Some Results of Screening for Early Lung Cancer

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Screening for lung cancer is somewhat controversial in that very few evaluations of the screening process have been made, and even fewer have involved the use of concomitant, unscreened controls. This report of the Mayo Lung Project provides evaluation of a randomly selected 4500 clinic patients, offered screening for lung cancer at four-month intervals for six years. Another 4500 randomly selected controls not offered screening were merely observed. Good screening is defined, the Mayo project is evaluated, and puzzling results are presented and discussed.

From the screened group, 98 new cases of lung cancer have been detected, 67 by study screening and 31 by spontaneous reporting of symptoms (15) or by x-ray examinations (16) done in other than study circumstances. From the controls, 64 new lung cancer cases have been detected, 43 by symptoms and 21 by other methods. Lung cancer mortality is 39 for study patients and 41 for controls. There is thus no evidence at this time that early case finding has decreased mortality from lung cancer.

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IN 1970[3] THE THORACIC DIVISION of the Mayo Clinic recommended that patients thought to be at high risk of lung cancer do three things: 1) stop smoking, 2) each year have a chest roentgenogram, and 3) each year have a sputum cytology examination. Specifically, this recommendation was directed to men over 45 who were heavy smokers.

In 1970 this advice was believed to be the best available medical wisdom, because the two tests were the only ones proved capable of detecting presymptomatic, potentially curable lung cancer. The recommendation was made with full realization that it was based on unproven assumptions about either the possibility or the efficacy of detection of early stage lung cancer. It was strictly empiric and pragmatic. It remains so today, and the recommendation remains in effect today.

Also in 1970, after many months of discussion, a group of Mayo investigators proposed to develop and evaluate a long-term lung cancer screening program for high-risk men.[2,4] The proposal was accepted by the National Cancer Institute, and late in 1971 the Mayo Lung Project (MLP) began screening.

This interim report reviews the status of the MLP at the end of 1979. It looks back at the 1970 proposal and asks whether the original objectives have been met. It also looks at the potential of lung cancer screening for reducing mortality in the future.

Methods

The goal of the MLP has been to determine if lung cancer mortality could be significantly reduced in high-risk Mayo outpatients if chest roentgenograms and sputum tests were obtained often enough. Tests have been obtained every four months, which is more often than in any previous lung cancer screening program. The four-month interval was also about as often as even health-conscious Mayo patients would tolerate.[2] Men in the comparison (control) group of the MLP were given the standard Mayo recommendation of annual chest roentgenography and sputum cytology. All patients in the MLP have been advised to stop smoking.

The design of the MLP is as follows: Non-volunteer Mayo outpatients in the high-risk group of men over 45 years of age who were chronic excessive cigarette smokers without known lung cancer received chest roentgenograms and cytology tests of three-day "pooled" collections of sputum. If either test proved positive for lung cancer on this initial screening, the patient became a "prevalence" case. (These prevalence cases are not studied here. Cases considered in this paper are "incidence" cases occurring after the result of the initial screening of the patient was found negative.)

Those who had negative initial screens and who met certain other criteria for continued screening were subsequently studied in two randomized groups. In the study (or screened) group the patients were asked to

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submit a chest roentgenogram, a sputum specimen, and a health questionnaire at four-monthly intervals; intensive efforts were made to secure compliance. These tests were paid for by the MLP. Most of them were done outside Mayo and submitted by mail. A comparison (or control) group received only the standard Mayo advice of stopping smoking and having yearly chest roentgenograms and sputum tests. No reminders about tests were sent, but contact was maintained by annual follow-up letter. No tests were paid for.

The Mayo Clinic patients considered for this study were all to receive a general examination in their clinic work-up. They were chosen only by age, sex, and history of smoking. Their numbers of pre-existing illnesses were doubtlessly more than one would expect in the general population. An analysis of these illnesses and the "incidence" of lung cancer may be made at a later date. At this writing, reliance is placed on two study procedures designed to select an appropriate population: 1) randomization, which balanced the screened and central groups for any pre-existing illnesses so that comparability was maintained, and 2) exclusion from future screening of those patients whose attending physicians did not judge them likely to survive at least five years.

One point should be emphasized. The question addressed by the MLP is simply, "Does offering screening for early lung cancer work?" The question is not, "Does screening work?" or "Can screening be accomplished inexpensively or at intervals greater than four months?" It is not, "Can it be done cheaply or less frequently?" These matters are irrelevant unless the screening itself can be shown to be beneficial. If that can be accomplished, then we will attempt, and we believe succeed, in making it cost-effective for appropriate groups of patients screened.

Screening

There have been two major concerns about screening in the MLP. How good has the process of screening been? What are the results? A screening program for cancer, if it is to be appropriate and well done, must fulfill certain conditions. Not all will be discussed at this time, but those that follow are of particular importance to the MLP.

Condition 1. Screening must be directed to a "high risk" target population consisting of people in whom cancer is not yet suspected: From the beginning, attempts were made to find suitable "high risk" or "prescreen" groups of middle-aged and older men who were chronic excessive cigarette smokers and who would be available for repeated screening. After initially investigating industrial sources for potential candidates, we

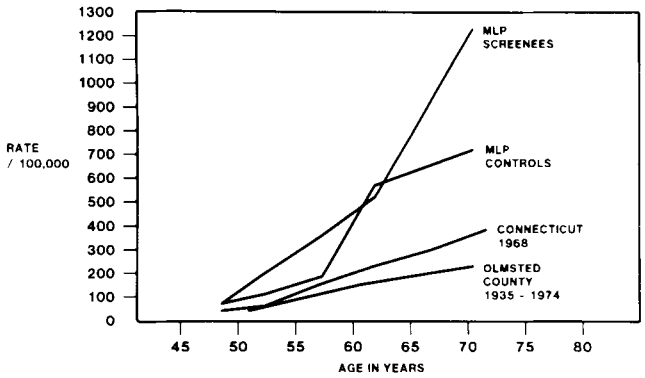

FIG. 1. Bronchogenic carcinoma incidence rates, by age, from Mayo Lung Project (MLP) and other sources of data.

decided to work within Mayo Clinic. Thus, the MLP "incidence" screening population comprised men over 45 who were smoking at least a pack of cigarettes a day on entry or within a year of entry into the study. All were Mayo Clinic outpatients who had been screened once by clinical examination, chest roentgenography, and sputum cytology and were found to be free of lung cancer.

The risk of lung cancer as subsequently found among the MLP subjects was high. Figure 1 shows age-specific lung cancer incidence rates from Connecticut, Olmsted County, Minnesota, and the MLP. MLP lung cancer mortality rates were also much higher than those for white males in the United States in 1976, especially at ages over 65.

Condition 2. Screening must be accepted by the target population: Each person in the four-monthly screened group was considered with respect to the time he had been observed. A determination was made of the number of times he should have completed and submitted a chest roentgenogram, a three-day sputum specimen for cytologic examination, and a health questionnaire. The totals of these expected submissions were then compared with the actual numbers submitted. The results are shown in Figure 2. During the first year of the

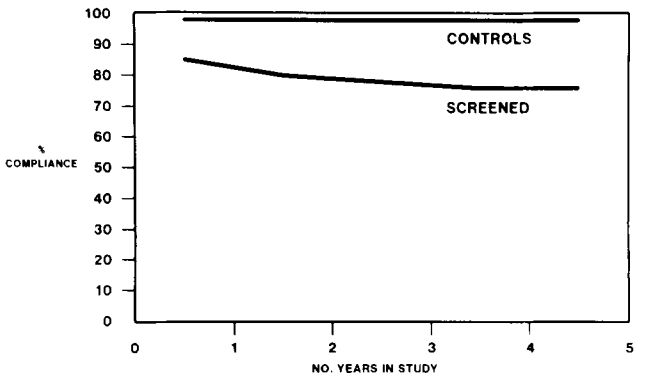

FIG. 2. Percentage compliance with study requirements.

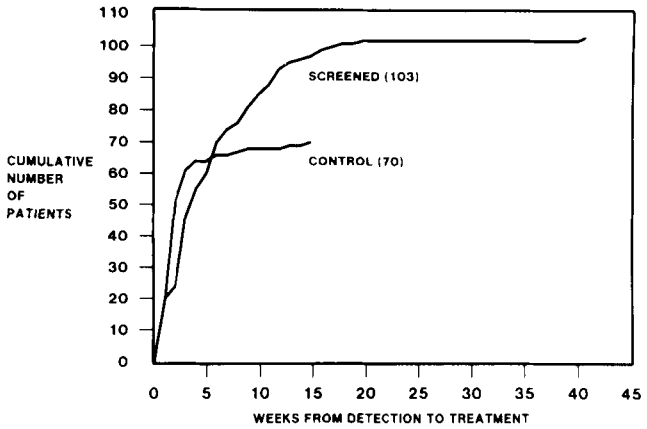

FIG. 3. Cumulative number of Mayo Lung Project patients receiving treatment by time from detection of lung cancer—control and screened patients.

study, 85% of the test requirements were met, but by the fifth year this had dropped to 76%. The compliance among controls who were asked merely to respond to an annual query was 98% for all five years considered. Compared with the compliance found in other screening projects, this is very good indeed.

Condition 3. Screening should not be offered to a target population already being tested routinely by private physicians or other means: This has been a source of concern in evaluating the MLP. It is known that a proportion of MLP patients has obtained their own roentgenographic examinations outside this study, many at Mayo Clinic. Among controls, nearly one third of the 72 new lung cancer cases were detected by nonstudy chest roentgenography (67% were detected by symptoms). Even among the screened subjects, 14% of the 104 cases were found by nonstudy chest roentgenography. This is an obstacle to the evaluation of screening because it reduces the contrast between the controls and screened patients.

TABLE 1. Lung Cancer in the Mayo Lung Project

	Screened	Control
Stage		
Postsurgical stage I (localized, low stage)	50 (48%)	15 (21%)
Higher stages (advanced, high stage)	54 (52%)	57 (79%)
Total	104 (100%)	72 (100%)
Detection method		
Study roentgenogram	57 (55%)	
Study cytology (roentgenographically "occult")	12 (12%)	
Nonstudy (symptoms, roentgenogram)	33 (32%)	72 (100%)
Autopsy	2 (2%)	
Cell type		
Small cell	28 (27%)	22 (31%)
Large cell	20 (19%)	10 (14%)
Adenocarcinoma	24 (23%)	17 (24%)
Squamous	32 (31%)	23 (32%)
Stage and detection		
Study roentgenogram	57	
Low stage	33 (58%)	
High stage	24 (42%)	
Study cytology	12	
Low stage	10 (83%)	
High stage	2 (17%)	
Nonstudy	35	
Low stage	7 (20%)	
High stage	28 (80%)	

Condition 4. Screening must bring suspicious cases to prompt diagnosis and treatment: Figure 3 shows the elapsed time between detection (symptoms, a suspicious x-ray, or sputum specimen) and first treatment. Half of the 70 control cases were treated within two weeks of detection, and 90% within four weeks. For study-detected cases, half received treatment within four weeks and 90% within 12 weeks. The time from detection of a tumor and its localization and treatment can be substantial, particularly in cases that are roentgenographically occult. The control cases tended to be more advanced when detected and, consequently, were diagnosed and treated faster than the screened cases, which often required more confirmatory studies.

The two conditions that follow are related to results of screening and not just the mechanics of the screening process.

Condition 5. Screening must detect significantly more cases, especially early stage cases, than would have been observed if screening had not been done: Table 1 provides data to demonstrate this. It indicates that among the patients rescreened every four months 104 new incidence cases of lung cancer have been detected; 50(48%) of them were classified as "AJC* postsurgical Stage I."[1] We designate them as "low stage" or "localized" here; all other AJC categories are considered "high stage" or "advanced." In the control group, only 72 cases have been detected, and 15 (21%) of these were low stage. It would certainly seem that four-monthly screening has found more cases (and more early cases) than appeared among control patients.

Table 1 shows that screening procedures detected two thirds of the cases in the group rescreened every four months. The remaining third were detected by symptoms, by nonstudy x-ray, or by autopsy. Four cell types occurred about equally in screened and in control groups (Table 1). Table 1 also shows that when cases were found by screening tests they were usually low stage, and when they were found by nonstudy methods, they were usually high stage. Among cases detected cytologically, 83% were low stage, whereas 58% of cases discovered by study-initiated roentgenographs were low stage.

* American Joint Committee for Cancer Staging and End-Results Reporting

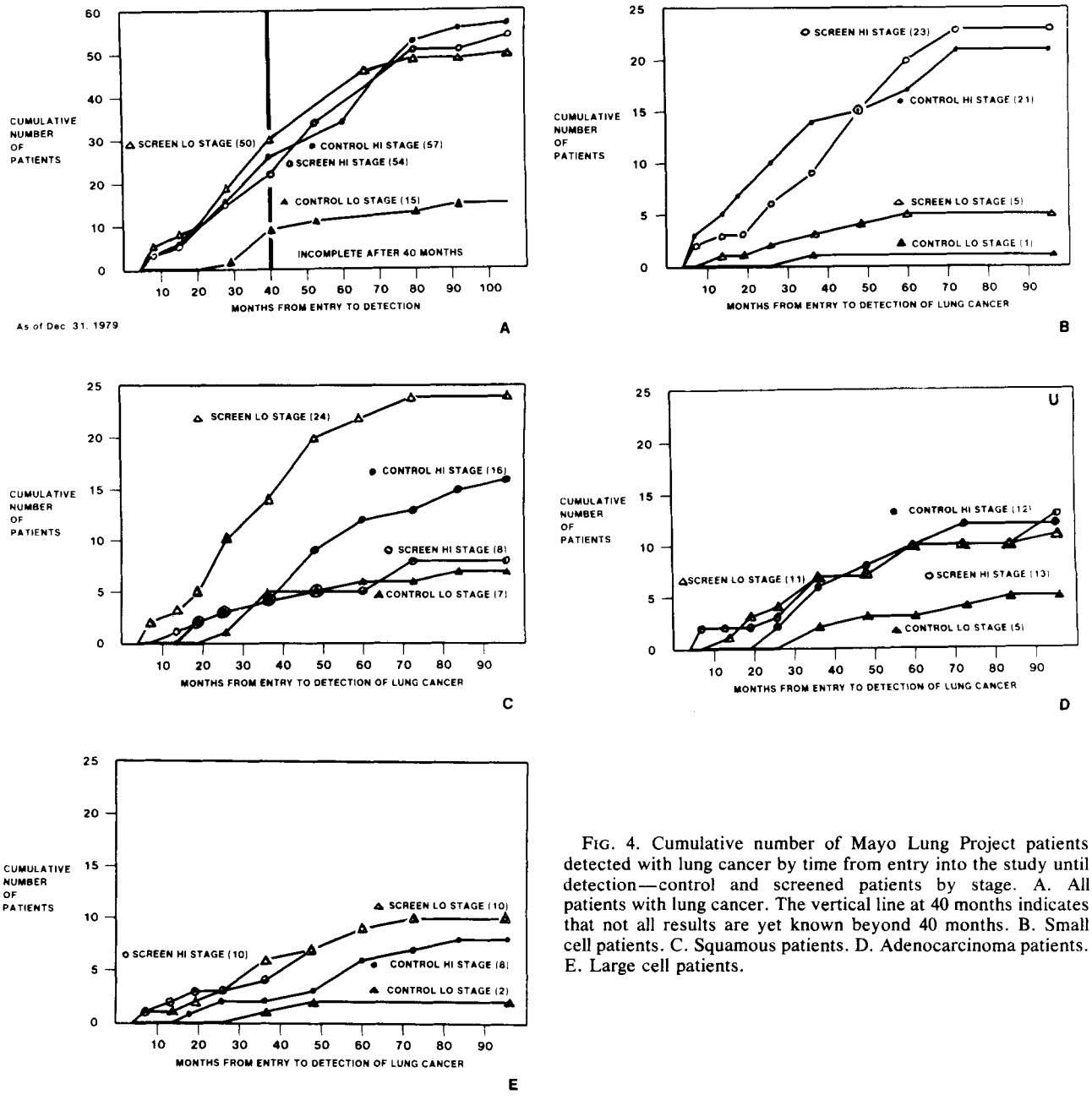

FIG. 4. Cumulative number of Mayo Lung Project patients detected with lung cancer by time from entry into the study until detection—control and screened patients by stage. A. All patients with lung cancer. The vertical line at 40 months indicates that not all results are yet known beyond 40 months. B. Small cell patients. C. Squamous patients. D. Adenocarcinoma patients. E. Large cell patients.

In Figures 4A–4E, consideration is given to the length of time from entry into the study until the detection of lung cancer either at low or high stage for control or screened patients. The Figures demonstrate both the time required for lung cancers to surface in various groups of patients and the number of lung cancers found. Figure 4A includes all lung cancer cases. Both screened and control patients were discovered to have cancer within four months of entry. Among the screened patients, both low and high stage diseases were found early in the study; however, only high stage patients appeared early among controls. The low stage cases found among controls appeared much later and in much smaller numbers. Even though results beyond 40 months are incomplete, we see in Figure 4A a small excess of high stage control cases after 60 months. We believe this disparity should increase in the future, when undiscovered cases in the control group surface as their disease progresses to a higher stage and symptoms appear.

Figures 4B–4E explore the complexity of lung cancer by examining the times of discovery of cases classified both by cell type and by stage. The various types of lung cancer behaved as though they were different diseases. The first point to be made is demonstrated by

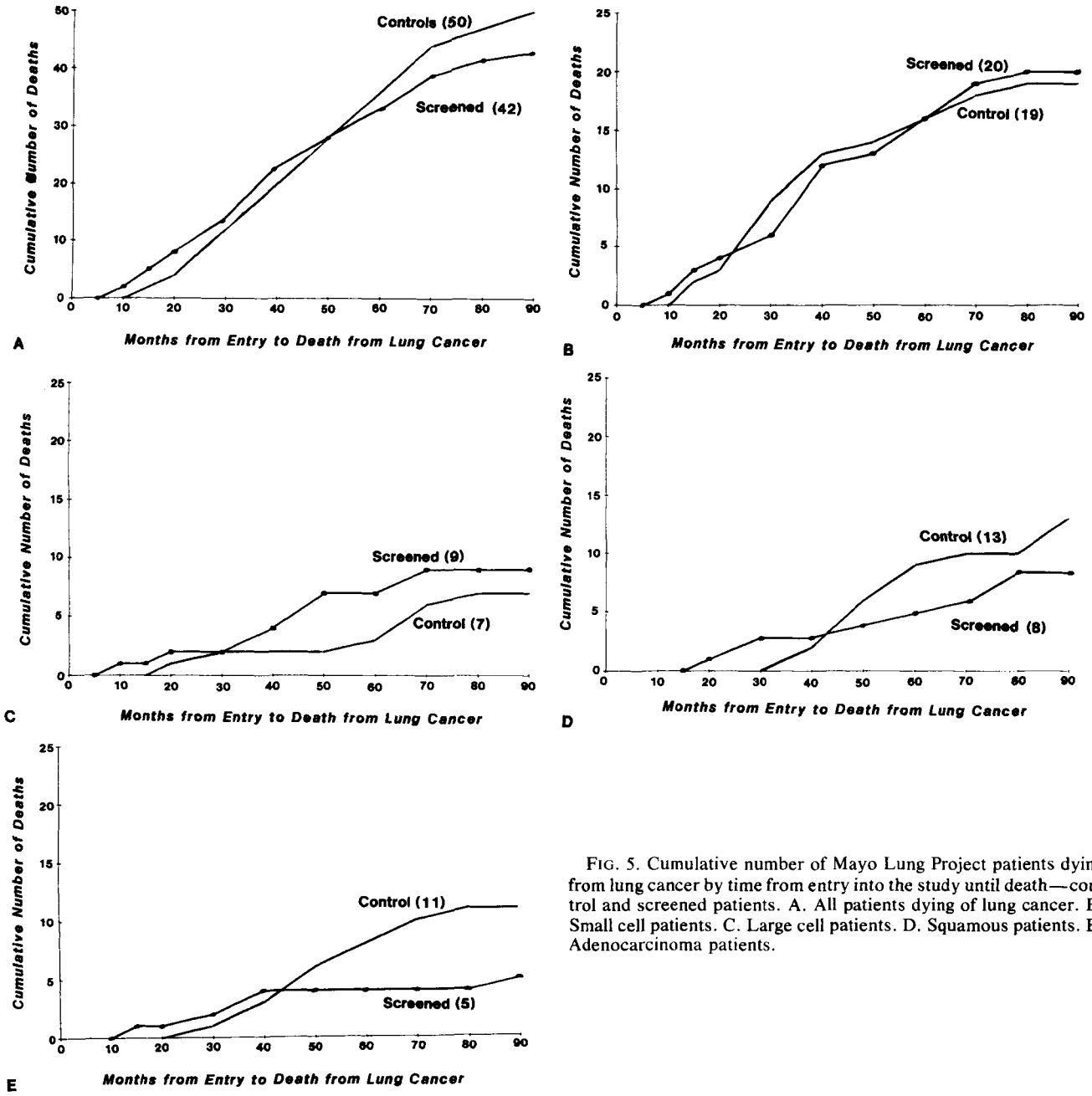

FIG. 5. Cumulative number of Mayo Lung Project patients dying from lung cancer by time from entry into the study until death—control and screened patients. A. All patients dying of lung cancer. B. Small cell patients. C. Large cell patients. D. Squamous patients. E. Adenocarcinoma patients.

Figure 4B. Very few low stage small cell cancers were found. For reasons that are not apparent, some high stage small cell cases were found even earlier in control patients than in screened ones, although this tended to even out as time went by. Five low stage cases were found by screening, only one in the controls. The impression is that screening by chest roentgenography and sputum cytology every four months does not pick up cases of small cell cancer earlier than those appearing among controls. Moreover, those cases detected by the screen are generally of high stage.

At the other end of the spectrum (Fig. 4C), five cases of squamous cancer were detected by screening before the first control case appeared. Squamous cancer showed a large excess of low stage cancers in the group screened every four months. These are the reasons for this. First, squamous cancer has the most favorable prognosis of any cell type of lung cancer. Second, the early favorable roentgenographically negative, cytologically positive "occult" lung cancer is almost always squamous. These facts explain part of the excess in Figure 1. In addition, there have been fewer high stage squamous

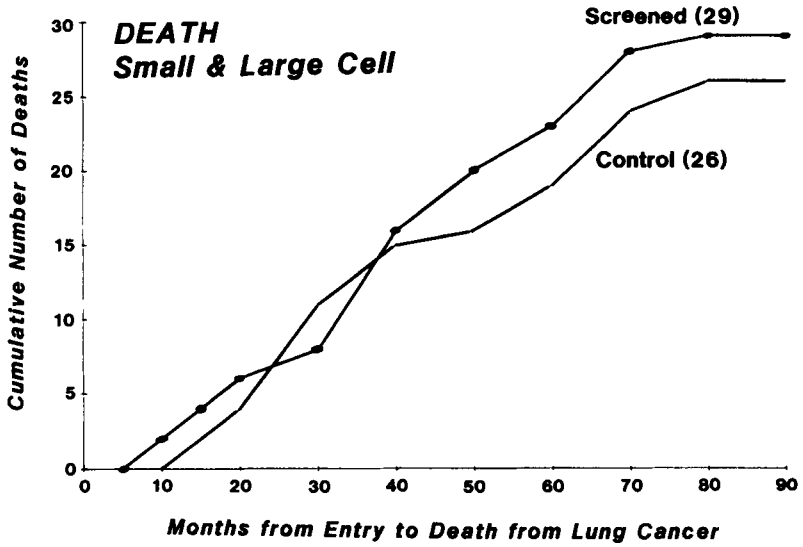

FIG. 6A. Figures 5B and 5C combined, small cell plus large cell.

cancers discovered in the screened group than in the control group, an indication of possible future benefits from screening.

Adenocarcinoma (Fig. 4D), like squamous carcinoma, showed a delayed appearance of cases in the control group compared with the screened. The first control case was found 21 months after entering the study, while the first screened case was detected at three months. As time went by, the cases of high stage adenocarcinoma were about the same in both groups. A benefit of screening seems to be that more Stage I adenocarcinomas were found in the screened group than among the controls.

In large cell cancer (Fig. 4E), screening found cases only a little earlier, but considerably more low stage cases were detected in the screened group than among the controls.

Screening for early lung cancer detects few low stage small cell tumors, but it detects many low stage squamous tumors. For large cell undifferentiated carcinoma and adenocarcinoma, screening every four months may be partially effective, but data concerning these two cell types are inconclusive now.

Condition 6. When a lung cancer screening program is made available to a group of people, there must be tangible benefits received by that group as a whole when compared with a similar group to whom screening was not made available: By tangible benefits, we mean reduction in mortality or significant improvement in the quality of life. Only mortality will be considered here. Figure 5A presents the number and timing of deaths from lung cancer among the screened and control groups as of December 31, 1979. There have been 42 lung cancer deaths in the group screened every four months and 50 lung cancer deaths in the control group. This is not a statistically significant difference.

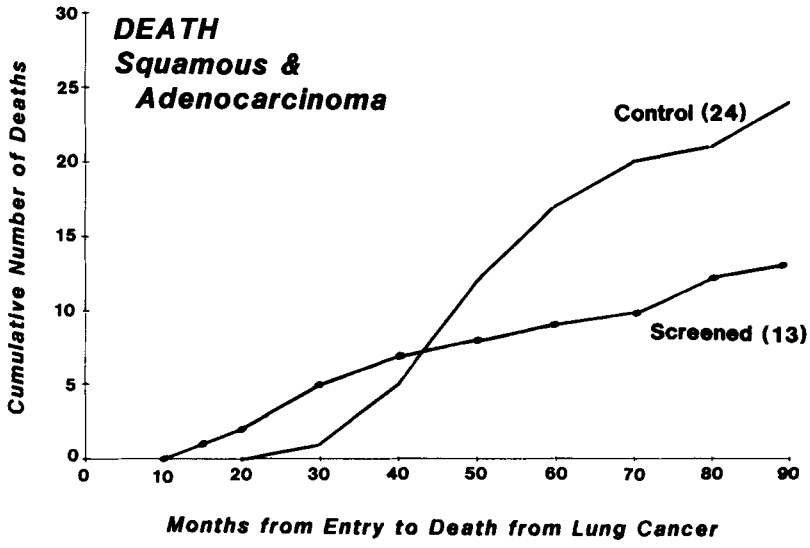

FIG. 6B. Figures 5D and 5E combined, squamous plus adenocarcinoma.

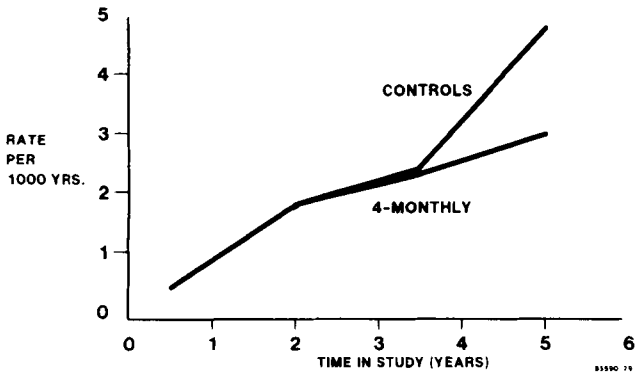

FIG. 7. Lung cancer death rates by time in study—control and screened patients.

In Figures 5B–5E, the various cell types of lung cancer are examined. Again, there were considerable differences. Small cell and large cell had one or two more lung cancer deaths in the screened group than in the control group, whereas among those with squamous and adenocarcinoma, there were quite a few more lung cancer deaths among the controls.

The most pessimistic picture of the benefits of screening appears when patients with small cell and large cell undifferentiated cancer are grouped together as in Figure 6A. Here, there is no evidence of any benefit from screening. The difference is three lung cancer deaths in the wrong direction—not favoring screening.

We get the most optimistic picture when squamous and adenocarcinoma patients are combined, as in Figure 6B. This Figure appears to show a strong benefit from screening. There were fewer deaths from lung cancer in the screened group compared with the controls. However, the difference between the two curves is not statistically significant.

Discussion

At this writing, lung cancer screening is not uniformly encouraging with respect to the reduction of mortality from lung cancer. However, there are some reasons for restrained optimism. First of all, at the time of this report (December 31, 1979), there are 32 more cases of lung cancer in the screened group than among the controls, and almost all of the difference is due to an excess number of low stage cases in the screened group. Probably, there are several cases of lung cancer among the controls that have not yet been discovered. These cases may surface in the next few years. Some should have progressed to high stage cancer by then, and mortality should result. The potential for this is demonstrated in Figure 4A with the small but pertinent observed excess of high stage controls after about 60 months in the study.

A second hopeful observation has to do with the actual lung cancer death rates for controls and screened patients, as shown in Figure 7. Attention is directed particularly to the rates for those patients who have been in the study four years or more. The death rate from lung cancer for the controls exceeds that of the screened group by a considerable amount, although this is not yet statistically significant either. However, this trend has been observed for the last three years, and the difference is growing.

We believe that lung cancer screening appears promising for squamous cancers and for adenocarcinomas but not for small or large cell undifferentiated tumors. Our recommendation now is to continue observation well into the follow-up phase (at least three to five more years). We suggest that no lung cancer screening projects be established for the general population of older male smokers at this time. But, we also suggest that we do not now know enough about this matter to make definitive statements.

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