7 Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? *Gastroenterology* 2000;119:333-8.
8 Woloshin S, Schwartz LM, Welch HG. Risk charts: putting cancer in context. *J Natl Cancer Inst* 2002;94:799-804.
9 Fennerty MB, Triadafilopoulos G. Barrett's-related esophageal adenocarcinoma: is chemoprevention a potential option? *Am J Gastroenterol* 2001;96:2302-5.
10 Sampliner RE and The Practice Parameters Committee of the American College of Gastroenterology. Updated guidelines for the diagnosis, surveillance, and therapy of Barrett's esophagus. *Am J Gastroenterol* 2002;97:1888-95.
11 Corley DA, Levin TR, Habel LA, Weiss NS, Buffler PA. Surveillance and survival in Barrett's adenocarcinomas: a population-based study. *Gastroenterology* 2002;122:633-40.
12 Provenzale D, Schmitt C, Wong JB. Barrett's esophagus: a new look at surveillance based on emerging estimates of cancer risk. *Am J Gastroenterol* 1999;94:2043-53.
13 Inadomi JM, Sampliner R, Lagergren J, Lieberman D, Fendrick AM, Vakil N. Screening and surveillance for Barrett esophagus in high-risk groups: a cost-utility analysis. *Ann Intern Med* 2003;138:176-86.

Screening for cancer with computed tomography

Advising patients is difficult given the lack of evidence

Whole body screening with computed tomography is the focus of a major advertising campaign in the United States. Enticing testimonials on billboards and radio spots urge the public to use this technology, implying that there is much to gain and little to lose. How should primary care doctors advise their patients?

In one sense screening with computed tomography has much to offer. As part of a study conducted by the National Institutes of Health, our centre has used computed tomography to screen for lung cancer for the past four years and has identified 56 lung cancers. Fully 62% of the non-small cell cancers were stage IA.[1] In the absence of screening, only 15-20% of lung cancers present at stage IA. Five year survival for stage I lung cancers, which is about 60-70%, is higher than for cancers diagnosed at more advanced stages. There is little doubt that computed tomography is more sensitive than chest *x* ray in detecting small, early stage lung cancers. We found two cancers measuring only 3 mm in diameter.

Recognising that we found 56 patients with lung cancer, one could ask why screening should not be advocated. Why wait until patients develop symptoms and later stage disease? Screening could potentially save hundreds of thousands of lives in just a few years. Several uncertainties, however, make it premature to advocate screening on a large scale with computed tomography.

Some lung cancers may progress too rapidly. Although computed tomography certainly achieves earlier detection, biological destiny may render this value moot. Angiogenesis occurs at 1-2 mm for many tumours,[2–5] and we do not know how early metastasis occurs.

Other lung cancers may progress too slowly. Over diagnosis of cancers that pose little or no clinical threat to the patient (pseudo disease) may be a confounding factor. We are finding more early stage lung cancers, but the more pivotal question is whether we will change the incidence of advanced stage tumours. If, for example, screening detects cancer in the same proportions among smokers and never smokers, it may be detecting lesions that patients would die with rather than from.[6]

The false positive rate of screening may be too high. In our series, over 70% of participants had a false positive finding for lung cancer. Fully 98% of uncalcified lung nodules were benign. There are more than 90 million current and past smokers in the United States. Extrapolating our findings to this high risk population indicates that screening would identify more than 180 million uncalcified, radiologically indeterminate nodules.

Investigating lesions detected at screening may be harmful. The mortality associated with surgery for benign nodules may offset the gains in disease specific mortality achieved by screening. Multicentre studies in the United States and Europe show that about 50% of lung nodules removed at surgery are benign,[7 8] but wedge resections of lung nodules (benign or malignant) carry a mortality of 3.8% at community hospitals in the United States.[9] Radiation exposure associated with follow up examinations might induce more deaths due to cancer than are prevented. The first duty of medicine is to do no harm.

The cost of screening may be too high. By some estimates, screening would cost $116 300 (£74 456; €107 002) to $2.3m per quality adjusted life year gained.[10]

High risk patients, the cohort most likely to benefit from screening, are at risk for comorbid illness. The benefits of early detection may be lost in smokers, who are arguably more likely to die from stroke, heart disease, or obstructive lung disease.

Whole body screening with computed tomography engages the same issues on a larger scale. In our cohort we found over 700 ancillary findings, including four renal cell carcinomas, three breast cancers, two lymphomas, two gastric tumours, one pheochromocytoma, and 114 abdominal aortic aneurysms.[1] However, most of these ancillary findings were falsely positive, the investigation of which adversely affected quality of life and resulted in unnecessary diagnostic and interventional procedures.

Although important scientific questions must be answered to know whether screening of the lung or the whole body with computed tomography results in more good than harm, it is unclear whether either the public or the marketers are willing to wait. A search of the internet will show hundreds of facilities offering screening with computed tomography from coast to coast.

Some of the best doctors in the world have sincere differences of opinion about the merits of such screening. This balance in opinion, which ethicists call equipoise, provides the ideal context for conducting a

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trial. The National Cancer Institute has launched the national lung screening trial, a controlled study of 50 000 people that randomises participants to chest screening by computed tomography or *x* ray and uses mortality as an end point. It is the right way to address this issue, but it could take a decade to produce an answer.

How should patients, especially those who smoke, be advised in the meantime? After providing counselling for nicotine dependence doctors could suggest that patients enrol in the national lung screening trial or similar trials. If patients simply want to get scanned, doctors should take the time to discuss the pros and cons. Doctors without financial conflicts of interest are best positioned to give balanced informed consent. As patients' fiduciary, doctors should tell patients in explicit terms that such screening has no proved benefit and that serious risks could outweigh benefits (if there are any). Patients should understand that the stakes are high.

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1 Swensen SJ, Jett JR, Hartman TE, Midthun DE, Sloan JA, Sykes AM, et al. Lung cancer screening with CT: Mayo clinic experience. *Radiology* 2003;226:756-61.
2 Yang M, Hasegawa S, Jiang P, Wang X, Tan Y, Chishima T. Widespread skeletal metastatic potential of human lung cancer revealed by green fluorescent protein expression. *Cancer Res* 1998;58:4217-21.
3 Folkman J. Seminars in medicine of the Beth Israel Hospital, Boston. Clinical applications of research on angiogenesis. *N Engl J Med* 1995;333:1757-63.
4 Rak JW, St Croix BD, Kerbel RS. Consequences of angiogenesis for tumor progression, metastasis and cancer therapy. *Anticancer Drugs* 1995;6:3-18.
5 Liotta LA, Kleinerman J, Saidel GM. Quantitative relationships of intravascular tumor cells, tumor vessels, and pulmonary metastases following tumor implantation. *Cancer Res* 1974;34:997-1004.
6 Sone S, Takashima S, Li F, Yang Z, Honda T, Maruyama Y, et al. Mass screening for lung cancer with mobile spiral computed tomography scanner. *Lancet* 1998;351:1242-5.
7 Bernard A. Resection of pulmonary nodules using video-assisted thoracic surgery. The Thorax Group. *Ann Thorac Surg* 1996:61;202-4.
8 Mack MJ, Hazelrigg SR, Landreneau RJ, Acuff TE. Thoracoscopy for the diagnosis of the indeterminate solitary pulmonary nodule. *Ann Thorac Surg* 1993;56:825-30.
9 Romano PS, Mark DH. Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. *Chest* 1992;101:1332-7.
10 Mahadevia PJ, Fleisher LA, Frick KD, Eng J, Goodman SN, Powe NR. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. *JAMA* 2003;289: 313-22.

Failures of the therapeutic chain as a cause of drug ineffectiveness

Promotion, misinformation, and economics work better than needs

Failure of drug treatment may be due to wrong diagnosis, selection of an inappropriate drug or dosage, use of an adulterated or fake drug, the patient's non-adherence, a drug's poor bioavailability or lack of efficacy, medication error, or occurrence of an adverse reaction. The potential causes of therapeutic failure depend on a complex interplay of social and medical factors. Failures can occur at every step of the therapeutic chain, which is the process describing the life of medicines in a community. This process includes development, regulation (including registration), marketing, distribution, prescription, dispensing, and use of the drug.[1]

The following are only some examples of failures in drug treatment. In 2001 the top five best selling medicines globally were atorvastatin, omeprazole, simvastatin, lansoprazole, and amlodipine, although available evidence indicates that only two of these drugs are first choice in their class. In recent years, various non-essential non-innovative drugs had to be withdrawn from the market because of serious adverse effects after a few years of growth in sales. One of these drugs, troglitazone, was associated with a risk of liver failure, which had been played down by the manufacturing company.[2] More recently, serious flaws in the published pivotal trial that served as the basis for the global promotion of celecoxib were made public,[3] and alosetron was reapproved by FDA amid accusations that the FDA had become a servant of the drug industry.[4]

Prescription patterns are far from optimal. Although evidence supports thiazide diuretics as the treatment of first choice of hypertension, angiotensin converting enzyme inhibitors and calcium channel blockers are the most consumed antihypertensive drugs. Although in multiple sclerosis azathioprine is backed by better evidence of long term efficacy and (perhaps because) it is 125 times cheaper than interferon beta, interferon beta is the preferred treatment in many specialised centres.[5] In the United States adverse drug effects rank fourth to sixth in the list of causes of death.[6] Ineffective drugs, such as cinnarizine or bovine gangliosides, have been identified in clinical trials and voluntary reporting systems as causes of serious adverse effects.[7 8]

How are these and many other failures possible? Firstly, the methods and objectives of medical research are driven mainly by industrial priorities and the fulfilment of regulatory requirements, rather than by a conceptual framework that aims to answer questions that arise in medical practice. Clinical trials are designed to evaluate drugs rather than patients or diseases.

Secondly, the term efficacy is merely a higher probability of clinical improvement, compared with placebo, in selected end points that may have varying clinical relevance. The implication is that in practice therapeutic failure is, and should be, common. In addition, efficacy does not necessarily translate into effectiveness in usual practice.[9]

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