Lung Cancer Screening: The Mayo Program

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The National Cancer Institute has sponsored three randomized controlled trials of screening for early lung cancer in large, high-risk populations to determine whether (1) lung cancer detection can be improved by adding sputum cytological screening every 4 months to chest roentgenography done either yearly or every 4 months; and (2) lung cancer mortality can be significantly reduced by this type of screening program, followed by appropriate treatment. Results of the three trials suggest that (1) sputum cytology alone detects 15% to 20% of lung cancers, almost all of which are squamous cancers with a favorable prognosis; and (2) chest roentgenography may be a more effective test for early-stage lung cancer than previous reports have suggested. Neverthless, results of the randomized trial conducted at the Mayo Clinic showed that offering both procedures to high-risk outpatients every 4 months conferred no mortality advantage over standard medical practice that included recommended annual testing.

Lung cancer continues to be a major medical problem. It has been estimated that in the United States there will be 149,000 new cases and 130,100 deaths from the disease during 1986. Lung cancer is now the leading cancer cause of death among both men and women.[1]

During the past 30 years the incidence rates and mortality rates associated with lung cancer have risen steadily and proportionally.[2] Resectability and 5-year survival rates have not changed appreciably, remaining about 25% and 10%, respectively.

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Although its effectiveness has been questioned, surgical resection continues to be the treatment of choice for all but the small-cell type of lung cancer.[3] Combination chemotherapy has benefitted some patients with small-cell cancer, but the proportion who experience prolonged, complete remission is woefully small.[4]

The most tragic aspect of the lung cancer problem is the fact that it is largely preventable, 80% being attributable to cigarette smoking.[5] Smoking history, age, and sex comprise an excellent "prescreen." The population at high risk consists of middle-aged and older men who have been chronic, excessive smokers of cigarettes.

The symptoms of early lung cancer tend to be nonspecific and are often attributed to smoking. By the time symptoms have become severe enough that medical attention is sought, the tumor is likely to be advanced and incurable.[6]

Today the chest x-ray film and the sputum cytology test are still the only reliable procedures for detecting presymptomatic, early-stage lung cancer.[7] The two procedures are complementary: the chest x-ray film is better for detecting peripheral tumors of the non-small cell type (especially adenocarcinomas), whereas sputum cytology is the best detector of centrally located, early-stage, intrabronchial squamous cancers (so-called "occult" cancer).[7,8] Posteroanterior (PA) stereoscopic or PA and lateral chest x-ray films taken at 125 to 140 kV are preferred because of their sensitivity, as are multiple-day "pooled" or induced specimens of sputum.[9,10] Neither procedure is likely to be helpful if the cancer is of the small-cell type.

The Saccomano technique for processing sputum and the flexible fiberoptic bronchoscope, both developed in the 1960s, have vastly improved detection and localization of occult cancers.[11,12] Because of these major advances, and in response to concerns expressed by patients, the Division of Thoracic Diseases of the Mayo Clinic recommended in 1970 that "any man aged 45

years or older who smokes one package of cigarettes or more each day should have a sputum cytology examination as well as a chest X-ray at least once a year."[13] This recommendation remains in effect today.

The following year the National Cancer Institute (NCI) began sponsorship of three large-scale, long-term, randomized controlled trials of screening for lung cancer, using chest x-ray films and sputum cytology.[14] The trials, which were completed in 1984, were conducted at Mayo Clinic, the Johns Hopkins Medical Institutions, and the Memorial Sloan-Kettering Cancer Center. The participating institutions have been designated the "NCI Cooperative Early Lung Cancer Group."[14]

The aims of the Cooperative Group have been to determine whether (1) detection of lung cancer can be improved by adding modern cytologic screening techniques to either yearly chest x-ray films (Hopkins; Memorial) or chest x-ray films done every 4 months (Mayo); (2) mortality from lung cancer can be reduced significantly by this type of screening program, followed by newer localizing methods and appropriate treatment of bronchogenic carcinoma.[14]

At the time these clinical trials were designed, it was assumed that yearly chest x-ray films would not affect lung cancer mortality, although this assumption has never been tested. There has never been a randomized controlled trial of screening for lung cancer alone by means of full-size, high kV chest x-ray film or modern, multiple-day or induced sputum cytology tests, separately or combined, compared with no testing at all.

The goal of the Mayo screening program, or Mayo Lung Project (MLP), was to determine whether chest x-ray film and sputum cytology tests, offered periodically to a group of Mayo Clinic outpatients at high risk of lung cancer and without a history of respiratory tract cancer, would result in a significant reduction of the lung cancer death rate compared with a control population not offered regular testing, but advised to have annual chest x-ray film and sputum cytology tests.[13] Persons at high risk were defined as men aged 45 and older who were smoking at least one pack of cigarettes daily, either at the time they entered the program or during the previous year. The tests were offered to the screened population every 4 months for 6 years. Mayo Clinic patients were chosen as subjects for the MLP primarily because it was believed that detection of early-stage lung cancer could be most easily accomplished through existing medical facilities and primary physicians.[13]

Prevalence Screen

From November 1971 through July 1976, 10,933 Mayo Clinic outpatients were interviewed who met the MLP age, sex, and smoking requirements. All of these patients received 36 cm × 43 cm stereoscopic chest roentgenograms, whereas 10,117 (92.5%) submitted 3-day "pooled" specimens of sputum that were considered satisfactory for cytologic examination.[15] None of these MLP candidates were suspected of having cancer of the respiratory tract. All were offered the tests because of the 1970 Mayo recommendation regarding annual testing of high-risk patients. If either test proved positive for lung cancer on this initial screening, the patient became a "prevalence" case. There were 91 such cases, a prevalence rate of 8.3/1,000 of those offered the screening. The prevalence rate was strongly age-dependent, ranging from 1/1,000 among men aged 45 to 49 to 17/1,000 among those aged 65 and older.[15]

Roentgenography was the most frequent method of detecting the prevalence cancers (Table 1). There were 59 cases detected by chest x-ray film alone, of which 30 (51%) were resectable "for cure." Cytology alone detected 17 cases, and 16 (94%) of these were considered completely resectable. Fifteen cases were detected by both screening modalities, but in only three (20%) of these were "curative" resections possible. Overall resectability was 54%.[15]

Among those prevalence cases detected by cytology alone, the 5-year survivorship (considering deaths from lung cancer only) was about 80%.[15,16] There were 36 asymptomatic prevalence cancers detected roentgenographically, and in these cases, the 5-year lung cancer survival approached 50%. The remaining 38 patients with abnormal chest x-ray films had vague symptoms, such as ill-defined chest pain, that were not suspected of being due to lung cancer when the patient entered the Mayo Clinic, but that later were proved to be after review of the findings of the medical examination. The 5-year lung cancer survival among these cases was less than 10%. All but one of the cases in which both the chest x-ray film and the sputum cytology test were abnormal were in this "symptomatic" category.[15]

The survival at 5 years from all causes of death among the 91 prevalence cases were approximately 30%. This is more than twice that observed in a large group of contemporary Mayo Clinic lung cancer cases matched for age and sex.[17] Considering only deaths from lung cancer, the 5-year survival rate among the prevalence cases was nearly 40%.[15]

Randomized Clinical Trial (Incidence Rescreening)

Only 9,211 of the 10,933 men who took part in the prevalence screening also qualified for the MLP randomized controlled clinical trial, or "incidence study."[17] Additional requirements for the randomized trial included a life expectancy of at least 5 years, a respiratory reserve considered sufficient to enable the patient to undergo lobectomy, if necessary, and completion of the prevalence screening with test results that were consid-

TABLE 1
Prevalence Lung Cancers: Method of Detection and Resectability

Method of Detection	No. of Cases	Complete Resections
Chest x-ray film	59	30 (51%)
Sputum cytology	17	16 (94%)
X-ray film and cytology	15	3 (20%)
Total	**91**	**49 (54%)**

ered satisfactory and negative for lung cancer. The 9,211 men who fulfilled the criteria for the trial were studied in two randomized groups.[18]

The screened group consisted of 4,618 patients who were asked, and reminded, to have chest roentgenograms and 3-day, "pooled" sputum cytology tests every 4 months for 6 years. Intensive efforts were made to secure compliance. Noncompliant patients and those who had completed 6 years of screening were contacted yearly by letter.[18] On July 1, 1983, all men in this group had completed the 6-year screening period. Postscreening follow-up ranged from 1 to 5.5 years. The median follow-up was 3 years.

The control group of 4,593 patients received only the standard 1970 Mayo recommendation concerning yearly chest x-ray film and sputum cytology tests. No reminders about tests were sent. Contact was maintained by annual follow-up letter that did not mention the tests.[18]

Compliance with the screening was excellent. For the 4-monthly screened group, compliance was 85% during the first year, after which it gradually fell, leveling off slightly below 75%. The response of the control group to the yearly letter remained constant at 98%.[18] During the entire randomized trial, only 26 patients were lost to follow-up.

A successful randomized trial of screening for lung cancer should initially detect more lung cancers and more early-stage cancers in the screened group than in the control group, due to the screening. Later, as screening concluded, and during the follow-up period, the number of lung cancers in the two groups would equalize, as previously undetected, asymptomatic, early-stage lung cancers in the control group progressed and finally emerged as symptomatic, advanced cancers. Eventually, if treatment were more effective for early-stage than for advanced cancers, there would be fewer lung cancer deaths in the screened group than in the control group.

From the beginning of the MLP trial, the incidence cases of lung cancer in the group screened every 4 months outnumbered the cases in the control group. On July 1, 1983, there were 206 confirmed lung cancers in the group screened every 4 months, an incidence rate of 5.5/1,000 person-years of surveillance. In the control group were 160 cases, or 4.3/1,000 person-years.

About one fourth of the lung cancers in both groups were small-cell cancers, which are not amenable to screening.[19] Moreover, only a third of the cancers in each group were squamous cancers, the type that traditionally has seemed to respond best to surgical treatment. This distribution is quite different and much less favorable than what had been expected when the MLP began.[19]

In the group screened every 4 months, 90 (44%) of the 206 confirmed cases of lung cancer were detected by the screening tests (Table 2). In 66 of these 90 cases, only the chest x-ray film was abnormal. Eighteen of the 90 cancers were detected by cytology alone, whereas six were detected by both screening modalities.

Among the 116 cases in the group screened every 4 months that were not detected by screening, 73 had symptoms of lung cancer, and 43 were discovered by nonstudy chest x-ray films obtained for other clinical reasons (emphysema, respiratory infections, heart disease, etc), or during general medical examinations of these heavy smokers.

TABLE 2
Incidence Lung Cancers: Method of Detection and Resectability

Method of Detection	Group Screened Every 4 Months		Control Group	
	No. of Cases	Complete Resections	No. of Cases	Complete Resections
Chest x-ray film every 4 months	66	41 (62%)		
Cytology every 4 months	18	15 (83%)		
Chest X-ray film and cytology every 4 months	6	4 (67%)		
Nonstudy chest x-ray film	43	27 (63%)	48	36 (75%)
Symptoms	73	7 (10%)	112	15 (13%)
Total	**206**	**94 (46%)**	**160**	**51 (32%)**

Fifteen of the 18 incidence cancers detected cytologically were resected (Table 2). Perhaps more significant was the observation that almost two thirds of the 115 cancers in the group screened every 4 months that were detected roentgenographically (by either screening or nonstudy x-ray film) were resectable.

Nearly a third of the lung cancers in the control group were detected by nonstudy x-ray film, and three fourths of these were resectable. This "contamination" of the control group was for clinical indications similar to those encountered in the group screened every 4 months. Approximately half of the control population received chest roentgenograms each year.

In addition to the 73 symptomatic cases of lung cancer in the group screened every 4 months, there were 112 in control group. Only 22 (12%) of these 185 symptomatic lung cancers were resectable (Table 2).

A total of 94 (46%) of the lung cancers in the group screened every four months were resectable, compared with 51 (32%) of the 160 in the control group. In clinical practice at the Mayo Clinic, the resectability rate for lung cancer is 27%.[17] However, it should be recalled that one of the requirements for participation in the MLP randomized trial was a respiratory reserve sufficient to permit lobectomy (should this be necessary). Obviously, not all of the lung cancer patients encountered in clinical practice at Mayo would have fulfilled this requirement.

Considering only deaths from lung cancer, 5-year survival among all cytologically detected incidence cases was more than 80%, and 5-year survival for all roentgenographically detected cases averaged 40%. The survival of the symptomatic cases at 5 years was less than 10%. Because of the distribution of the lung cancer cases in the two study groups by method of detection, the 5-year survival (lung cancer deaths only) in the group screened every 4 months was approximately 35%. It was less tha 15% in the control group.

There were 43 more resectable lung cancers in the group screened every 4 months than in the control group

(Table 2). However, there were also three more unresectable cancers in the group screened every 4 months (112 compared with 109 in the control group). Although approximately half of the patients were resectable cancers survived their disease 5 years, it was rare for those with unresectable cancers to do so.

The hoped-for "trade off" of successful lung cancer screening did not occur. More lung cancers and more early-stage, resectable lung cancers were detected in the group screened every 4 months than were observed in the control group. However, these were not offset by an equally larger number of advanced, unresectable cancers among the control subjects. The cumulative numbers of unresectable lung cancers in the two groups were almost identical, both during the 6 years of active screening and afterwards.

In the MLP randomized trial, the death rates from all causes (per 1,000 person-years) were high: 24.8% in the screened every 4 months and 24.6% in the control group. The major competing death risk was ischemic cardiovascular disease.[19]

There were 122 lung cancer deaths in the group screened every 4 months and 115 in the control group. Seven deaths in the group screened every 4 months and six deaths in the control group were attributed to surgery for lung cancer. These were treated as lung cancer deaths.

The death rate from lung cancer was 3.2/1,000 person-years in the group screened every 4 months and 3.0 among the control subjects. Like the cumulative numbers of unresectable cancers, the cumulative numbers of lung cancer deaths in the two groups were comparable, both during and after the period of active screening.

Comments

The results of the MLP randomized controlled trial do not justify recommending large-scale programs of radiological or cytological screening for lung cancer. Such programs are usually initiated by those who conduct them and should benefit the participants by reducing lung cancer mortality.[20] The MLP trial did not demonstrate this sort of benefit.

Neither do the results of the MLP mean that testing high-risk patients for lung cancer by chest x-ray film or sputum cytology is not useful, as some have claimed.[21] All who participated in the MLP trial received an initial (prevalence) radiological and cytological screening. The randomized trial simply shows that offering the two procedures every 4 months to high-risk Mayo outpatients who have had one negative screening confers no morality advantage over routine Mayo Clinic practice with a recommendation of annual testing.

The randomized, controlled trials conducted at the Johns Hopkins Medical Institutions and at the Memorial Sloan-Kettering Cancer Center offered all participants annual chest roentgenograms. In addition, half of the men in each of these trials were randomly allocated to a group offered sputum cytology every 4 months. Results from both trials indicate that in the populations screened by x-ray film only, as well as in the populations screened by x-ray film and cytology, the proportion of early-stage, resectable lung cancers and the lung cancer survivorship have been substantially better than those observed in previously reported lung cancer screening programs. However, like the MLP, no significant difference in lung cancer mortality has been observed between the two populations in either the Hopkins or the Memorial trial.[20]

It should be emphasized that when the NCI randomized controlled trials commenced, it was generally accepted that yearly chest roentgenograms would not reduce lung cancer mortality. It was also believed that a large proportion of lung cancers would be detected cytologically, and the trials were designed with this in mind. Yet in all three screening programs, the great majority of lung cancers have been detected radiologically. Furthermore, sizable numbers were detected by nonstudy chest x-ray films in the control group of the MLP and by annual chest x-ray films in the control populations of the other two trials. It would be of interest to know what might have happened in these cases if chest roentgenograms had not been available to the control subjects.

The randomized controlled trial is ideal for assessing new procedures such as mammography, or new application of procedures such as screening populations at high risk of lung cancer by sputum cytology. Unfortunately, once a procedure has become an established part of medical practice, as the chest roentgenogram has (more than 80 million are taken year in the United States), it may become necessary to resort to other, less precise methods of evaluation, such as case-control studies.[22,23]

Summary

Three large, long-term randomized controlled trials of screening for early-stage lung cancer by periodic chest x-ray film and sputum cytology have been conducted under the auspices of the National Cancer Institute. Cytological screening alone has detected only a small proportion of the lung cancers in these programs, although cytologically detected lung cancers tend to have a very favorble prognosis. Modern chest roentgenography appears to be a better method of detecting early-stage, resectable lung cancer than previous studies have indicated.

Everyone who participated in the Mayo Clinic randomized trial had a satisfactory and negative initial (prevalence) radiological and cytological screening. The study group was then offered rescreening every 4 months, while the control group was offered standard medical care and advised to have annual chest radiography and sputum cytology.

The Mayo trial has shown significantly increased lung cancer detection, resectability, and survivorship in the study group compared with that of the control groups. Yet the death rates from lung cancer and from all causes have been almost identical in the two groups.

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