. Test findings among all 42 lung cancers in the screened group

Test results	
Sputum result	N=38
Abnormal	17 (80
Normal	21 (55%)
No sputum or both cytology/cytometry inadequate	4
Cytology result	
Abnormal	12 (32%)
Normal	26 (68%)
Cytometry result	
Abnormal	5 (13%)
Normal	33 (87%)
Worst AFB result:	N=11
Carcinoma	2 (18%)
Moderate dysplasia	2 (18%)
Squamous metaplasia	1 (9%)
No abnormality	6 (55%)
Sputum and LDCT results:	N=42
No sputum samples (hence no LDCT)	4 [2][1]
Sputum normal throughout study (hence no LDCT)	21 [3][1]
Sputum abnormal, LDCT detected cancer directly afterwards[2]	8
Sputum abnormal, LDCT detected cancer at a later follow-up[3]	7
Sputum abnormal, LDCT did not flag for cancer investigation[4]	1
Sputum abnormal, but no LDCT done	1

1. The numbers in square brackets are lung cancers found by the exit chest radiography at 5 years
2. The abnormal sputum result led directly to an abnormal CT (i.e. a nodule ≥9mm), and the individuals were referred for immediate diagnostic investigations
3. Individuals had an abnormal sputum, and the abnormal CT that found the cancer was one of the later follow-up scans. In 3 cases, the first CT with a nodule ≥9mm was some years before the cancer diagnosis but subsequent CTs indicated that the nodule had shrunk before the final CT that led to diagnostic investigations showed nodule growth.
4. Individual had normal annual CT scans during the trial. The cancer was found by a CT scan given outside of the protocol when the person finished the study; a suspicious large nodule had appeared (≥9mm).

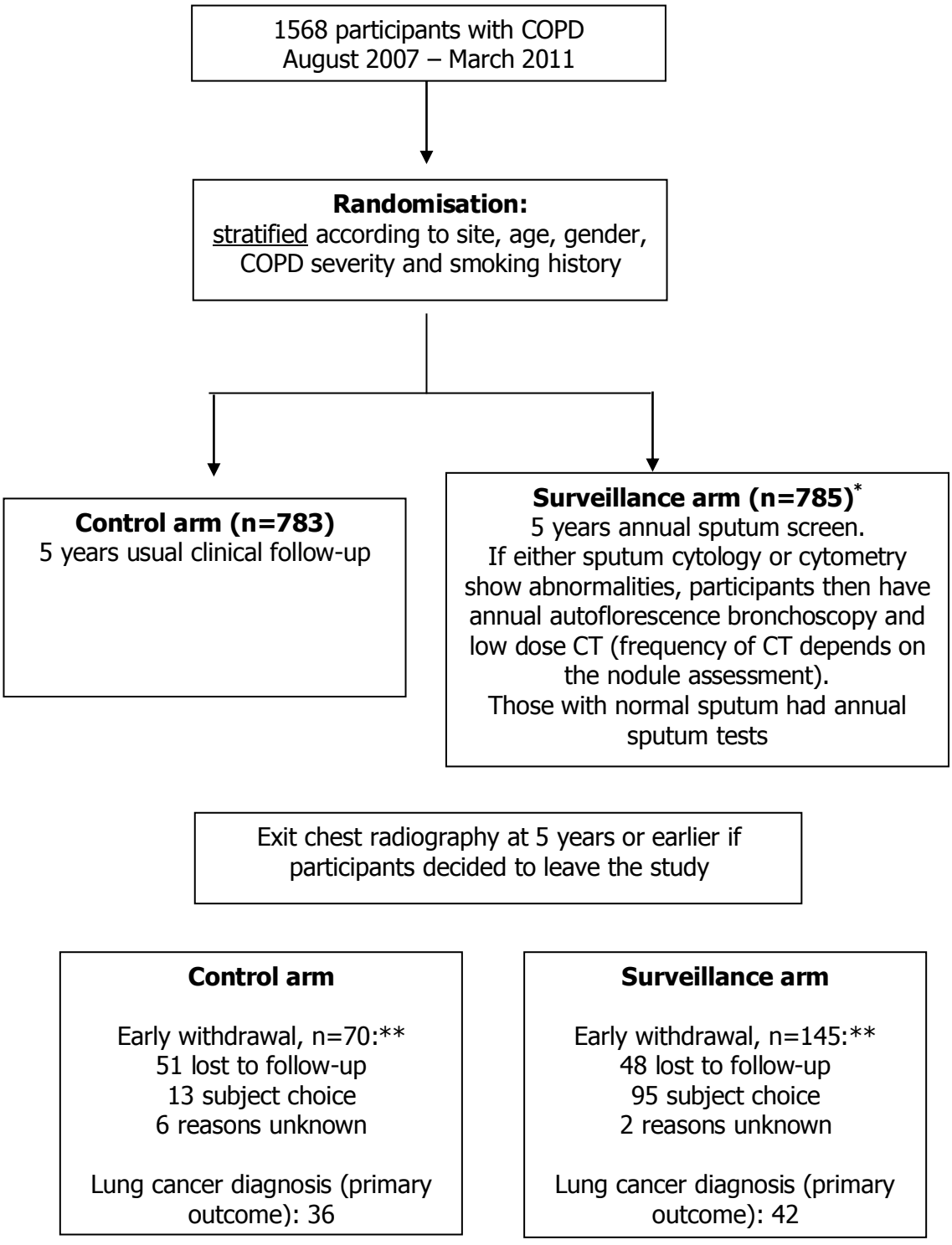


Figure 1. CONSORT diagram

*It transpired that one person actually had lung cancer >1 year prior to randomisation but did not inform the trial staff (they would have been ineligible). Because this was only discovered at the end of the trial (cancer notification by the national registry), the person is kept in the intention-to-screen analyses. The person had normal sputum samples throughout, and no AFB or CT (and not counted as a cancer case). Counting this as a cancer case has only a small effect on sensitivity (44.7% without it [Figure 2] and 43.6% with it).
**Even though some participants withdrew from the trial procedures before 5 years, they were still flagged for cancer occurrence.

Appendix Table 1 provides further details about number of participants approached and trial uptake

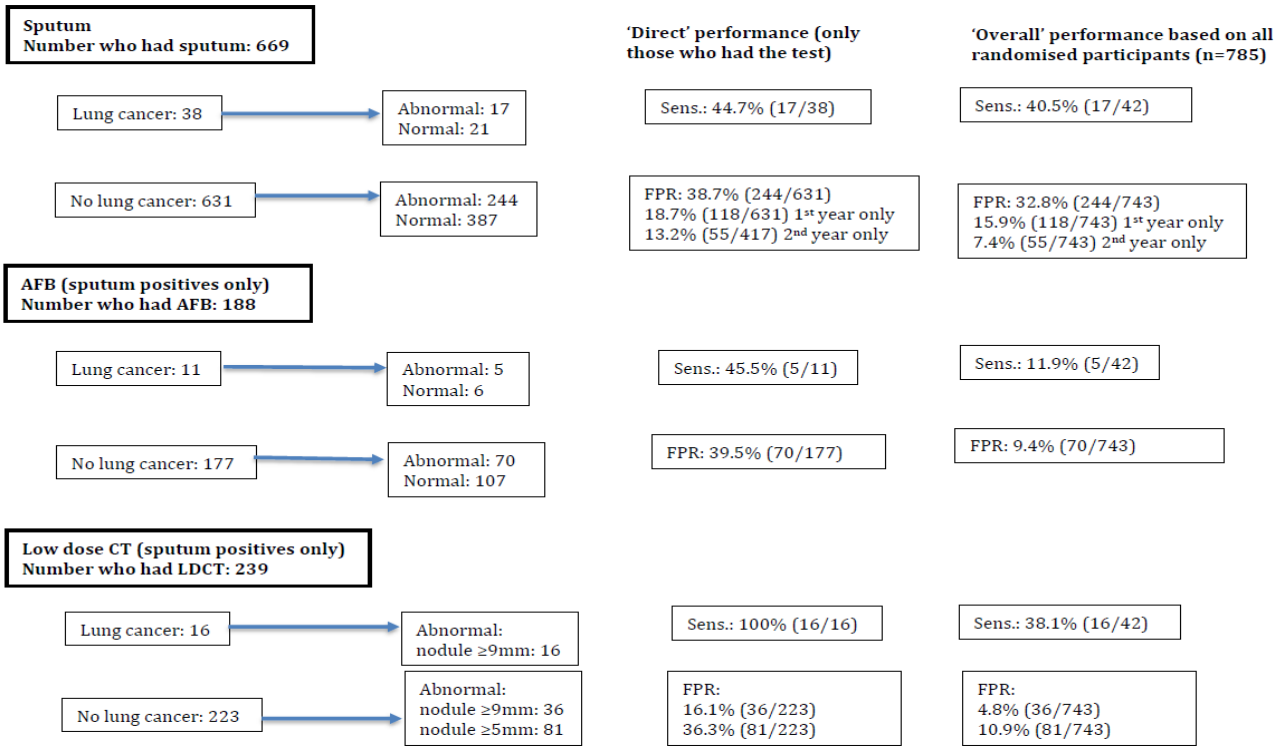


Figure 2. Summary of screening performance for the three tests in the surveillance group, based on results at any time during the trial. Sensitivity (sens.): % of cancers with abnormal results, and FPR: false-positive rate, % of people without lung cancer with abnormal results (same as 1 minus specificity)

Supplemental Appendix

Appendix Text 1	Further details and methods of the sputum sampling
Appendix Text 2	Further details of auto-florescence bronchoscopy
Appendix Text 3	Further details of the low dose CT scan (LDCT)
Appendix Text 4	Description of screening performance for the 3 tests used (sputum, AFB and LDCT)
Appendix Table 1	Distribution of trial participants across the 10 centres
Appendix Table 2	Summary of recruitment activity among the 7 centres that had screening logs
Appendix Table 3	The odds ratio (95% CI) of declining to participate in LungSEARCH according to geographical location (centre), age and sex
Appendix Table 4	End of trial status, including the exit chest radiography
Appendix Figure 1	Flow diagram for trial participants in the screened arm
Appendix Figure 2	Kaplan-Meier plot for the incidence of lung cancer
Appendix Figure 3	Kaplan-Meier plots for deaths due to lung cancer (upper), and all-cause mortality (lower)

Appendix Text 1. Further details of the sputum sampling

Individuals in the screened group provided annual sputum samples (three pots) at home. Samples were posted to the central laboratory at University College London Hospital, who prepared four slides using Thin-Prep-2000 processor (Cytyc UK). Two had Papanicolaou staining[a] for cytology review, and two were stained with a modified Feulgen's reagent[b] for cytometry.

- Cytology samples were considered assessable if each contained ≥5 alveolar macrophages and/or bronchial cells. Morphological parameters were graded using the Bethesda classification system[c] for Squamous Intraepithelial Lesions (SIL). The presence of any atypia, either low- or high-grade SIL was considered 'abnormal'.
- Cytometry: a semi-automated system was used (Fairfield DNA ploidy, Fairfield Imaging, Nottingham, UK), in which DNA histograms were examined and samples classified as having normal or abnormal DNA contents using published criteria.[d]

a. Papanicolaou GN. A new procedure for staining vaginal smears. Science. 1942; 95: 438–439.

b. Schulte E, Wittekind DH. Standarization of the Feulgen reaction: the influence of chromatin condensation on the kinetics of acid hydrolysis. Annal Cell Pathol 1990; 2:149–157.

c. Solomon D, Nayar R. The Bethesda System for Reporting Cervical Cytology. Definitions, Critera and Explanatory Notes., 2nd ed. Springer Verlag, New York;2004:1-191.

d. Sudbo J, Kildal W, Risberg B, Koppang HS, Danielsen HE, Reith A. DNA content as a prognostic marker in patients with oral leukoplakia. N Engl J Med. 2001;344:1270-8.

Appendix Text 2. Further details of auto-florescence bronchoscopy (AFB)

Delivery of AFB

AFB was performed under conscious sedation, and the bronchial tree examined under different lights using optical filters incorporated into the bronchoscope (D-light auto-fluorescence system, Karl Storz Gmbh, Germany; or auto-fluorescence video-bronchoscope, Olympus Medical, Japan). If AFB appeared abnormal under either white or blue light, 1-3 bronchial biopsies (for histology review) were taken from each affected area, and also an area with normal appearance on the contralateral side. For individuals without an abnormality, three biopsies were taken from a single area of normal appearance. Specimens were reviewed locally by an expert pulmonary histopathologist, categorized as squamous metaplasia, mild to severe dysplasia, carcinoma *in situ* or carcinoma.

Categories of dysplasia using AFB and subsequent histopathology:
1 = Squamous metaplasia
2 = Mild dysplasia
3 = Moderate dysplasia
4 = Severe dysplasia
5 = Carcinoma-in-situ
6 = Carcinoma

If no pre-invasive lesion were found after histopathology review of the bronchial biopsy tissue samples, AFB was repeated annually.

If a pre-invasive lesion were found by histopathology, AFB was repeated at intervals according to the grade of pre-invasive lesion:

- for carcinoma in situ and severe dysplasia (categories 4-5) the interval could be approximately 5 months
- for moderate to mild dysplasia (categories 2-3) the interval would be approximately 8 months.

If an invasive lesion (category 6) were found the individual was referred for other investigations and treatment via the normal hospital systems.

Appendix Text 3. Further details of the low dose CT scan (LDCT)

LDCT (target radiation dose <2mSv) was conducted without contrast, and assessment of nodules largely determined the frequency of subsequent follow-up using LDCT. Suspicion of cancer (a nodule size ≥9mm) could lead directly to CT with contrast, PET/CT or other investigations for cancer according to local practice.

LDCT delivery

No Intravenous contrast for initial scan

- Width section needs to be 1mm or equivalent with a multi-detector row CT scanner
- Axial +/- coronal reformats if available [Review MIPs from work stations if available]
- Low dose CT equivalent [depending on local practice /Dose modulation CT packages available, and patient's habitus]. Standard dose for CT scan if the nodule demonstrates growth or suspicious features with IV contrast.
- Images viewed from computer workstations with standard lung / soft tissue and bone settings.

Assessment of Nodules

- Document for non-calcified nodules
  1. Anatomical site
  2. Size-Volume assessment with maximum diameter all three planes. Growth of >25% is considered significant and further follow-up required
  3. Morphology:
     - Round or oval
     - Smooth or irregular margin
     - Solid or ground glass / semisolid
     - +/- cavitation
     - calcific foci

Those with mass lesions suspicious for lung cancer underwent urgent investigations as deemed appropriate by their clinician. Indeterminate non-calcified nodules were to be followed up according to their size as reported by references a-d below:

Nodule size	Recommended frequency of CT scan	
< 5 mm	Annually	Follow-up non contrast-enhanced CT, to look for growth.
≥ 5 to < 7 mm	At 6, 12 and 18-24 months	Follow-up non contrast-enhanced CT. If growth assess with IV contrast.
≥ 7 to < 9 mm	At 4, 8, 12 and 24 months	Follow-up non contrast-enhanced CT. If growth assess with IV contrast.
≥ 9 mm	(a) If nodule appears benign: CT at 4, 8, 12 and 24 months (b) If nodule appears malignant: CT with contrast	Follow-up (IV) contrast-enhanced CT. For malignant-looking nodules: investigate for cancer with dynamic CT, PET/CT, biopsy, FNA, or surgery, as indicated by local practice.

a. Henschke CI, McCauley DI, Yankelvitz DF et al. Early detection lung project: overall design and findings from baseline screening. Lancet 1999;354:99-105.
b. Swensen SJ, MD, Jett JR, Sloan JA, et al. Screening for lung Cancer with low dose helical computed tomography. Am J Respir Crit Care Med. 2002; 165:508-513.
c. Pastorino U, Bellomi M, Landoni C, et al., Early lung-cancer detection with spiral CT and positron emission tomography in heavy smokers: 2-year results Lancet 2003;362:593–97.
d. Fleischner society, Radiology 237, 2,395-400 2005

Central quality control audit

Two chest radiologists at UCLH (not managing trial patients) conducted independent quality assurance audits between April 2009 and July 2014. Double blind reviews of randomly selected LDCT scans retrieved from all sites were carried out, and the LDCT case report forms (CRFs) were also audited. Early in the trial, double reporting of scans at each site was undertaken, contributing to delays in sending the data to the trials centre. The independent review confirmed a high concordance between local reports, so that single reporting was implemented for the remainder of the trial (which consequently improved CRF return). The central review demonstrated a delay between a positive sputum result and having a LDCT in some cases, successfully leading to a change in practice which minimized/avoided the delay. The central review resulted in the same outcomes of the scans (i.e. cancer referral or timing of next follow-up scan) as the local assessment in the majority (97%) of cases.

Appendix Text 4. Description of screening performance for the 3 tests used (sputum, AFB and LDCT)

33.2% (261/785) of all individuals in the screened arm had an abnormal sputum result at any time, of which 22.5% (177/785) had abnormal cytology, and 12.6% (99/785) had abnormal cytometry. Among these 261, only 15 had both abnormal cytology and cytometry (162 abnormal cytology alone and 84 abnormal cytometry alone). 38 of all lung cancers in the screened group had sputum results, and 17 were abnormal at some point: 12 abnormal cytology alone and 5 abnormal cytometry alone (Table 5).

Table 5 shows that 21 lung cancer cases had a normal sputum throughout and were diagnosed outwith the trial procedures (4 adenocarcinoma, 5 squamous, 8 small cell, 1 large cell, and 3 other types). 8 (38.1%) were at an early stage, much lower than among the 17 cases that had an abnormal sputum, where 14 were diagnosed at an early stage (82.4%) and all were found by LDCT. Among the 3 cases with abnormal sputum diagnosed at late stage, two were found by LDCT directly following the abnormal sputum result, and the other case had neither an AFB nor LDCT.

No cancer had both abnormal cytology and cytometry. There was no discernable association between type of sputum test and histology, particularly with having only few cases.

When examining only those who had sputum results, the direct sensitivity was 44.7% (17/38), and corresponding FPR 38.7% (244/631); Figure 2. When considering all 42 lung cancers found and all 743 individuals without lung cancer, the overall sensitivity was 40.5%, and FPR 32.8%. These are cumulative FPRs by year 5. The direct FPR at baseline only was 18.7% (118/631) and in the subsequent year only it was 13.2% (55/417).

188 individuals had an AFB at any time during the trial (an additional 74 declined or did not attend; uptake 71.7% [188/188+74]). Of these, 39.9% (75/188) were abnormal (metaplasia, dysplasia, carcinoma or carcinoma *in situ*). The overall prevalence of pre-invasive disease among participants with abnormal sputum was 38% (72/188 had mild to severe dysplasia or metaplasia; but only 3 of these [2 moderate dysplasia and 1 squamous metaplasia], later developed lung cancer, 2.3-10.1 months later). Of the 17 lung cancers who had abnormal sputum, 6 never had AFB; whilst 11 did, of which 5 had suspicious lesions/dysplasia: direct sensitivity 45.4% and FPR 39.5% (Figure 2). Two of these 5 were confirmed as cancer after histopathology review (Table 5), where one was visualized by AFB on the right main bronchus (missing information for the other). For two other cases, AFB appeared normal but histopathology of the biopsy taken exhibited dysplasia.

239 (30.4%) individuals had a LDCT at any time during the trial (an additional 22 declined or did not attend; uptake 91.6% [239/239+22]). Of these, 21.8% (52/239) had at least one nodule of ≥9mm, considered for immediate diagnostic investigation. 18.8% (45/239) had nodules between 5 and 9mm, requiring LDCT scans more regularly than annually, but no immediate cancer investigations, and none of these 45 were diagnosed with lung cancer during the study. Among all 42 lung cancers, 16 had a LDCT (Table 5), of which 15 had an abnormal finding (nodule ≥9mm) during the trial and then referred for cancer diagnoses, and the other case was found by LDCT performed at trial exit (a nodule ≥9mm). Figure 2 shows that the direct sensitivity was 100%; and FPR 16.1% (36/223, using nodule size ≥9mm) or 36.3% (81/223, using ≥5mm).

Appendix Table 1. Distribution of trial participants across the 10 centres.

	N=1568
Chelsea & Westminster	348 (22%)
Cambridge	301 (19%)
University College Hospital London	277 (18%)
Leeds	206 (13%)
Belfast	106 (7%)
Leicester	89 (6%)
Royal Brompton	75 (5%)
Manchester	65 (4%)
Coventry	61 (4%)
Sunderland	40 (3%)

Appendix Table 2. Summary of recruitment activity among the 7 centres that had screening logs

	Number contacted	Number who did not reply	Number who replied to invitation		Number who were randomized#
			Declined to participate	Accepted	
UCH	1580	400 (25%)	470 (30%)	710 (45%)	277
Brompton	225	67 (30%)	39 (17%)	119 (53%)	75
Chelsea & Westminster					
Hospitals	64	5 (8%)	19 (30%)	40 (62%)	4
GPs	2437	368* (15%)	1003* (41%)	1066* (44%)	344
Cambridge	1368	212 (15%)	738 (54%)	418 (31%)	301
Leeds	1622	362 (22%)	709 (44%)	551 (34%)	206
Belfast	702	343 (49%)	164 (23%)	195 (28%)	106
Total	7998	1757 (23%)	3142 (39%)	3099 (39%)	1313**

*approximate
** 1568 in total in the trial
# out of those who accepted the invitation and were eligible after baseline tests

39% (3099/7998) of all those contacted by telephone after the initial search accepted the invitation to attend the pre-trial assessment, of which 42% (1313/3099) were randomized.

Appendix Table 3. The odds ratio (95% CI) of declining to participate in LungSEARCH according to geographical location (centre), age and sex.

Factor	Univariable (based on all available data for the factors)	Univariable (only subjects with non-missing data for all 3 factors)	Multivariable (only subjects with non-missing data for all 3 factors)*
Location:			
No. subjects	4327	3747	3747
No. who declined	2974	2394	2394
UCH	1.0	1.0	1.0
Brompton	0.83 (0.56-1.23)	0.31 (0.16-0.58)	0.29 (0.15-0.55)
Chelsea & Westminster	1.07 (0.85-1.35)	0.76 (0.57-1.00)	0.74 (0.56-0.98)
Cambridge	3.65 (2.94-4.54)	5.71 (4.49-7.26)	5.41 (4.25-6.90)
Leeds	5.94 (4.72-7.48)	9.57 (7.45-12.30)	9.63 (7.47-12.41)
Belfast	1.27 (0.93-1.75)	2.01 (1.44-2.81)	2.01 (1.43-2.81)
Sunderland	9.52 (6.56-13.81)	3.41 (2.21-5.28)	3.63 (2.34-5.64)
	P<0.0001	P<0.0001	P<0.0001
Age:			
No. subjects	3755	3747	3747
No. who declined	2402	2394	2394
Age <50 years	1.0	1.0	1.0
50-59	1.95 (1.47-2.59)	1.96 (1.48-2.60)	1.27 (0.92-1.76)
60-69	1.84 (1.41-2.39)	1.85 (1.42-2.41)	1.22 (0.90-1.65)
70+	2.53 (1.92-3.34)	2.54 (1.93-3.35)	1.92 (1.40-2.63)
	P<0.0001	P<0.0001	P<0.0001
Sex:			
No. subjects	4300	3747	3747
No. who declined	2947	2394	2394
Males	1.0	1.0	1.0
Females	1.10 (0.96-1.25)	1.13 (0.99-1.29)	1.02 (0.88-1.19)
	P=0.16	P=0.08	P=0.80

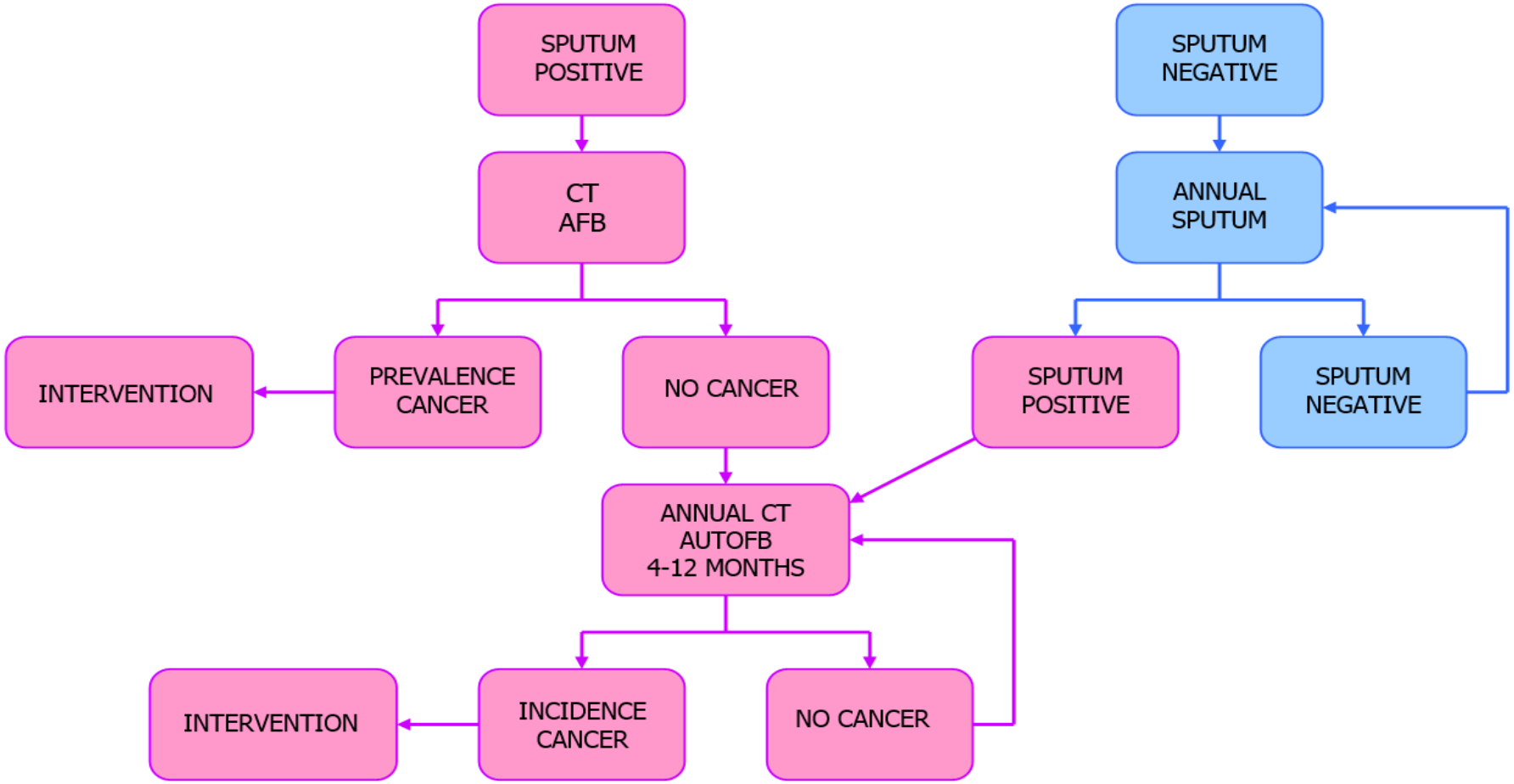
*Odds ratios are adjusted for the other two factors in the table

Univariable and multivariable logistic regressions were used to examine the odds of declining to participate (adjusted for age, sex and geographical location). This information could be used to consider potential factors that might influence future lung screening uptake in the UK (acknowledging that here, people were asked for participation in a randomized study of screening, rather than screening per se). People from Belfast, Cambridge, Leeds and Sunderland were more likely to decline than those from the University College London Hospital area (odds ratios of 2.01, 5.41, 9.63 and 3.63 respectively), while those from the Brompton Hospital and Chelsea and Westminster areas were less likely to decline (odds ratios of 0.29 and 0.74 respectively). The reasons for these geographical differences are unclear, but might include different approaches to recruitment by staff. However, this does not explain the difference in participation between UCH and the Brompton because the same research nurses were used for both centres.

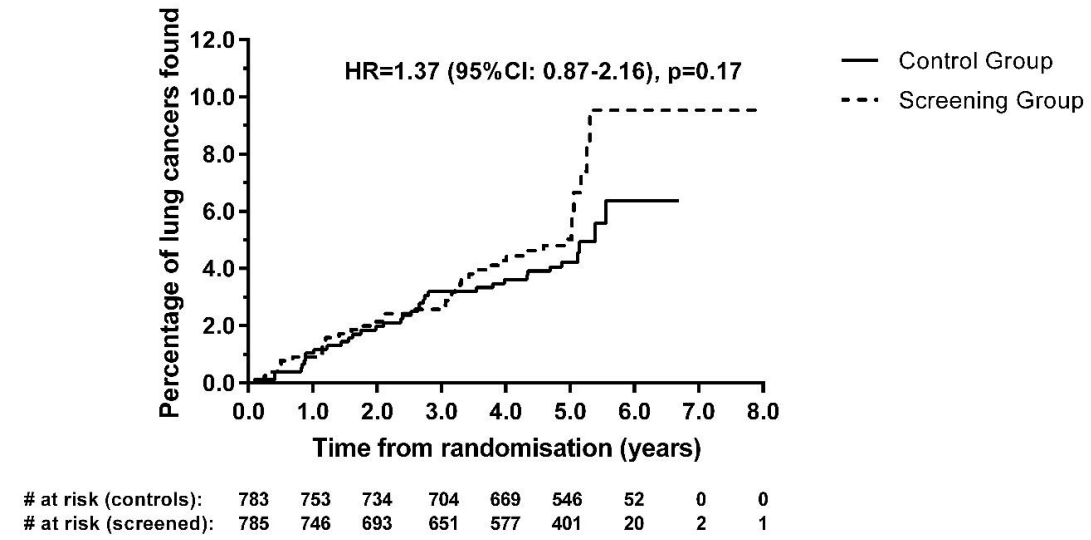
Appendix Table 4. End of trial status, including the exit chest radiography

	Control group N=783	Screened group N=785
Lung cancer	36 (5%)	42 (5%)
Other cancers	51 (7%)	47 (6%)
Deaths	96 (12%)	70 (9%)
Lung cancer	21	16
Other cancer	17	14
All other causes	48	38
Unknown cause	10	2
Smoking status:		
Current smoker that continued	242 (31%)	220 (28%)
Current smoker that reduced	46 (6%)	55 (7%)
Current smoker that stopped	51 (7%)	59 (8%)
Ex-smoker no change	284 (36%)	277 (35%)
Ex-smoker re-started	7 (1%)	3 (0%)
unknown/missing	*153 (20%)*	*171 (22%)*
Exit chest radiography:		
At end of 5 years	451	393
Before 5 years (among withdrawals)	35	37

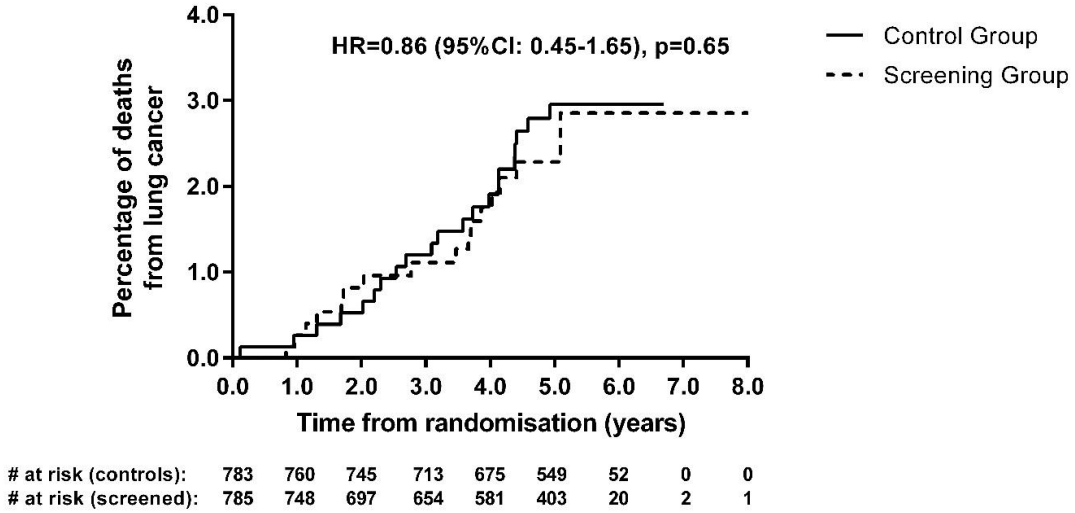
Because the hospital respiratory units recruited trial participants and so had an interest in the study through their lead clinical investigator, it is possible they were more proactive with managing these particular participants. However, the percentage of lung cancers found among those recruited from general practice/family physicians (4.6%, 57/1241) did not significantly differ from the hospitals (6.4%, 21/327), p=0.22.

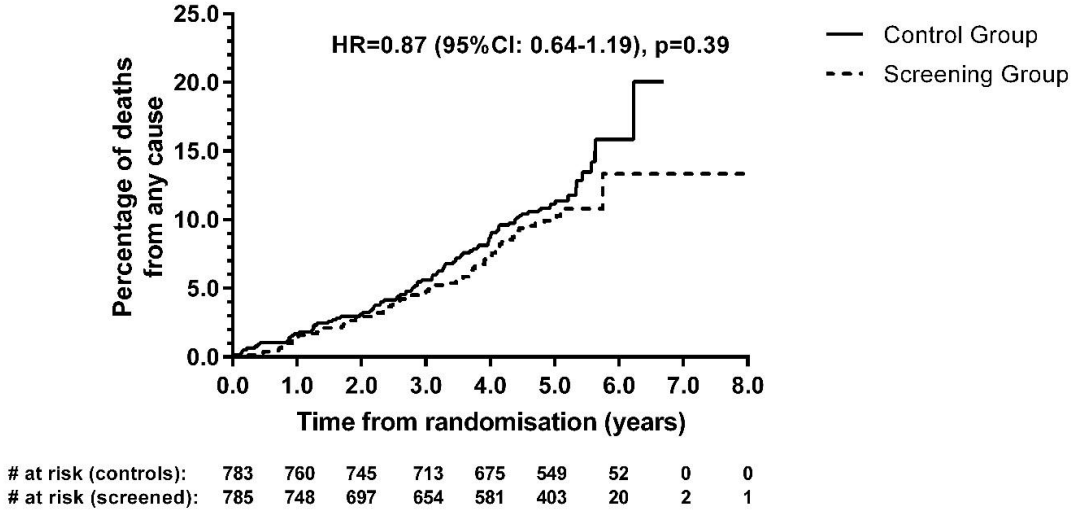


Appendix Figure 1. Flow diagram for trial participants in the screened arm. CT (low dose spiral CT scan), AFB (auto-florescence bronchoscopy)



Appendix Figure 2. Kaplan-Meier plot for the incidence of lung cancer.
The apparent increase in the risk of lung cancer diagnosis after 5 years is mainly due to the size of the steps in the Kaplan-Meier plot being exaggerated because there are relatively few individuals followed up for this long, with very few events. The trial protocol specified 5 years follow up, a few patients appeared to have longer than this mainly because of flexibility given to the date of their exit scans.





Appendix Figure 3. Kaplan-Meier plots for deaths due to lung cancer (upper), and all cause mortality (lower)