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Lung Cancer: Early Diagnosis and Screening

David R Baldwin[1]* and Richard B Hubbard[2]

[1]*Consultant Respiratory Physician, Nottingham University Hospitals and Honorary Associate Professor, University of Nottingham, Respiratory Medicine Unit, David Evans Centre, UK*
[2]*GSK/BLF Professor of Respiratory Epidemiology, University of Nottingham, Clinical Sciences Building, Nottingham City Hospital, UK*

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Background

Lung cancer accounts for an estimated 1.4 million deaths globally that is, 18.4% of all cancer deaths [1]. More than 35,000 people died from lung cancer in 2008 in the UK. In males this was almost a quarter of all cancer deaths and in females just over a fifth [2]. By comparison, 16% of female cancer deaths were from breast cancer and the second commonest cause of cancer death overall (colorectal) accounts for 10% of all cancer deaths. The majority of people with lung cancer (three quarters in the UK [3]) present with stage IIIb or IV disease where cure is impossible and so survival low in comparison with other common cancers.

There are two ways in which we are likely to diminish the huge public health burden that mortality from lung cancer constitutes: smoking cessation and earlier diagnosis. Smoking cessation has already produced dramatic falls in the age-adjusted incidence of lung cancer and it appears that lung cancer incidence has passed its peak in males at least [4]. Continued efforts to reduce the prevalence of smoking across all sectors of society are a key public health priority [4,5]. However there remains a large population at risk of developing lung cancer. In the US in 2007 there were an estimated 94 million people with a history of smoking and about half of these were current smokers [6]. Thus the second way mortality may be substantially altered by early detection initiatives that lead to diagnosis at an earlier stage. There are, in turn, two ways in which people may be diagnosed earlier: by the use of early diagnosis and awareness initiatives and by population screening. The first of these methods is unproven and the second has only recently been shown to be effective.

Early Diagnosis and Awareness

There is evidence for variation in the timeliness of presentation between different countries, where people present later this could be a target to improve outcomes. For example two recent publications have reported that people with lung cancer in England and to a lesser extent Denmark, do worse than those from other similarly developed countries [7,8]. Using lung cancer registry data the authors found that for both men and women and for people in all age groups, the 5 year survival from lung cancer was lower in England than Norway, Sweden, Australia and Canada. Most of the difference in survival between the countries was the result of particularly poor early survival in England. Overall the authors concluded that clinically relevant differences in survival are present between the countries and that access to health care services, population awareness and possibly differences in treatment are likely explanations of these differences.

Thus there is evidence that in some countries at least, late presentation may be a factor in poor survival. By tackling this it may be possible to improve mortality but to do that we need to know more about population awareness and behavior. To date research in this area has been limited but further analysis of data from the international benchmarking project may help [8]. Information on possible patient-related reasons for delays in the UK comes from a study by Corner et al. [9] who interviewed 22 patients with recently diagnosed lung cancer and compared their recollection of the emergence of their respiratory symptoms and their interaction with their general practitioner with information from the primary and secondary health care records. The most common symptoms that patients reported were cough (68%), breathing changes (68%) and chest pain (55%). In total more than 30 different symptoms were reported and the median time between the self-reported onset of the symptom and diagnosis was 12 months. In contrast the median time delay between the symptom which triggered the presentation to the general practitioner and the diagnosis was only 2 months. The authors conclude that people with lung cancer often have symptoms for a considerable period of time before they consult their general practitioner, and that this is major source of delay in the diagnostic process. However, this is a small study and patients without lung cancer were not surveyed for similar perception of early symptoms. A rather narrower time interval between symptom onset and presentation was found in an interview survey of 360 Scottish people with newly diagnosed lung cancer. In this study Smith et al. [10] found that about half the people with lung cancer had symptoms for more than 14 weeks before they presented to their general practitioner. People who lived alone had COPD or longer smoking histories tended to have longer times between the onset of symptoms and consulting their general practitioner.

Developing a system for improving the way primary care practitioners interact with people at risk of lung cancer also has little research evidence. In one case-control study of 247 people with lung cancer and 1,235 age and sex matched controls registered with 21 general practices in Exeter a number of symptoms (haemoptysis, loss of weight, loss of appetite, dyspnoea, chest pain, fatigue, cough), a clinical sign (clubbing) and abnormal investigations (thrombocytosis and abnormal spirometry) all predicted the presence of lung cancer in the two years before the cancer was diagnosed [11]. The researchers then excluded the last 180 days of consultations before the cancer diagnoses to test the ability of these variables to predict lung cancer at an earlier stage and the factors that remained associated with lung cancer diagnoses were haemoptysis, dyspnoea, abnormal spirometry and being a current or ex-smoker. In a larger study of 375 general

***Corresponding author:** Dr. David R Baldwin, Consultant Respiratory Physician, Nottingham University Hospitals and Honorary Associate Professor, University of Nottingham, Respiratory Medicine Unit, David Evans Centre, Nottingham City Hospital Campus, NG5 1PB, UK, Tel: 0115 9691169 (ext 57462); Fax: 0115 9627723; E-mail: David.baldwin@nuh.nhs.uk

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practices and 3785 incident cases of lung cancer, a risk algorithm was developed that showed that the 10% of patients with the highest predicted risk included 77% of lung cancer cases diagnosed in the next 2 years [12]. Independent predictors were haemoptysis, appetite loss, weight loss, cough, body mass index, deprivation score, smoking status, chronic obstructive airways disease, anemia, and prior cancer (females only). Thus risk stratification scores might be used to assist primary care practitioners to better target diagnostic tests such as chest radiography, or refer patients earlier.

Although the currently available evidence is limited, it does suggest lung cancer could be diagnosed earlier by improving both public awareness of lung cancer and by helping primary care physicians to risk stratify the people that consult them for their risk of lung cancer. One example of a public health intervention designed to tackle both of these approaches is the early intervention in lung cancer within Doncaster (ElCID) project [13]. This project involved people from local public health departments, secondary care respiratory medicine, nursing, Sheffield Hallam University and a media company. Six areas of Doncaster believed to be at particularly high risk of lung cancer were identified and a combination of a social marketing campaign to highlight awareness of lung cancer symptoms and training for General Practice Surgeries around lung cancer was established. The provisional results of the project suggest that the campaign led to more people with a troublesome cough visiting their general practitioner and asking for a chest radiograph and more chest radiographs being requested by primary care physicians. However, no improvement in stage at diagnosis has been shown. In symptomatic patients the chest radiograph is the single most useful test that can be easily accessed in primary care that distinguishes those with symptoms who have lung cancer from those who do not [14]. In the UK the National Early Diagnosis and Awareness Initiative (NAEDI) is a partnership between the Department of Health, the National Cancer Action Team, and Cancer Research UK to coordinate and support activities and research into this area [15].

Although awareness initiatives are important their main benefit may, intuitively, not be in reducing mortality because early stage lung cancer does not generally cause symptoms. Instead, important benefits may be seen in that patients may have better levels of fitness and therefore benefit more from active treatment and fewer patients will experience the often distressing, emergency admission to hospital as their first presentation.

Screening

Some early studies of lung cancer screening with chest radiography and sputum cytology showed initial promise in that greater numbers of patients with lung cancer were detected in the screening arm and survival appeared to be better [16-22]. However, these findings were found by randomised controlled trials, to be largely explained by over-diagnosis, lead time and length time bias. Mortality was not altered. Hundreds of thousand of patients were randomised to these studies with no benefit confirmed [23-25]. Moreover, the recently published results of the PLCO trial have confirmed that chest radiograph is not effective as a screening test for lung cancer [26]. After 4 annual screens and a 6 year follow-up, the RR for mortality was 0.99 (0.87-1.22).

CT is a far more sensitive screening test than chest radiography and other methods employed in earlier studies so initial uncontrolled trials detected yet more lung cancers and survival appeared good [27,28]. Also, where patients had nodules detected that were not given treatment with curative intent, survival was less, implying that CT screening might be effective [29]. The efficacy of CT screening in reducing mortality has now been confirmed in one randomised controlled trial. The US National Lung Cancer Screening Trial (NLST) randomised 53454 people between the ages of 55 and 74 to either annual chest radiograph or annual CT for 3 years. The result, one year before the study was to finish was a 20.0% (95% CI 6.8 to 26.7) reduction in mortality from lung cancer and a 6.7% (95% CI 1.2 to 13.6) reduction in all cause mortality [30]. As a result of this, in the US at least there begins the process of CT screening for people that would have been eligible for inclusion into NLST. The National Comprehensive Cancer Network has produced guidelines for the implementation of CT screening in the United States [31]. These recommend screening those people who would have met the inclusion criteria for NLST and suggest screening for an additional group of patients with a lesser smoking history (≥ 20 pack year) and other defined risk factors. For those people at lower risk, CT screening is not recommended. In other countries a number of other studies, all smaller than NLST are on-going [32-38]. The two largest are the Dutch- Belgian NELSON trial and the United Kingdom Lung Screen (UKLS) and these exploit the now more advanced features of modern CT scanners and employ different screening protocols. The question has been asked, quite reasonably, why trials should continue to run and why should there not be wide-spread introduction of CT screening programs. To address this issue and others, the International Association for the Study of Lung Cancer (IASLC) published a consensus statement on CT screening that dealt with important issues that we now face following publication of the results of NLST [39]. The recommendations reflect the extent to which the results can be applied to other populations, the differences in healthcare systems and the need for further information to ensure that optimal screening programmes are implemented. One of the key questions is the cost effectiveness of screening. A paper modelling the cost effectiveness of CT screening has produced results that would not be acceptable in the UK even when smoking cessation (known to be cost effective) is included [40]. The results of the cost effectiveness data from NLST are eagerly awaited. The UKLS investigators have published a statement on the questions that need to be answered before a screening programme can begin in the UK [41]. Included in that statement is a series of recommendations, to those in the independent sector (non-National Health Service), who would wish to offer screening now. Here, cost effectiveness is less emphasised and therefore of over-riding importance is the risk: benefit ratio and strict adherence to quality standards inferred by trial protocols.

Minimally invasive techniques such as autofluorescence fiberoptic bronchoscopy in high risk groups are also being evaluated in trials in high risk groups but have not so far to be promising in screening. Many biomarkers have been studied, and if shown to have adequate accuracy, could serve to risk stratify those currently ineligible for CT screening.

In summary there is evidence that both patient and health service factors may contribute to delays in presentation to healthcare services but it is not yet clear what is the magnitude of effect improving these factors will have. Intuitively, earlier diagnosis, by even a few months may serve to increase active treatment rates and diminish distressing emergency presentations. Further research is required to answer these questions. Low dose CT screening of high risk populations has been shown to substantially reduce mortality and the remaining questions here centre on the exact design of CT screening programs to ensure cost effectiveness, defining the population that may benefit, including those at lower risk, and establishing the optimum management of screen detected nodules.

Declarations

Lead Respiratory Physician on United Kingdom Lung Cancer Screening project.

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