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Title: Evaluation of a health service adopting proactive approach to reduce high risk of lung cancer: the Liverpool Healthy Lung Programme.

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Highlights

- This community-based early diagnosis programme is reaching a deprived population
- The programme detected lung cancers at an early stage, 76% at stage I or II
- The earlier detection implied a projected 22% decrease in risk of death from lung cancer

Abstract

Objectives

This Liverpool Healthy Lung Programme is a response to high rates of lung cancer and respiratory diseases locally and aims to diagnose lung cancer at an earlier stage by proactive approach to those at high risk of lung cancer. The objective of this study is to evaluate the programme in terms of its likely effect on mortality from lung cancer and its delivery to deprived populations.

Methods

Persons aged 58-75 years, with a history of smoking or a diagnosis of chronic obstructive pulmonary disease (COPD)[1] according to general practice records were invited for lung health check in a community health hub setting. A detailed risk assessment and spirometry were performed in eligible patients. Those with a 5% or greater five-year risk of lung cancer were referred for a low dose CT[2] scan.

Results

A total of 4 566 subjects attended the appointment for risk assessment and 3 591 (79%) consented to data sharing. More than 80% of the patients were in the most deprived quintile of the index of multiple deprivation. Of those attending, 63% underwent spirometry and 43% were recommended for a CT scan. A total of 25 cancers were diagnosed, of which 16 (64%) were

[1] COPD, chronic obstructive pulmonary disease;

[2] CT, computed tomography

stage I. Comparison with the national stage distribution implied that the programme was reducing lung cancer mortality by 22%.

Conclusions

Community based proactive approaches to early diagnosis of lung cancer in health deprived regions are likely to be effective in early detection of lung cancer.

Key words

Lung Cancer, Chronic Obstructive Pulmonary Disease, Smoking, Low-Dose CT, Early Diagnosis, Health Inequalities

Evaluation of a health service adopting proactive approach to reduce high risk of lung cancer: the Liverpool Healthy Lung Programme.

Background

Lung cancer remains the leading cause of cancer mortality in both males and females in the United Kingdom (UK) with around 35 600 deaths in 2016[1]. Lung cancer survival has shown little improvement in the last 40 years in the UK[2] and survival rates are lower than elsewhere in Europe[3,4]. This is thought to be largely due to late stage diagnosis in the UK compared with other European countries[5].

Several studies have shown that smaller sized and earlier stage lung cancers can be detected more accurately by low dose computed tomography (CT) than by symptoms or chest X-ray[6–9]. The National Lung Screening Trial (NLST) in the United States (US) showed a 20% reduction in lung cancer mortality with early detection using low dose CT as compared to annual chest X-ray[9].

The vast majority of lung cancers (80-90%) can be attributed to cigarette smoking[10], with lesser effects of other factors including environmental exposures and genetic susceptibility[11,12].

Socio-economic inequalities have been shown to have a significant impact on survival rates for the large majority of cancers[13], with poorer outcomes in more deprived populations, suggesting that progress in early diagnosis and treatment may have occurred more in affluent populations[14,15]. Many studies have reported worse lung cancer survival rates in patients of lower socio-economic status[16–18]. Recent data have shown that lung cancer has the largest number of excess cases and deaths compared with other cancers in the most deprived quintile of the population based on the index of multiple deprivation (IMD)[19].

In the UK, the city of Liverpool has one of the highest respiratory morbidity rates[20]. The Liverpool Healthy Lung Programme (LHLP) is an initiative taken by the Liverpool Clinical Commissioning Group (CCG) to respond to the high rates of respiratory diseases and health inequalities with respect to these.

The programme had two sequential phases. The first was a series of coordinated focused public engagement events throughout the city, starting in areas with the highest lung cancer incidence. The main aim was to promote positive messages around lung health as well as address attitudes of fear and fatalism around lung cancer.

The second phase, reported on here, was a programme of individual lung health consultations, risk assessments and referrals to CT scans for those at more than 5% risk of lung cancer in the next five years. It aimed to diagnose respiratory diseases at a more treatable stage thereby increase survival rates.

Material and methods

Patients aged 58-75 years with a history of smoking or a diagnosis of chronic obstructive pulmonary disease (COPD) according to participating general practice records were invited for a lung health check (LHC) with a respiratory nurse in a community health hub setting. The first invitation letter was followed by a second one in case of non-attendance, and if there was no response to the second letter either, the patient was contacted by telephone.

During the LHC, a detailed risk assessment was performed using information from the subject's medical history and other risk factor information, including exposure to asbestos, family history of lung cancer, history of malignancy and smoking duration. Spirometry was used to assess lung function in those without a pre-existing diagnosis of COPD. Patients with abnormal lung function, defined by FEV1/FVC ratio less than 70% on spirometry, were referred for further investigation. In addition to this, all currently smoking patients were offered smoking related advice and referred to the National Health Service (NHS) smoking cessation clinics if they consented to this.

Five-year risk of lung cancer was estimated using the 'MyLungRisk' calculator, based on the Liverpool Lung Project (LLP) risk model[21]. Those with risk of 5% or more were referred to a low-dose CT scan. The participating patients were requested to provide consent to share their data with the evaluation team (i.e. the CCG).

Among the subjects recommended and attending the CT scan, those with clinical signs of lung cancer or nodules of diameter 10 mm or greater were referred to cancer services. Those with non-calcified nodules of diameter 6.1-9.9 mm were suggested to have a follow-up CT scan at 3 months, while those with non-calcified nodules of diameter 5-6 mm were offered a scan at 12 months. No further action was taken for calcified benign nodules and non-calcified nodules of diameter less than 5 mm.

Here we report on participation, health status, scanning and diagnostic activity between April 2016 and January 2018. We also carried out surveys of patients post health check and post CT

scan, to elicit patient experience, satisfaction and information needs. These will be reported on separately.

We compared demographics, risk factors and clinical attributes of patients between the most deprived IMD quintile and the four remaining IMD quintiles using logistic regression. The stage distribution of lung cancers diagnosed was compared to the national stage distribution using the chi-squared test. We estimated the likely effect on lung cancer mortality by applying national stage-specific fatality rates to the cancers diagnosed in the LHLP and comparing the expected number of deaths to the mortality expected from the national stage distribution. A confidence interval was calculated by assuming that the observed cancer stages were multinomially distributed and national figures were fixed. All the statistical analyses were performed using Stata version 13.

Results

A total of 11 526 invitations were sent in the first round and 4 566 (40%) attended the appointment. Among the attenders, 3 591 (79%) consented for data sharing, 1 264 (35%) took part after the first letter, 1 539 (43%) after the second and 788 (22%) after the telephone call.

(Table 1)

We had tabular data on non-consenters and non-responders for the 11 526 invitations corresponding to the consultations reported on here, plus a further 1 980 from invitations subsequent to those for the 3 591 consenters here. Comparing the patients who responded to the invitation to a LHC and consented to individual data sharing with those who did not respond and those who attended but did not consent to data sharing (Table 1), the age and sex distributions were found to be similar for all the groups, although there was a slightly higher proportion of females among the non-consenters. The IMD distributions were also slightly different among the groups, with 81% in the most deprived quintile among the consenters and 83% for both non-responders and non-consenters. Correspondingly, approximately 6% of the

responders and less than 5% of the non-responders and the non-consenters were in the two least deprived quintiles.

(Table 2)

Table 2 summarises the attributes of those attending the appointments. Patients were categorised into two groups based on their IMD, most deprived (quintile 1) and less deprived (quintiles 2 and above). The median age of the patients in the two groups did not differ substantially but, in bivariate analysis, age of the patients was found to be significantly (p <0.001) associated with deprivation, with those in the most deprived quintile being slightly younger than the less deprived patients. The number of patients who had ever smoked in their lifetime and the duration of smoking of the patients were significantly higher (p <0.001) in the most deprived category than the less deprived. The presences of previous non-lung malignancy and non-malignant lung disease were similar in both groups, except for COPD (p < 0.001), which was higher in the most deprived category. Likewise, the 5-year risk of lung cancer was also slightly but significantly (p = 0.005) greater in the most deprived group (4.63% vs. 3.45%).

In both groups, more than 30% reported exposure to asbestos. Of the 1 244 subjects reporting exposure in both groups, 338 (27%) were female.

Of the patients attending the health checks, 745 agreed to receive smoking cessation advice. While we did not have data on whether ever smokers were current or ex-smokers, the post-check patient survey suggested that 29% of the reported 2 607 ever smokers were current regular or occasional smokers. This would imply that 756 patients were current smokers, and 99% of them agreed to receive cessation advice. In addition, 128 (17% of estimated current smokers) agreed to be referred to a smoking cessation clinic. It is, however, possible that smoking is under-recorded in the database.

(Table 3)

Table 3 shows the diagnostic cascade for the patients. A total of 2 255 (63%) underwent spirometry and 845 (37% of those tested) with a resulting FEV1/FVC ratio of less than 70% were referred for further investigation. There were 1 557 (43% of attenders) patients with 5-year lung cancer risk greater than or equal to 5% and 1,548 of these (99%) were recommended for a CT scan. Of those recommended, 1 318 (85%) had a CT scan at the time data collection was closed. Of those undergoing a scan, 119 (9%) were referred for further investigation (follow-up CT scan at 3 or 12 months, or immediate referral to pathway) and 25 (1.9%) were diagnosed with lung cancer. A further 11 had suspected lung cancer and were undergoing further investigation at the time of data download.

(Table 4)

Table 4 shows the expected stage distribution for 25 lung cancers in the general population in the UK, and their expected 5-year fatality based on national stage specific survival[22]. This was used to calculate the number of predicted deaths in the population by stage.

The table also shows the staging for the 25 cancers detected within the LHLP. Among these, 16 (64%) were stage I, 3 (12%) were stage II, 6 (24%) were stage III and none were stage IV. Stage I and II cancers comprised 76% of the lung cancers diagnosed, significantly greater than the 22% expected from the general lung tumour population ($p = 0.003$). In absolute terms, there were 11 fewer Stage III and IV cancers than expected.

Using national rates of 5-year fatality, it was possible to predict the mortality for the LHLP-detected cancers. Based on the stage of cancers diagnosed, we expect about 18 deaths from 25 lung cancers detected within the LHLP in the five years following diagnosis. If the LHLP-detected cancers had the same stage distribution as the national population of lung cancers, we would have expected 23 deaths, suggesting that the programme may be decreasing lung cancer mortality risk in patients by 22% (95% CI, 16-30%). Within this cohort, this amounts to just under 5 deaths prevented in the coming five years. However, the actual number of deaths prevented

will be larger than this, since there are cancer data pending from those still under investigation. With the current information, it can be said that, among those consenting, the programme is expected to have prevented 4-5 deaths from lung cancer. This gives an absolute figure of 264-330 CT scans needed per death prevented.

In terms of socioeconomic status, 23 (92%) of the cancers were diagnosed in the most deprived IMD quintile.

Discussion

This community-based study was conducted in one of the most deprived regions of the UK as part of efforts to address health inequalities in the area. Phase 2 of the LHLP has now been running since April 2016 and has conducted 4 566 lung health checks up to 10th January 2018 (40% of the invited population).

In those referred for and attending a CT scan, a relatively high prevalence (1.9%) of cancers was observed. Of the cancers, 76% were at stage I or II, and application of national stage-specific survival rates suggest that participation in the programme is associated with a 22% decrease in risk of death from lung cancer. This is similar to that observed in the US NLST trial[9]. This relative risk reduction corresponds to an absolute prevention of one lung cancer death per 264-330 CT scans, rather more than observed in the NLST trial, possibly due to the very high-risk level required for eligibility for a CT scan in the LHLP.

It should be noted that the projected reduction in mortality from lung cancer is tentative at this stage. The Danish randomised trial of CT screening found a shift to earlier stage [23] in the CT arm but no corresponding reduction in lung cancer mortality [24]. The stage shift could be a length bias phenomenon or might at least partly represent overdiagnosis. Further follow-up for lung cancer diagnosis and death in the whole screened cohort will clarify this issue.

Studies have found participation in lung cancer screening to be significantly lower among current smokers; especially those living in socio-economically deprived areas [25–28]. Psychological factors have been implicated in their low uptake, including fatalistic perceptions of the disease, low perceived benefit, individual perceived susceptibility, and perceived stigmatisation of a lung cancer diagnosis[28–33]. In our study, uptake was slightly lower in groups of lower socio-economic background, but more than 80% of both responders and non-consenters were in the most deprived IMD quintile, indicating that the programme was successful in reaching this population. Of our patients, 43% attended after the second letter and 22% after the telephone call, which indicates that subsequent contact for initial non-attenders was productive.

In common with others, we found that smoking was more prevalent in the most deprived population[34,35]. Smoking is a considerable causal factor of lung disease and premature mortality[36,37] mainly from lung cancer and COPD[1,38]. Smoking status was self-reported in this research, and the system of data capture and coding for smoking may be incomplete. It is likely that the 73% reported as ever smokers is an underestimate. The project, however, found that large proportions of patients agreed to receiving smoking cessation advice, and to be referred to smoking cessation services. The protocol of the LHLP has now changed so that patients who smoke are referred to smoking cessation services on an opt-out basis. More complete and more detailed smoking history should be routinely recorded for future evaluation.

Approximately one quarter (23%) of patients were found to have an existing diagnosis of COPD. Following spirometry of those who did not already have COPD, 845 (24%) patients had abnormal lung function, and from previous local clinical experience it is anticipated that 287 (8%) subjects will in due course be diagnosed with and treated for COPD, although rather higher conversion rates have been reported in the literature[39]. Even though 85% of those offered a CT scan underwent the procedure, this figure is likely to increase as the data for those referred after a consultation in January had not yet been processed at the time of download.

We observed a rate of around 9% of nodules requiring further workup. This is a considerably lower rate than observed in previous randomised trials[9,40]. It is at least partly due to the fact that, in the LHLP, nodules smaller than 5 mm in diameter were not acted on in order to comply with recent guidelines[41]. There is a need for further follow-up of all subjects undergoing health checks to assess the extent to which the risk eligibility criteria and the diagnostic algorithm might be causing cancers to be missed. Both the low rate of further investigations following a CT scan and the promising results with respect to stage of disease are consistent with results from a similar project in Manchester[42].

There are some limitations to this study in terms of the evaluation and the health intervention. First of all, the number of detected cancers is small. However, the stage distribution is so markedly different from that of the national lung cancer population that a statistically significant improvement was observed. However, further follow-up is indicated, since as noted above length bias may have contributed to the very favourable stage distribution.

In terms of the health intervention itself, our surveys, which will be reported on in detail elsewhere, suggested a gap in information given to patients in terms of the purpose of both the health check appointments and the CT scans. Revisiting information materials to address the issue and making necessary changes for future application are indicated. Lack of awareness of risk factors in female patients was also observed, notably with respect to air pollution, personal smoking history and history of non-malignant respiratory disease. With respect to the latter two, it would be worthwhile to consider strengthening the printed information or oral information given at consultation.

The threshold in 5-year lung cancer risk used in the LHLP for referring a patient to a CT scan was 5%. From the receiver operating characteristics of the LLP model, 42% of lung cancers would be estimated to arise in this risk group. Relaxing the criterion to 4% would imply capturing 50% of lung cancers, and a 3% criterion would be able to detect 58%. Thus, with a 3% or 4% risk criterion, the majority of lung cancers could potentially be diagnosed early in the programme.

In this population, in addition to the 1 557 subjects meeting the 5% criterion, 290 more would meet the 4% criterion and a further 337 the 3%. Thus, the increase in scanning activity would lead to similar proportional increases in cancers potentially detected early.

This study suggests that community based proactive approaches to early diagnosis of lung cancer in health deprived regions are likely to be effective in early detection of lung cancer and possibly COPD. In addition, we could also surmise that such community targeted interventions would contribute to improve the population's health, reduce health inequalities and improve lifestyle and life expectancy in the areas where they are implemented. Furthermore, the findings also imply that it is feasible to achieve similar clinical outcome benefits to those observed in the US trial of low-dose CT screening for lung cancer, with lesser harm in terms of unnecessary diagnostic activity[9]. However, this needs confirmation with extended follow-up, larger numbers of lung cancers diagnosed, and the addition of mortality data. Further randomised trial results would also add to the precision of estimation of benefits and harms, in particular mortality results from the large European trial, NELSON[43]. A substantial mortality benefit from CT screening has been reported in a conference presentation from NELSON[44], and the published results are awaited with great interest.

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Author contributions

All authors contributed to drafting and editing the article and have provided final approval of the version to be published. MT, LJ, RA, ML, LL, PR, FC, KG, SWD, JFK were responsible for study concept, oversight and conduct. BG, SWD, RM, DV, ZS, MM, SH, DF and SM contributed to data management and analysis. SGS and SQ were responsible for surveys.

Conflict of Interest

The authors declare no conflict of interest.

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Tables

Table 1. Age, sex and IMD for the responders giving consent to individual data sharing, the non-responders, and the responders not giving consent to individual data sharing.

Factor	Category/quantity	Responders (N = 3,591) n (%)	Non-responders (N = 8,898) n (%)	Non-consenters (N = 1,017) n (%)
Age	Mean (SD)	65.9 (4.3)	65.4 (4.6)	66.2 (4.7)
Sex	Male	1,853 (52)	4,679 (53)	499 (49)
	Female	1,738 (48)	4,219 (47)	518 (51)
IMD quintile*	1 (most deprived)	2,897 (81)	7,415 (83)	846 (83)
	2	275 (8)	725 (8)	69 (7)
	3	212 (6)	415 (5)	61 (6)
	4	194 (5)	317 (4)	40 (4)
	5 (least deprived)	12 (<1)	26 (<1)	1 (<1)

* One responder had missing IMD data.
SD = Standard Deviation
IMD = Index of Multiple Deprivation

Table 2. Demographics and respiratory characteristics of patients attending healthy lung appointment (consented patients only).*

		Most deprived (IMD quintile = 1) n (%)	**Less deprived** (IMD quintile >= 2) n (%)	***p* value**
Factors	**Category/quantity**			
Total patients		2,897 (80.7)	693 (19.3)	
Age	Median (p25,p75)	66 (62, 69)	67 (63, 70)	<0.001
Sex	Female	1,418 (48.9)	319 (46.0)	0.168
	Male	1,479 (51.1)	374 (54.0)	
Ever smoker	Yes	2,141 (73.9)	461 (66.5)	<0.001
	No	756 (26.1)	232 (33.5)	
Years smoked	Median (p25,p75)	40 (25, 47)	30 (16, 44)	<0.001
FEV1/FVC ratio	Median (p25,p75)	0.73 (0.67, 0.77)	0.73 (0.67, 0.77)	0.361
Previous non-lung malignancy	Yes	420 (14.5)	106 (15.3)	0.594
	No	2,477 (85.5)	587 (84.7)	
Non-malignant lung disease	Emphysema	103 (3.6)	16 (2.3)	0.102
	Pneumonia	511 (17.6)	121 (17.5)	0.912
	COPD	717 (24.75)	114 (16.45)	<0.001
	Bronchitis	983 (33.9)	223 (32.2)	0.380
	Tuberculosis	53 (1.8)	11 (1.6)	0.665
Asbestos exposure	Yes	992 (34.2)	252 (36.4)	0.292
	No	1905 (65.8)	441 (63.6)	
Family history of lung cancer	Yes	966 (33.3)	206 (29.7)	0.068
	No	1,931 (66.7)	487 (70.3)	
Lung cancer risk	Median (p25, p75)	4.63 (2.16, 8.66)	3.46 (1.66, 7.68)	0.005
	More than 5%	1,492 (53.5)	414 (61.4)	
	Less than 5%	1,295 (46.5)	260 (38.6)	

* One attender had missing IMD data and is therefore not represented in this table.
FVC = Forced Vital Capacity, FEV1 = Forced expiratory volume in one second

Table 3. Diagnostic cascade within LHLP (consented patients only).

Outcome	Number	Percentage
Patients attending	3,591	
Spirometry	2,255	63% (of attenders)
CT scan recommended	1,548	43% (of attenders)
CT scan carried out	1,318	37%(of attenders), 85% (of recommended)
Further investigation for nodules	119	9% (of scanned)
Lung cancer	25	1.9% (of scanned)
Suspicious lesion under investigation	11	0.8% (of scanned)

LHLP = Liverpool Healthy Lung Programme
CT = Computed Tomography

Table 4. Stage distribution of the UK lung cancer population and of the LHLP-detected lung cancers, with expected numbers of deaths in five years predicted from national stage-specific survival rates.

Stage	**UK expected population frequency** (n, %)	**UK 5-year fatality** (%)	**UK predicted deaths** (n)	**LHLP observed frequency** (%)	**LHLP predicted deaths** (n)
Unknown	2 (10)	94	1.9	0 (0)	0
I	4 (15)	65	2.6	16 (64)	10.4
II*	2 (7)	79	1.6	3 (12)	2.4
III	5 (19)	94	4.7	6 (24)	5.6
IV	12 (49)	100	12	0 (0)	0
Total	25 (100)	90	22.8	25 (100)	18.4

*One thymoma is included with the stage II cancers
UK = United Kingdom
LHLP = Liverpool Healthy Lung Programme