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Best evidence topic - Thoracic general

Does lung cancer screening with chest X-ray improve disease-free survival?

Ian Hunt[a,*], Mayooran Siva[a], Rachel Southon[b], Tom Treasure[a]

[a]*Department of Cardiothoracic Surgery Centre, Guy's Hospital, St Thomas Street, London, SE1 7EH, UK*
[b]*Information Scientist, Royal College of Surgeons of England, Lincolns Inn Fields, London, UK*

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Summary

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was whether screening an asymptomatic person with a routine chest X-ray would detect lung cancer early and, most importantly, improve that person's disease-free survival from lung cancer. Altogether 136 papers were identified using the search below. Ten papers presented the best evidence to answer the clinical question. The author, journal, date and country of publication, patient group studied, study type, relevant outcomes, results, and study weaknesses of the papers are tabulated. We conclude that despite methodological criticisms and concerns regarding biases inherent to screening studies, there is currently no evidence to support the use of chest X-ray to screen an asymptomatic person for lung cancer.

Keywords: Evidence-based medicine; Lung neoplasms; Mass screening; Tomography

1. Introduction

A best evidence topic was constructed according to a structured protocol. This protocol is fully described in the ICVTS [1].

2. Clinical scenario

You are a chest registrar seeing a 55-year-old patient in a rapid access out-patient clinic who has recently presented with cough and hemopytsis. He is a smoker and had these symptoms for just a few weeks before being sent for a chest X-ray. It shows a large lesion in the right upper zone. The patient suspects he has lung cancer, which he probably does. He wants to know why he could not have had a chest X-ray before he was sick to pick up his lung cancer.

3. Three part question

In (asymptomatic patients with risk factors for lung cancer) is the use of (Chest X-ray) of benefit in terms of (improved disease-free survival).

4. Search strategy

Medline 1966 – Feb 2006 and Embase 1980 – Feb 2006 using the Dialog Datastar interface [Lung-Neoplasms#.DE. OR Lung-Tumor#.DE. OR (Lung NEAR (Neoplasm$ OR Cancer$ OR Carcinoma$ OR Adenocarcinoma$ OR Angiosarcoma$ OR Chrondosarcoma$ OR Sarcoma$ OR Teratoma$ OR Lymphoma$ OR Blastoma$ OR Microcytic$ OR Carcinogenesis OR Tumor$ OR Tumour$ OR Metast$4)).TI,AB. OR NSCLC.TI,AB. OR SCLC.TI,AB.] AND [Mass-Screening.DE. OR Cancer-Screening.DE. OR (Screen$3 OR Case ADJ Finding OR Casefinding OR Case-Finding).TI,AB.] AND [Radiography-Toracic.DE. OR Mass-Chest-X-Ray.DE. OR Tomography-X-Ray.DE. OR Thorax-Radiography.DE. OR X-Ray.DE.] OR ((Chest OR Thoracic) NEAR (X ADJ Ray$ OR X-Ray$)).TI,AB.] limit to English. This search was repeated in Cochrane Central Register of Controlled Trials.

5. Search outcome

A total of 136 papers were found of which 10 were deemed to be relevant. Only Randomised Control Trials (RCTs) or reviews of RCTs were included. Several systematic reviews and Guidelines for screening were reviewed including the most recent and only meta-analysis on chest X-ray screening. The same group has subsequently updated its previous Cochrane review. The individual randomised trials are presented with the subsequent meta-analysis (Table 1).

6. Comments

The trials reviewed included only male current smokers over 40–45 years of age, and generally assessed more intense screening with chest X-ray ± sputum cytology versus less intense chest X-ray screening. Typically the studies

*Corresponding author. Tel.: +44 207 928 203; fax: +44 207 188 7703.
E-mail address: ian.hunt@gstt.nhs.uk (I. Hunt).

Table 1
Summary of best evidence topics

Author, Date & Country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
Brett GZ, North London Study, 1960–1964 UK [2]	$N=55034$ Males ≥ 40 Smokers and non-smokers	Cluster RCT	Resectability of patients with lung cancer	6 monthly CXR (I) 29% versus CXR at entry and exit of study (C) 44%	Limitation of screening biases
			Disease-specific 5-year survival	5-year survival of patients with lung cancer for intervention 15% over control group 6%	Comparison is between intensive versus less intensive screening patients
			Lung cancer mortality in population per 1000 patients/year	No benefit shown between intervention (0.7) over control group (0.8) RR (screen group/control) was 1.03 (95% CI, 0.74–1.42)	
Wilde J, Erfurt County Study, 1972–1977 Germany [3]	$N=104880$ Males aged 40–65 years Smokers and non-smokers	Cluster RCT	Resectability of patients with lung cancer	6 monthly CXR (I) 28% vs. 18 monthly CXR (C) 19%	Limitation of screening biases
			Disease-specific 5-year survival	5-year survival of patients with lung cancer for intervention 14% over control group 8%	Compliance with scheduled screening was not described in detail
			Lung cancer mortality in population per 1000 patients/year	No benefit shown between intervention (0.6) over control group (0.8) RR (screen group/control) was 1.34 (95% CI, 0.94–1.98)	
Frost JK, Johns Hopkins Study, 1973–1978 USA [4]	$N=10384$ Males 45	RCT	Lung cancer detection rate in population per 1000 patients/year	Annual CXR and 4 monthly sputum 4.8 versus annual CXR 5.5	Comparison is between intensive versus less intensive screening patients
			Resectability of patients with lung cancer	Annual CXR & 4-monthly sputum (I) 4.8% versus annual CXR (C) 5.5%	Adherence to strict protocol was poor
			Disease-specific 5-year survival	5-year survival of patients with lung cancer for intervention 47% over control group 44%	
			Lung cancer mortality in population per 1000 patients /year	No benefit shown between intervention (0.6) over control group (0.8) RR (screen group/control) was 0.80 (95% CI, 0.65–1.00)	
Mayo Lung Project, 1971–1976 USA [5,6]	$N=10933$ Males ≥ 45 Heavy smokers	RCT	Lung cancer detection rate in population per 1000 patients/year	4 monthly CXR and sputum 4.5 versus advised annual CXR and sputum 3.5	Lung cancer mortality is higher in intervention group compared to control group due to possible over diagnosis bias
			Resectability of patients with lung cancer	4-monthly CXR and sputum (I) 4.5% versus annual CXR and sputum (C) 3.5%	Comparison is between intensive versus less intensive screening patients
			Disease-specific 5-year	5-year survival of patients with lung cancer for	

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Table 1 *(Continued)*

Author, Date & Country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
			survival	intervention 46% over control group 32%	
			Lung cancer mortality in population per 1000 patients /year	No benefit shown between intervention (3.2) over control group (3.0) RR (screen group/control) was 1.11 (95% CI, 0.95–1.28)	
Memorial Sloan-Kettering Study, 1974–1978 USA [7,8]	$N=10040$ Age >45 years old Smokers	RCT	Resectability of patients with lung cancer	Annual CXR and sputum (I) 53% versus annual CXR (C) 51%	
			Disease-specific 5-year survival	5-year survival of patients with lung cancer for intervention 37% over control group 33%	
			Lung cancer mortality in population per 1000 patients /year	No benefit shown between intervention (2.7) over control group (2.7) RR (screen group/control) was 0.98 (95% CI, 0.76–1.26)	
Czech Study, 1976–1982, Czechoslovakia [9]	$N=6364$ Males aged 40–64 years	RCT	Resectability of patients with lung cancer	6-monthly CXR years 1, 2, 4 and annual CXR years 4, 5, 6 (I) 25% versus CXR years 4, 5, 6 (C) 16%	No unscreened control group
	Current heavy smokers		Disease-specific 5-year survival	5-year survival of patients with lung cancer for intervention 26% over control group 0%	
			Lung cancer mortality in population per 1000 patients /year	No benefit shown between intervention (1.7) over control group (1.5) RR (screen group/control) was 1.14 (95% CI, 0.96–1.36)	
Manser RL, 2003 and 2004, Australia [10,11]	$N=245$ 610 Age >40 years old	A systematic review and meta-analysis of controlled trials	Lung cancer mortality was significantly greater in the group undergoing more frequent CXR than in those receiving less frequent screening ($P=0.05$)	More frequent CXR screening was associated with an 11% relative increase in mortality over less frequent screening (RR 1.11, 95% CI, 1.00 to 1.23) A non-statistically trend to reduced mortality from lung cancer was observed when screening with CXR and sputum cytology was compared to CXR alone (RR 0.88, 95% CI 0.74 to 1.03)	Most of the trials reviewed excluded women, young patients <45 years old and ex-smokers
ACCP guidelines, 2003, USA [12,13]	Review of 5 RCTs comparing CXR$\pm$ sputum cytology versus control	Non-systematic review	Prolong life expectancy of individual with disease	Neither CXR and/or sputum was of benefit	Review not systematic with no further statistical analysis
			Test not harmful or painful	Not addressed in sufficient detail in any of the studies reviewed	

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Table 1 *(Continued)*

Author, Date & Country	Patient group	Study type (level of evidence)	Outcomes	Key results	Study weaknesses
US Preventive Services Task Force, USPSTF 2004, USA, [14]	Systematic review & guideline of 6 RCTs and 1 non-RCT comparing CXR ± sputum cytology versus control having searched Medline from 1966 to 2003	Systematic review and guideline	Studies were graded according to criteria developed by USPSTF (see ref.)	None of the 6 CXR ± sputum cytology RCTs showed benefit among those screened All studies were limited because some level of screening occurred in control group 4 control-studies from Japan suggested benefit to both high and low-risk participants, with screening using CXR ± sputum cytology occurring within 1 year of diagnosis, OR range 0.4–0.72	
Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) trial report of baseline screen, 2005, USA, [15]	154942 participants, aged 55–74 years with no history of PLCO cancer, randomly assigned to an intervention arm (77465)	RCT, baseline screen report	Number of initial suspicious CXR	8.9% (9.5% CI = 8.7%–9.2%) (N = 5991) CXRS suspicious for Lung cancer, 206 (3.4%, 95% CI = 3–3.9%) biopsies, 126 (61.2%, 95% CI = 54.5–67.8%) diagnosed with lung cancer	Baseline report of large RCT with no further survival data available currently
			Number of lung cancers detected per 1000 screens	1.9 lung cancers were detected per 1000 screens, with positive predictive value 2.1% (95% CI = 1.7–2.5%)	
			Number of lung cancers detected per 1000 screens of smokers or ex-smokers	6.3 lung cancers were detected per 1000 screens, amongst current smoker; and 4.9 per 1000 screens amongst ex-smokers (less than 15 years)	
			Detection of early stage lung cancer	Among cancers diagnosed, 44% (95% CI = 35–52%) were stage I NSCLC	

(RCT = randomised controlled trial; I = intervention; C = Control group; RR = relative risks; CI = confidence interval; OR = Odds Ratio; Chest X-ray = CXR; NSCLC = Non-Small Cell Lung Carcinoma).

tended to show a higher incidence of lung cancer, a higher rate of surgical resection and a better survival in the more intensely screened groups. However, overall there appeared to be no significant reduction in mortality from lung cancer in the intense screening group compared to the less intense screened group. In fact, the subsequent meta-analysis [10] demonstrated that more frequent chest X-ray screening was associated with an 11% relative increase in mortality over less frequent screening. A non-statistically trend to reduced mortality from lung cancer was observed when screening with chest X-ray and sputum cytology was compared to chest X-ray alone (RR 0.88, 95% CI 0.74 to 1.03) [10,14].

The methodology of all the screening studies has been questioned. Criticisms include under-powering of the studies to detect a significant reduction in lung cancer mortality between the groups and adherence to study protocol. Others issues related to biases inherent to screening trials have been suggested to account for this apparent disparity. For example in the Mayo Lung project [6] rates of early tumours in the intense screening group were increased compared to the control group, without altering numbers of advanced cancers detected or mortality rates. This may reflect the fact that intense screening is diagnosing indolent tumours. This is referred to as an over-diagnosis bias, the detection of cancers that would not have become clinically apparent before that person died of other causes.

As well as overdiagnosis bias screening studies may be flawed by other biases; Lead-time bias is where early diagnosis in a screen-detected lung cancer patient falsely appears to prolong survival, despite the actual course of the disease ending in mortality, is the same whether you screen or not. Length bias refers to overestimation of survival duration among screening-detected lung cancer

caused by the relative excess of slowly progressing cases. Screening over-represents less aggressive disease. Thus, a comparison between screen-detected lung cancer and others detected by the person developing symptoms or signs appears to overestimate benefit because the former consists of cases that were diagnosed earlier, progress more slowly, and may never become clinically relevant. Such biases all appear to inflate the survival of screen-detected cases

7. Clinical bottom line

The current evidence does not support the use of chest X-ray (with or without sputum cytology) as a screening test for lung cancer.

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