Is screening for lung cancer meaningful?

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The incidence of lung cancer, with attendant mortality, remains high in the developed world and is rising rapidly in developing countries throughout the world [1]. Surgery remains the best hope of cure for this condition but the characteristic late clinical presentation ensures more patients are inoperable at diagnosis because of local or distant tumour spread. The implementation of screening for lung cancer with the aim of early detection at an operable stage offers an attractive approach to reducing mortality rates. The Erfurt 10 yr prospective study of 6 versus 12–24 monthly radiological screening for lung cancer was recently published in this journal [2]. Although no reduction in mortality was shown in the 6 monthly screened group over that of the control group screened approximately every 18 months, the paper concluded that annual screening of male smokers of high cigarette consumption should be instituted to reduce mortality rates in this group. But is such a recommendation justified on the available evidence?

The earliest prospective studies of lung cancer screening were unable to demonstrate a mortality benefit in the populations screened [3–7]. The Philadelphia Pulmonary Neoplasm Detection Research Project [7] illustrates some of the reasons for this lack of success.

In the Philadelphia study fluoroscopy screening was instituted at approximately 6 month intervals over a 10 yr follow-up period in a population of 6,027 male smokers over the age of 45 yrs who volunteered for the study. One hundred and twenty one subjects developed lung cancer during follow-up, their survival was a disappointing 8% at 5 yrs. Forty five percent of those developing lung cancer did so between 6–12 months following their previous radiological examination due to default in attendance. Twenty percent of lung cancers were detected within the 6 month screening period but appropriate recall, investigation and referral added a 3 month delay in management. Fifty one percent of subjects with lung cancer were found to be inoperable because of advanced age or serious concomitant medical illness. In all, 84% of men with lung cancer suffered one or more of these disadvantages. Overall there was no significant reduction in mortality compared with historical population controls. This failure can be mainly attributed to the rapid doubling time of lung cancer combined with the relative insensitivity of radiology in early detection of this malignancy.

In response to these studies the US National Cancer Institute Co-operative Early Lung Cancer Detection Programme [8] was organized to assess the additional sensitivity to early screening that sputum cytology might convey and to prospectively study mortality figures. Three centres were involved, Johns Hopkins [9] and Sloan-Kettering Memorial Hospitals [10] and the Mayo Clinic [11]. The former two centres used volunteer subjects and an initial prevalence screen randomized subjects to either chest radiography alone or to dual screening with a chest radiograph and sputum cytology. Incidence screening was to be by annual radiography versus annual radiography combined with 4 monthly sputum cytology. The Mayo study design differed, subjects were outpatients attending for unrelated disorders and all underwent a dual prevalence screen of chest radiography and sputum cytology before being randomized to dual screening, in this centre on a 4 monthly basis, or recommended annual attendance with a radiograph. 31,260 male subjects over the age of 45 yrs who were currently smoking 20 or more cigarettes a day were recruited into the three studies.

21,127 subjects underwent dual screening and 160 lung cancers were detected in the initial prevalence study. One hundred and twenty three (77%) lung cancers were detected radiologically, 67 (42%) by cytology and 37 (23%) by cytology alone. 10,233 men underwent radiological screening only, which detected 63 lung cancers, a prevalence of 0.62%. This was statistically insignificantly different from the prevalence in the dual screening group. Cytologically detected tumours were of squamous cell origin, centrally located and mainly stage I (American Joint Committee on Cancer Classification [12]), whereas a high proportion of the radiologically detected tumours were peripheral and usually adenocarcinoma or large cell types. The sensitivities of the two techniques were 72% for radiology and 42% for cytology with specificities of 90% and 99%, respectively. Although the two techniques appeared complimentary three-quarters of cancers were detected radiologically and no statistically significant benefit was gained from adding cytological screening to the overall detection rates.

The high prevalence of stage I disease produced high resection rates in those screened with an overall 5 yr survival of 80% in those undergoing successful surgery and 35–55% overall, irrespective of staging, of cancer patients diagnosed in the dual screening programmes. The comparative historical survival for cases of all stages presenting clinically is 10% [13]. These figures, although
on first inspection encouraging, should be interpreted with caution. The apparent improvement in survival observed in those having undergone resection may be an artefact of lead time bias. Early detection would lead to an apparent increase in survival compared with subjects detected clinically at a more advanced stage of disease. Furthermore, length-biased sampling may occur as prevalence studies are more likely to detect the slow growing tumours, which will have a better prognosis than faster growing tumours; small cell tumours were notably of low prevalence in the study.

These reservations were confirmed by the results of the incidence studies. A much higher proportion of rapidly growing cancers was found, often diagnosed by investigations made outside of the study. Squamous cell carcinomas contributed only a third of tumours detected within the screening programme [14]. Sputum cytology was useful in diagnosis in a mere 16% of cases in the Sloan-Kettering study, which concluded that this investigation was of no additional value to a radiological screening programme.

In the Mayo study however, comparing 4 monthly screening with their normal medical practice of annual clinic visits with a radiograph, a greater number of cancers were detected and resected in the 4 monthly screened group than in the control group (94 vs 51). These subjects did very well with 5 yr survival being far superior to those presenting with symptoms. Only 44% of the cancers in the screened group were detected by scheduled screening investigations, the remainder presenting with symptoms or clinical signs. The number of unresectable cancers, therefore, was the same in both groups and the overall mortality rates from lung cancer did not differ between the screened and control groups [15]. These results suggest a continuing length-biased sampling effect with slow growing tumours present clinically at an unresectable stage regardless of screening procedures.

The studies discussed above have investigated dissimilar population groups making comparisons difficult which may have obscured some value of screening. The Erfurt study included all males over the age of 15 yrs in a 10 yr follow-up. Few of these younger subjects would be likely to develop lung cancer, which biases the study against showing an overall improvement in mortality for the entire study population. The Sloan-Kettering and Johns Hopkins studies included volunteers, who are not representative of the general population and not strictly comparable with the Mayo or Erfurt studies. The Mayo subjects were already involved in medical outpatients follow-up and were further selected for the incidence study when subjects with poor lung function or limited life expectancy were excluded. The results from these populations cannot be extrapolated to more general population groups.

Screening programmes for all male smokers or even those over 45 yrs of age have not proved to be a mortality benefit, but screening smaller populations particularly at risk might produce greater benefit. The prevalence of lung cancer increases with age from less than 5:1000 in the 45–55 yr age group to 20:1000 for the over 65 yr old [16, 17] and screening the elderly should produce more positive results. Unfortunately some subjects in this group are less able to tolerate surgery for reasons of age and concomitant illness. Slow growing tumours in such subjects may not be the cause of death and early diagnosis may produce increased anxiety about a condition for which no curative treatment is possible. Although surgical resection in the young offers the most improved life expectancy this group will have a relatively low detection rate making screening less cost effective.

This final consideration of health economics is important. The Philadelphia and Erfurt studies suggest that a maximum interval of 6 months between screening might be required to prove effective. Enormous resources of administration would be needed to recall subjects for review and to ensure prompt investigation of abnormal or equivocal results. Each positive or equivocal test would then require immediate further investigation to establish a diagnosis followed by appropriate surgical referral if the lessons of the Philadelphia study are to be learnt. In the AJCC study [17] 11% of the prevalence study radiographs required further investigations with only 2% of these subjects having a final diagnosis of cancer. Thus, for every true positive test many subjects with equivocal screens underwent unnecessary investigation with considerable accompanying anxiety. Such resources would have to be competed for with established preventative care measures within a finite health budget.

To the question “is screening for lung cancer meaningful?”, the answer must currently be no. Slow growing tumours may well present at a resectable stage within the bounds of usual clinical practice whereas the relatively rapid doubling time of most lung cancers means that currently available screening methods are unlikely to be effective in reducing population mortality from this condition.

References