Early detection for lung cancer

New tools for casefinding

Stephen Lam, MD, FRCPC, FCCP Bing Lam, MB, MRCP Thomas L. Petty, MD, FCCP

abstract

OBJECTIVE To review data from published population trials and clinical practice guidelines on screening for lung cancer to provide a recommendation for early detection of lung cancer.

QUALITY OF EVIDENCE Literature was searched via MEDLINE using the MeSH headings "lung neoplasm," "mass screening," "thoracic radiography," and "sputum." Only prospective randomized controlled trials with large numbers of subjects were selected.

MAIN MESSAGE Risk of lung cancer among long-term heavy smokers continues even years after stopping smoking. Risk is highest in smokers with chronic obstructive pulmonary disease. Canadian clinical practice guidelines currently recommend that sputum cytology examination and chest radiography (CXR) not be used for lung cancer screening. This guideline was deducted from four randomized population trials in the 1970s that have serious limitations and applies to *asymptomatic* adults only. A CXR and sputum cytology examination are indicated in symptomatic current and former smokers older than 45 years with a smoking history of 30 pack-years or more and airflow obstruction defined as a forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) of 70% or less and a FEV_1 lower than 70%. Curative treatment is available for early lung cancer. Substantial advances in innovative technologies for early detection using low-dose spiral CT and newer sputum tests have been made in the last three decades. Additional studies are under way to evaluate these new technologies.

CONCLUSION Primary care physicians have an important role in identifying people at risk of developing lung cancer and in supporting research to evaluate new screening technology.

résumé

OBJECTIF Examiner les données publiées, tirées d'essais sur la population et de guides de pratique clinique sur le dépistage du cancer du poumon, en vue de dégager une recommandation concernant la détection précoce de cette affection.

QUALITÉ DES DONNÉES Une recension des ouvrages scientifiques a été réalisée dans MEDLINE à l'aide des rubriques MeSH en anglais pour «néoplasme pulmonaire», «dépistage systématique», «radiographie thoracique» et «expectorations». Seules les études prospectives aléatoires contrôlées comportant un grand nombre de sujets ont été retenues.

PRINCIPAL MESSAGE Le risque de cancer du poumon chez les gros fumeurs de longue date persiste même pendant des années après qu'ils ont cessé de fumer. Le risque est le plus élevé chez les fumeurs souffrant de bronchopneumopathie chronique obstructive. Les guides de pratique canadiens recommandent actuellement de ne pas procéder à un examen cytologique des expectorations ni à une radiographie thoracique aux fins de dépistage du cancer du poumon. Cette ligne directive se fonde sur quatre essais aléatoires dans la population réalisés au cours des années 1970 et qui comportaient de sérieuses limites, et elle ne s'applique qu'aux adultes *asymptomatiques*. Une radiographie thoracique et un examen cytologique des expectorations se révèlent indiqués dans le cas d'actuels et anciens fumeurs symptomatiques de plus de 45 ans qui ont des antécédents de 30 ans ou plus de tabagisme à raison d'un paquet par jour et une obstruction des voies respiratoires définie comme étant un rapport entre le volume expiratoire maximal par seconde et la capacité vitale forcée (VEMS/CVF) de 70% ou moins, et un VEMS de moins de 70%. Des traitements curatifs sont disponibles pour les stades initiaux du cancer du poumon. Des progrès considérables ont été réalisés au cours des trois dernières décennies dans des technologies novatrices aux fins de détection précoce à l'aide de la scanographie spiralée à faible dose et de toutes nouvelles épreuves sur les expectorations. Des études additionnelles sont entreprises présentement pour évaluer ces nouvelles technologies.

CONCLUSION Les médecins de première ligne jouent un rôle important dans l'identification des personnes à risque de développer un cancer du poumon et dans l'appui à la recherche en vue d'évaluer les nouvelles techniques de dépistage.

This article has been peer reviewed.

Cet article a fait l'objet d'une évaluation externe.

Can Fam Physician 2001;47:537-544.

CME

Early detection for lung cancer

Lung cancer is the most common cause of cancer death in North America. More patients die from lung cancer than breast cancer, colorectal cancer, and prostate cancer combined.[1] Overall 5-year survival of lung cancer patients is 14%.[1] The primary reason for such a dismal cure rate is that nearly all lung cancers are found at a very late stage, making curative treatment impossible.

As presence of symptoms usually indicates advanced disease, a potentially more effective way to improve outcomes is to detect the cancer when curative treatment, such as surgery, can be applied. Early detection has been shown to improve survival in patients with cancer of the cervix and breast. Can a similar strategy be applied to lung cancer control?

Quality of evidence

A MEDLINE search from 1980 to 1999 was conducted using the MeSH headings "lung neoplasm," "mass screening," "thoracic radiography," and "sputum." The search was limited to English-language articles. Only prospective randomized controlled trials (RCTs) with large numbers of subjects were selected.

Previous screening studies

A total of 37 724 male cigarette smokers participated in four randomized population trials on lung cancer screening, all of which were initiated in the mid-1970s. These studies were conducted at Memorial Sloan-Kettering Cancer Center,[2] Johns Hopkins University,[3] and the Mayo Clinic,[4] and in Czechoslovakia.[5]

The Memorial[2] and Hopkins[3] studies had identical designs. Lung cancer detection rates using annual chest radiography (CXR) alone and annual CXR plus sputum cytology examination every 4 months were compared. There was no significant difference in lung cancer mortality when sputum cytology examination was added to annual CXR. However, the proportion of patients with early stage lung cancer (stages I and II) and 5-year survival was approximately threefold higher than that predicted by contemporary national statistics.

Dr S. Lam *is a Professor of Medicine, and* **Dr B. Lam** *was a Clinical Fellow, in the Department of Medicine at the University of British Columbia when this article was written.* **Dr B. Lam** *is now a Medical Officer at Queen Mary Hospital in Hong Kong.* **Dr Petty** *is a Professor of Medicine at the University of Colorado Health Sciences Centre and is Chairman of the National Lung Health Education Program.*

In the Mayo Lung Project,[4] following a prevalence screen with CXR and sputum cytology, participants were randomized to an experimental group undergoing CXR and sputum cytology every 4 months or to a control group that was not regularly screened. However, those in the control group were recommended to have annual CXR, standard practice at the Mayo Clinic at that time. During the study, 73% of the control subjects received CXR. The stage distribution, resectability, and 5-year survival were significantly better in the screened group, but there was no difference in mortality rate, even on extended follow up.[6]

In the Czechoslovakian study,[5] following prevalence screening with CXR and sputum cytology examination, participants were randomized to a screened group, who underwent CXR and sputum cytology every 6 months for 3 years or to a control group, who underwent no screening until the end of the third year, when CXR and sputum cytology were performed again. Then both groups received CXR at the end of the fourth, fifth, and sixth years. There were significantly more early, resectable lung cancers in the screened group. The 5-year survival was 23% in the study group versus 0% in the control group. However, similar to the Mayo Lung Project,[4] there was no significant difference in mortality rate between the two groups.

These studies have several limitations. All studied men only. They might not apply to the current situation, where incidence of lung cancer is rising rapidly among women and decreasing among men. The Memorial and Hopkins studies could evaluate only the incremental effect of sputum cytology to an annual CXR. The conclusion one can draw from these two studies is that sputum cytology, as practised in the early 1970s, did not meet the expectation that it could be the Pap test equivalent for lung cancer.

Both the Mayo and Czechoslovakian studies had a prevalence screen before randomization into screened and control groups. In other words, even those who were subsequently randomized to the control group received at least one screening. In addition, the control group in the Mayo study was heavily contaminated in that 73% of the subjects had CXR by self-request or ordered by a referring physician during the course of the study. In the Czechoslovakian study, the control group was screened again at the end of the third year. Therefore, there was no "unscreened" control group in either study.

One can at best conclude from the Mayo study that, following initial screening with CXR and sputum cytology, CXR and sputum cytology examinations every

4 months for 5 years did not reduce lung cancer mortality compared with CXR alone some time during those 5 years. In the Czechoslovakian study, an alternative interpretation would be that CXR and sputum cytology every 3 years was as effective as having these examinations every 6 months. The potential usefulness of CXR in lung cancer screening is being evaluated in the large US Prostate, Lung, Colon, and Ovary (PLCO) trial. This trial has adequate power to demonstrate a 20% reduction in mortality from lung cancer.[7]

The lesson that can be learned from these four randomized clinical trials is that, if one uses a detection method that has low sensitivity for early, curable lung cancer, it would not affect lung cancer mortality substantially whether one applies these tests frequently every few months or once every 1 to 3 years.

High-risk groups

Fewer than 20% of people who smoke develop lung cancer in their lifetime. In order to maximize the effectiveness of screening, one needs to define the population at the greatest risk. Lung cancer is uncommon among those who are younger than 45 years of age. Incidence rises sharply after age 50. The risk of lung cancer is higher among those who started smoking early (younger than 15 years) and among those who smoke longer and more heavily (eg, one pack of cigarettes or more daily for 30 years or longer). Those who give up smoking later on in life (eg, after age 50) retain a significant risk.[8] Currently, approximately 50% of patients diagnosed with lung cancer are former smokers; a large proportion has given up smoking for 5 years or more.[9,10] Women are more susceptible to lung cancer than men smoking the same amount of tobacco.[11]

Besides age, sex, and smoking history, there is an association between lung cancer and chronic obstructive pulmonary disease (COPD).[12] The association of airflow obstruction and lung cancer is stronger in men than in women.[13] The Lung Health Study evaluated 5887 relatively young (mean age 48 years) smokers with airflow obstructions (forced expiratory volume in 1 second/forced vital capacity [FEV_1/FVC] of 70% or less). At the end of 5 years, the most common cause of death in this group was lung cancer.[14] The latest figure showed that 3.9% of this largely middle-aged population have developed lung cancer (personal communication from John E. Connett, 1999). Recent studies in patients undergoing lung volume reduction surgery for severe pulmonary emphysema showed a lung cancer prevalence of up to 5%.[15] Other factors that increase risk of lung cancer include a family history of lung cancer; occupational exposure to asbestos, nickel, chromium, chloromethyl ethers, polycyclic aromatic hydrocarbons, or radioactive isotopes; and air pollution.

Recent advances in early detection methods

Sputum cytology examination. Using two 3-day pooled sputum specimens and a standardized processing method, a recent study in Denver, Colo, evaluated a group of high-risk patients (defined as 40 pack-years of smoking, FEV_1/FVC ratio of 70% or less, and a FEV_1 of less than 70% predicted).[16] In 533 subjects, preinvasive lung cancer (carcinoma in situ, stage 0) was found in 1.2% and stage I lung cancer in another 0.6%. These figures are considerably higher than those currently obtained by cytologic screening for cervical cancer and screening mammography for breast cancer, which are about 0.3% to 0.8%. Computer-assisted image analysis of sputum cells,[17] immunostaining using tumour markers,[18] and molecular analysis based on polymerase chain reactions[19] could further improve the detection rate of early lung cancer. Sputum detection methods have the advantage of being the only noninvasive methods that can detect preinvasive lung cancer.

Fluorescence bronchoscopy. Finding abnormal cells in sputum cytology examinations does not tell us where the cells originate. Approximately 10% of patients with negative CXR films and malignant cells in their sputum cytology specimens have cancer in the upper respiratory tract. A careful otolaryngologic examination should be performed along with bronchoscopy.

Carcinoma in situ and microinvasive cancers present a challenging diagnostic problem, even for experienced bronchoscopists. These cancers are only a few cell layers thick (0.2 to 1.0 mm) and a few millimetres in surface diameter. Because of this, the lesions sometimes do not produce any visible abnormality on conventional white-light bronchoscopy. In a study by Woolner,[20] in situ carcinomas were visible bronchoscopically in less than 30% of cases. If no lesion is found on white-light examination, repeat bronchoscopy with multiple brushings and biopsies must be performed for localization.

A new development in bronchoscopic localization of atypical or malignant cells found in expectorated sputum is fluorescence bronchoscopy.[21] When the bronchial surface is illuminated by light, the light can be reflected, be backscattered, be absorbed, or induce tissue fluorescence. Conventional white-light

bronchoscopy makes use of the first three optical phenomena. Tissue autofluorescence is not visible because the intensity is very low and overwhelmed by the background illuminating light. With suitable use of instruments, however, tissue autofluorescence can be made visible to enhance our ability to localize areas of preinvasive cancer in the tracheobronchial tree. Using the Light Imaging Fluorescence Endoscopic device (LIFE-Lung) originally developed by scientists at the British Columbia Cancer Agency, the detection rate of preinvasive lung cancer was found to improve several times compared with conventional white-light bronchoscopy.[21,22]

Low-dose spiral computed tomography. There are several problems with using CXR for early detection of lung cancer. Observer error is an important issue. In the screening studies described above, analysts found in retrospect that radiographic abnormality had been present many months before the cancers were actually diagnosed in 90% of the peripheral cancers and 65% to 70% of the central cancers.[23,24] Physicians fail to identify lesions most frequently in the upper lobes, particularly in the paramediastinal region of the right upper lobe in the frontal view, and areas covered by spine in the lateral projection.

Recently, low-dose spiral CT of the chest was found to be superior to conventional CXR for detecting peripheral lung cancers among high-risk patients. The Early Lung Cancer Action Project (ELCAP) enrolled 1000 symptom-free volunteers who were 60 years or older and who had at least 10 pack-years of smoking history.[25] Lung cancer was detected in 2.7% by spiral CT versus in 0.7% by CXR. Eighty-one percent of cancers discovered by spiral CT, but only 15% discovered by CXR, were stage IA.[25] The average size of lung cancers detected by spiral CT is approximately 1 cm compared with 3 cm by CXR.[26] Additional larger-scale studies are under way in the United States, United Kingdom, Germany, and Israel to establish the efficacy and cost-effectiveness of low-dose spiral CT for early lung cancer detection.

When small (<1 cm) lung nodules are found using spiral CT, diagnosis of malignancy can be obtained by follow-up CT, CT-guided needle biopsy, or thoracoscopy. With innovative three-dimensional imaging, even small tumour growth can be quantified by CT, removing the need for biopsy for diagnosis. Other imaging methods, such as electron beam tomography, offer the possibility of detecting coronary artery calcification or osteoporosis as well as early lung cancer, providing additional value for lung cancer screening.

None of the technologies described above were available in the 1970s.

Treatment for early lung cancer

Early detection would not make sense unless curative treatment were available. Effective treatment (such as photodynamic therapy,[27] cryotherapy,[28] YAG [yttrium-aluminum-garnet] laser therapy,[29] and electrocautery[30]) that can eradicate carcinoma in situ and microinvasive lung cancers is now available in addition to surgery.[31] For stage I lung cancer, the Memorial,[2] Hopkins,[3] and Mayo[4] studies showed that approximately 70% of patients treated surgically survived more than 5 years compared with only 2% of those who did not have surgery.[32] The 5-year survival of patients with stage IA lung cancer discovered by spiral CT is even better, more than 80%.[33] Identification and treatment of patients harbouring preinvasive or early invasive lung cancers would therefore have a substantial effect on mortality from lung cancer.

Clinical practice guidelines

In Canada, the Canadian Task Force on the Periodic Health Examination,[34] the British Columbia Council on Clinical Practice Guidelines,[35] and The Saskatchewan Health Services Utilization and Research Commission[36] on selective chest radiography do not recommend CXR for symptom-free adults. It is important to recognize that clinical practice guidelines apply only to symptom-free people. They do not apply to high-risk groups with chest symptoms and patients with COPD. The Saskatchewan Health Services Utilization and Research Commission[37] on selective chest radiography guidelines stated that, although CXR alone cannot diagnose COPD, it is an important part of the diagnostic workup for this condition and of documenting its course. Maintaining a record of baseline and subsequent films for comparison was also thought to be helpful.[37] Making previous CXR films available for comparison is one of the cheapest ways to diagnose lung cancer when an abnormality is found. Appearance of a new density or increased size of an existing density suggest a high probability of lung cancer.

Medical practice varies from country to country. In contrast to Canadian clinical practice guidelines, periodic CXR and sputum cytology examination in heavy smokers have been the standard of care in Japan for more than two decades. These services are funded by Japan's public health care system. Recently, mobile spiral CT scanners have been used to assess high-risk patients in rural Japan.[38]

Evaluation of new evidence

Whether RCTs using lung cancer mortality as the end point are the only method for evaluating the effectiveness of new technologies for lung cancer was hotly debated at several recent international conferences.[33,39-42] Some experts propose instead a single-arm study using stage shift and improvement in survival as the end point. They argue whether one can ethically obtain informed consent to enrol people into clinical trials with the knowledge that a test such as spiral CT is four times as sensitive as CXR and that early lung cancer is highly curable by current therapies.

With increasing privatization of procedures not funded by public health care providers, contamination of the "control" arm and selecting people in lower socioeconomic groups for the study who have different risk profiles and adherence to follow-up instructions could also make the data difficult to interpret.

Furthermore, no RCT on cervical cancer or prostate cancer screening has been performed. Cervical cancer screening with Pap smears has been shown to reduce the incidence and mortality of cervical cancer.[42] The 14% decline in the prostate cancer death rate between 1990 and 1995 is also thought to be related to widespread use of prostate cancer screening based on prostate-specific antigen detection.[43] Given the fact that no substantial improvement in therapy for advanced lung cancer has appeared in the past two decades and that nothing revolutionary is on the horizon, increasing detection and treating disease at an earlier stage might be more realistic end points for evaluating new detection technologies.

Other experts fear, however, that screening might actually cause harm. Diagnosing morphologically malignant but biologically indolent lesions that would not progress to clinical cancer during a person's lifetime (overdiagnosis) would artifically increase the 5-year survival rate without a concomitant decrease in cancer mortality rate–the bottom line in evaluating the success of any cancer control program.[44] In fact, cancer mortality rates can increase if treatments are harmful. Only RCTs with cancer mortality as the end point can determine the extent of overdiagnosis and length bias (ie, detection of slow-growing tumours by screening,whereas fast-growing tumours appear as interval cases between the screens). To establish evidence-based health care policies for lung cancer screening, RCTs are important.

Figure 1. Determination of lung cancer risk

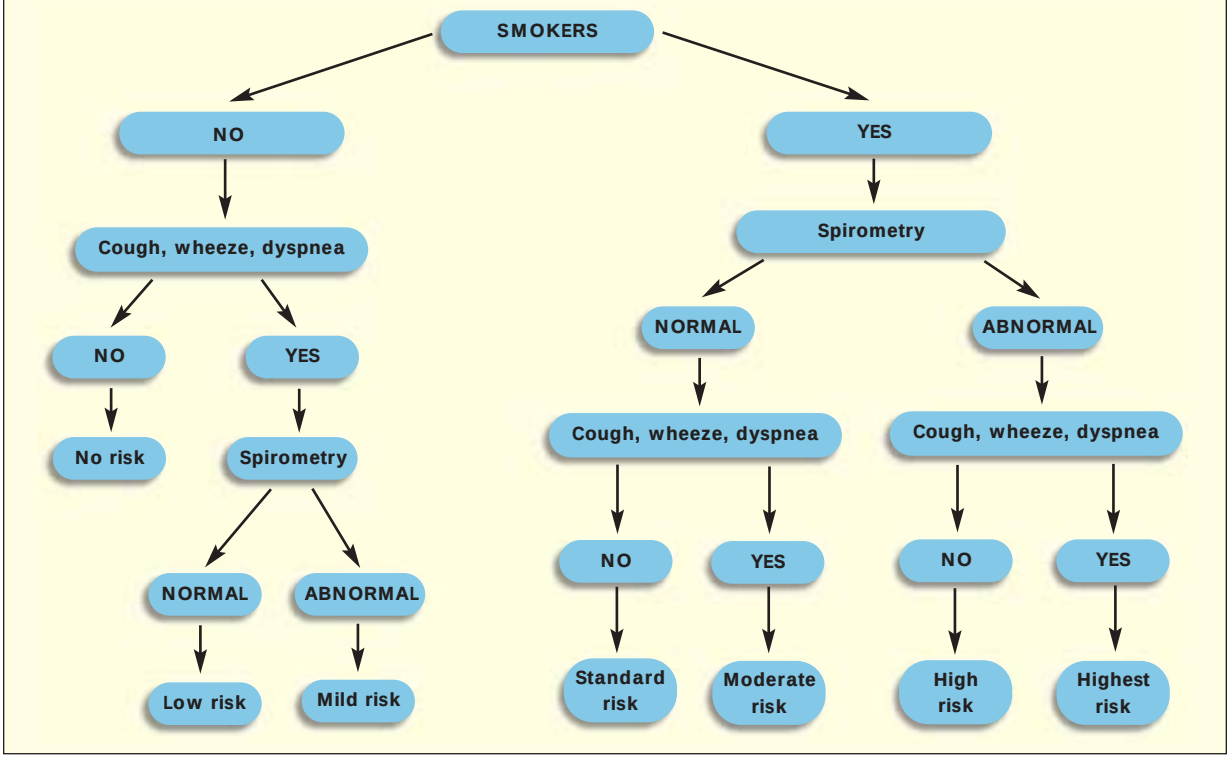
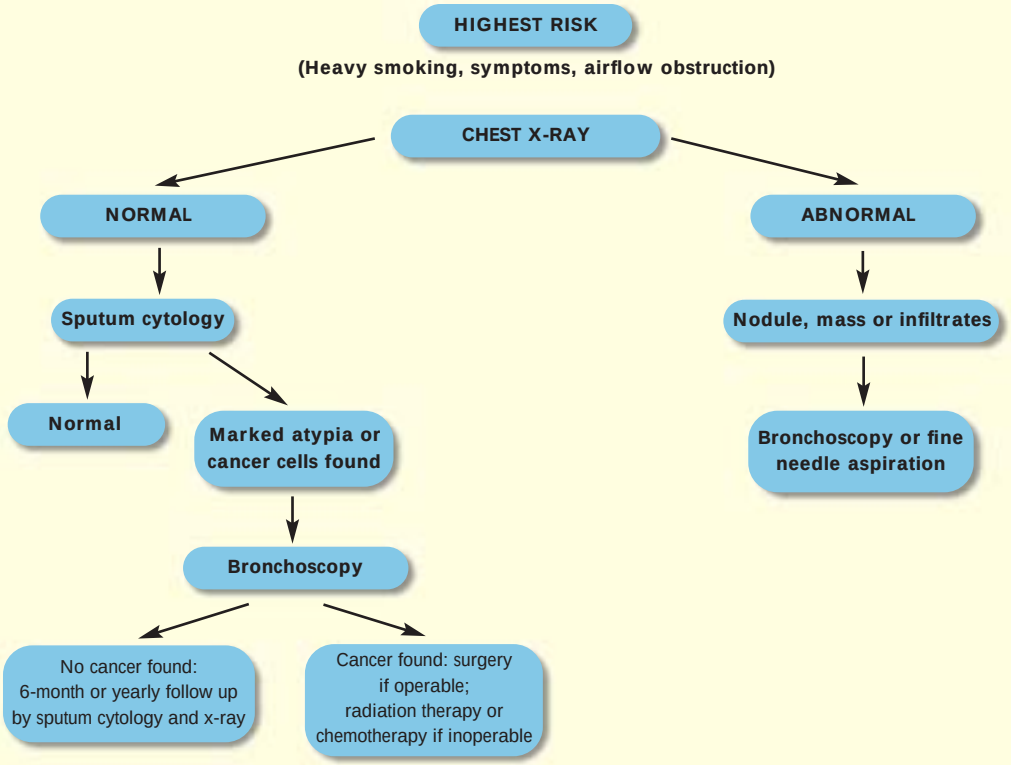


Figure 2. Identification of lung cancer



What can primary care physicians do?

Taking into account all the information presented, what should family physicians do? Current and former smokers must be advised of their continuing risk of lung cancer. Current smokers should be offered assistance in smoking cessation. The recently updated clinical practice guidelines sponsored by the US Department of Health and Human Services are an excellent resource.[45]

The paradigm laid out by Petty (**Figures 1** and **2**) for assessing lung cancer risk and for identifying lung cancer provides a practical approach in line with current clinical practice guidelines in Canada. Chest radiography and sputum cytology examination are indicated in symptomatic current or former smokers older than 45 years with a smoking history of 30 pack-years or more and airflow obstruction defined as FEV_1/FVC of 70% or less and FEV_1 less than 70%. These tests are also indicated for those with clinical symptoms indicating lung cancer, such as a change in chronic smokers' cough or hemoptysis, even if they do not satisfy the smoking intensity or lung function criteria, and especially if they are women.

Conclusion

It is important to understand the objectives and designs of reported clinical trials on lung cancer screening and the limitations of these studies. Lung cancer is no different from other types of cancers in that the disease is highly curable when discovered in its early stage. Family physicians can help to improve management of lung cancer by selective use of CXR and sputum cytology examination while waiting for additional data on the cost-effectiveness of new early-detection technologies. Organizations and health professionals should support research evaluating these new diagnostic techniques and should develop recommendations on how high-risk patients can make informed decisions about monitoring for lung cancer.[46]

Competing interests

None declared

***Correspondence to**: Dr Stephen Lam, 2775 Heather St, Vancouver, BC V5Z 3J5; telephone (604) 875-4325; fax (604) 875-5799; e-mail* sclam@interchange.ubc.ca

Editor's key points

- Family physicians have been discouraged from ordering routine screening chest x-ray examinations to detect lung cancer, based on studies from the 1970s that, when re-examined, were found to have methodologic flaws.
- Recent diagnostic advances have improved the sensitivity of screening methods: more sophisticated sputum cytology, fluorescence bronchoscopy, and computed tomography.
- Treatment for early forms of lung cancer, which includes photodynamic therapy, cryotherapy, YAG (yttrium-aluminum-garnet) laser, and electrocautery, is very effective.
- Recommend chest x-ray examination and sputum cytology for current and former smokers older than 45 years with smoking histories of 30 pack-years or more, with chronic obstructive pulmonary disease, or with forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) of 70% or less and $FEV_1 < 70\%$.

Points de repère du rédacteur

- On a découragé la pratique chez les médecins de famille de prescrire systématiquement des radiographies du thorax pour détecter le cancer du poumon, en se fondant sur des études réalisées durant les années 1970 qui, à la lumière d'un nouvel examen, comportaient des lacunes sur le plan de la méthodologie.
- Les récents progrès en diagnostic ont amélioré la sensibilité des méthodes de dépistage: une cytologie plus perfectionnée des expectorations, la bronchoscopie par fluorescence et la scanographie assistée par ordinateur.
- Le traitement pour les phases initiales du cancer du poumon, notamment la photothérapie, la cryothérapie, le laser YAG (au grenat d'yttrium et d'aluminium) et l'électrocautérisation, est très efficace.
- Il y a lieu de recommander un examen radiologique du thorax et une cytologie des expectorations chez les anciens et actuels fumeurs de plus de 45 ans dont les antécédents de tabagisme remontent à 30 ans et plus à raison d'un paquet par jour, souffrant de bronchopneumopathie chronique obstructive ou dont le rapport entre le volume expiratoire maximal par seconde et la capacité vitale forcée (VEMS/CVF) est de 70% ou moins et le VEMS est de moins de 70%.

References

1. Greenlee RT, Murary T, Bolden S, Wingo PA. Cancer statistics, 1999. *CA Cancer J Clin* 2000;50:7-33.
2. Flehinger BJ, Melamed MR, Zaman MB, Heelan RT, Perchick WB, Martini N. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Memorial Sloan-Kettering Study. *Am Rev Respir Dis* 1984;130:555-60.
3. Frost JK, Ball WC, Levin ML, Tockman MS, Baker RR, Carter D, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. *Am Rev Respir Dis* 1984;130:549-54.
4. Fontana RS, Sanderson DR, Taylor WF, Woolner LB, Miller WE, Muhm JR, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic study. *Am Rev Respir Dis* 1984;130:549-54.
5. Kubik A, Polak J. Lung cancer detection: results of a randomized prospective study in Czechoslovakia. *Cancer* 1986;57:2428-37.
6. Marcus PM, Berstralh EJ, Fagerstrom RM, Williams DE, Fontana TWF, Prorok PC. Lung cancer mortality in the Mayo Lung Project: impact of extended follow-up. *J Natl Cancer Inst* 2000;92:1308-16.
7. Gohagan JK, Prorok PC, Kramer BS, Hayes RB, Cornett JC. The prostate, lung, colorectal, and ovarian screening trial of the National Cancer Institute. *Cancer Suppl* 1995;75:1869-73.
8. Halpern MT, Gillespie BW, Warner KE. Patterns of absolute risk of lung cancer mortality in former smokers. *J Natl Cancer Inst* 1993;85:457-64.
9. Tong L, Spitz MR, Fueger JJ, Amos CA. Lung cancer in former smokers. *Cancer* 1996;78:1004-10.
10. Strauss G, DeCamp M, Dibiccaro E, Richards W, Harpole D, Healy E, et al. Lung cancer diagnosis is being made with increasing frequency in former cigarette smokers [abstract 1106]. In: *Program proceedings of the American Society of Clinical Oncology.* Alexandria, Va: American Society of Clinical Oncology; 1995 p.362.
11. Zang EA, Wynder EL. Differences in lung cancer risk between men and women: examination of the evidence. *J Natl Cancer Inst* 1996;88:183-92.
12. Skillrud DM, Offord KP, Miller RD. Higher risk of lung cancer in chronic obstructive pulmonary disease: a prospective, matched, controlled study. *Ann Intern Med* 1986;105(4):503-7.
13. Lam S, leRiche JC, Zheng Y, Coldman A, MacAulay C, Hawk E, et al. Sex-related differences in bronchial epithelial changes associated with tobacco smoking. *J Natl Cancer Inst* 1999;91:691-6.
14. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist A, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV-1: the Lung Health Study. *JAMA* 1994;272(19):1497-505.
15. Rozenshtein A, White CS, Austin JHM, Romney BM, Protopapas Z, Krasna MJ. Incidental lung carcinoma detected at CT in patients selected for lung volume reduction surgery to treat severe pulmonary emphysema. *Radiology* 1998;207:487-90.
16. Kennedy TC, Proudfoot S, Franklin WA, Merrick TA, Saccomanno G, Corkill ME, et al. Cytopathological analysis of sputum in patients with airflow obstruction and significant smoking histories. *Cancer Res* 1996;56:4673-8.
17. Payne PW, Sebo TJ, Doudkine A, Garner D, MacAulay C, Lam S, et al. Sputum screening by quantitative microscopy: a reexamination of a portion of the National Cancer Institute Cooperative Early Lung Cancer study. *Mayo Clin Proc* 1997;72(8):697-704.
18. Tockman MS, Mulshine JL, Piantadosi S, Erozan YS, Gupta PK, Ruckdeschel JC, et al. Prospective detection of preclinical lung cancer: results from two studies of hnRNP overexpression. *Clin Cancer Res* 1997;3:2237-46.
19. Mao L, Hruban RH, Boyle JO, Tockman M, Sidransky D. Detection of oncogene mutations in sputum precedes diagnosis of lung cancer. *Cancer Res* 1994;54:1634-7.
20. Woolner LB. Pathology of cancer detected cytologically. In: National Cancer Institute Co-operative Early Lung Cancer Group. *Atlas of early lung cancer.* Tokyo, Japan: Igaku-Shoin; 1983. p. 107-213.
21. Lam S, Profio AE. Fluorescence tumour detection. In: Hetzel MR, editor. *Minimally invasive techniques in thoracic medicine and surgery.* London, England: Chapman & Hall; 1995. p. 179-91.
22. Lam S, Kennedy T, Unger M, Miller Y, Gelmont D, Rusch V, et al. Localization of bronchial intraepithelial neoplastic lesions by fluorescence bronchoscopy. *Chest* 1998;113:696-702.
23. Austin JHM, Romney BM, Goldsmith LS. Missed bronchogenic carcinoma: radiographic findings in 27 patients with a potentially resectable lesion evident in retrospect. *Radiology* 1992;182:115-22.
24. Mhum JR, Miller WE, Fontana DR, Uhlenhopp MA. Lung cancer detected during a screening program using four-month chest radiographs. *Radiology* 1983;148:609-15.
25. Henschke CI, McCauley DI, Yankelevitz DF, Naidich DP, McGuinness, Miettinen OS, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. *Lancet* 1999;354:99-105.
26. Kaneko M, Eguchi K, Ohmatsu H, Kankinuma R, Naruke T, Suemasu K, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. *Radiology* 1996;201:798-802.
27. Lam S. Photodynamic therapy of lung cancer. *Semin Oncol* 1994;21:15-9.

28. Ozenne G, Vergnon JM, Roulier A. Cryotherapy of in-situ or microinvasive bronchial carcinoma. *Chest Suppl* 1990;98:105-7.
29. Cavaliere S, Foccoli P, Toninelli C, Feijo S. Nd:YAG laser therapy in lung cancer: an 11 year experience with 2,253 applications in 1,585 patients. *J Bronchol* 1994;1:105-11.
30. Van Boxem TJ, Venmans BJ, Schramel FM, van Mourik JC, Golding R, Postmus PE, et al. Radiographically occult lung cancer treated with fiberoptic bronchoscopic electrocautery: a pilot study of a simple and inexpensive technique. *Eur Respir J* 1998;11:169-72.
31. Cortese DA, Pairolero PC, Bergtralh EJ, Woolner LB, Uhlenhopp MA, Piehler JM, et al. Roentgenographically occult lung cancer. A 10-year experience. *J Thorac Cardiovasc Surg* 1983;86:373-80.
32. Flehinger BJ, Kimmel M, Melamed MR. The effect of surgical treatment on survival from early lung cancer. Implications for screening. *Chest* 1992;101:1013-8.
33. Watanabe Y, Murakami S, Oda M, Ohta Y, Watanabe S, Nozaki Z, et al. *Surgical treatment of hilar and peripheral early NSCLC. Cancer* 2000;89(Suppl 11):2438-44.
34. Morrison BJ. Interventions other than smoking cessation to prevent lung cancer. In: The Canadian Task Force on the Periodic Health Examination. *The Canadian guide to clinical preventive health care.* Ottawa, Ont: Supply and Services Canada; 1994. p. 780-6.
35. British Columbia Council Clinical Practice Guidelines. *Chest x-rays in asymptomatic adults* (monograph on-line). Victoria, BC: Ministry of Health, Management Support Branch, Resource Management Division; October 1996 [updated July 2000]. Available from: http://www.hlth.gov.bc.ca/msp/protoguides/gps/chestxray/chestfu.html. Accessed 2001 February 1.
36. The Saskatchewan Health Services Utilization and Research Commission. *Selective chest radiography guidelines* [monograph on-line]. Saskatoon, Sask: Saskatchewan Health Services Utilization and Research Commission; October 1997. Available from: http://www.hsurc.sk.ca/research_studies/pdf.php3?id=22&section=4. Accessed 2001 February 1.
37. The Saskatchewan Health Services Utilization and Research Commission. *Chest radiography: a summary of the evidence supporting selective clinical practice guidelines and recommendations for implementation* [monograph on-line]. Saskatoon, Sask: Saskatchewan Health Services Utilization and Research commission; September 1997. Available from: http://www.hsurc.sk.ca/research_studies/pdf.php3?id=22&section=1. Accessed 2001 February 1.
38. 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.
39. *The First International Conference on Screening for Lung Cancer*. New York, NY: Weill Medical College of Cornell University; October 1999.
40. *National Cancer Institute Workshop on spiral CT screening for lung cancer*. Washington, DC: National Cancer Institute; October 26, 1999.
41. *Second International Conference on Screening for Lung Cancer*. New York, NY: Weill Medical College of Cornell University; February 2000. Available from: http://icscreen.med.cornell.edu/mconf2sitecompare.htm. Accessed 2001 February 1.
42. Anderson GH, Boyes DA, Benedet JL, LeRiche JC, Matisic JP, Suen K, et al. Organization and results of the cervical cytology screening program in British Columbia, 1955-85. *BMJ* 1988;296:975-8.
43. Smith RA, Mettlin CJ, Davis KJ, Eyre H. American Cancer Society guidelines for the early detection of cancer. *CA Cancer J Clin* 2000;50:34-49.
44. Welch HG, Schwartz LM, Woloshin S. Are increasing 5-year survival rates evidence of success against cancer? *JAMA* 2000; 283: 2975-8.
45. Fiore MC, Bailey WC, Cohen SJ, Dorfman SF, Goldstein MG, Gritz ER, et al. *Treating tobacco use and dependence. Clinical practice guideline.* Rockville, Md: US Department of Health and Human Services, Public Health Service; 2000.
46. Strauss G, Dominioni L. Varese meeting report. *Lung Cancer* 1999;23:171-2.