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Early Lung Cancer as a Potential Target for Chemoprevention

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Abstract Carcinoma of the lung is the most common cause of death from cancer in the United States. In considering lung cancer for possible chemoprevention trials, we have analyzed the data collected by the collaborative NCI program on early lung cancer. The data indicate that at least 12 years of study of 80,000 people at risk for lung cancer (adult male cigarette smokers) would be required to establish a 25% reduction in squamous carcinoma of the lung. No intermediate markers of developing lung cancer are presently available to shorten the observation period. It is concluded that a study of the magnitude required is not feasible at the present time. © 1993 Wiley-Liss, Inc.

Key words: Cancer detection, chemoprevention, chest x-rays, cigarette smoking, lung cancer, sputum cytology

Carcinoma of the lung is the most common cause of death from cancer in both men and women in the United States [1]. In women the age-adjusted death rate from lung cancer exceeded that of breast cancer in the mid-1980's, and continues to increase at a rapid rate. An estimated 168,000 new cases of lung cancer are expected for 1992, with 146,000 deaths from this disease. The male to female ratio is now less than 2 to 1 due to the rapid rise in lung cancer among women over the last two decades [1]. As part of an effort to prevent death from this disease, the National Cancer Institute undertook a 10 year program to evaluate early detection of lung cancer in 1971; data from that study are of value in considering lung cancer as a model for possible chemoprevention trials.

The primary objective of the study was to determine whether sputum cytology supplementing the chest x-ray could improve early detection of lung cancer, and whether early detection coupled with early surgical treatment would increase survival and decrease death from lung cancer. There were a number of reports at that time indicating that sputum cytology was capable of detecting radiologically occult lung cancer at an *in situ* or early invasive stage [2–8]. The Japanese had developed fiber optic bronchoscopes that made it possible to visualize segmental and subsegmental bronchi and to obtain brush specimens for cytology. It became feasible to localize the source of exfoliated cancer cells in sputum specimens [9] and to resect early lung cancers. Prior lung cancer detection studies relying entirely on chest x-rays were unsuccessful in reducing deaths from lung cancer.

STUDY DESIGN

Study design required 30,000 high-risk subjects, so it was undertaken by three collaborating institutions: Mayo Clinic (MC), Johns Hopkins Medical Institution (JHH), and Memorial Sloan-Kettering Cancer Center (MSK). The

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study procedures are described in detail in a manual of procedures published by the U.S. Government Printing Office [10]. To secure a sufficiently large population at risk of lung cancer, male cigarette smokers who were over the age of 45 years and had no history of prior respiratory tract carcinoma were enrolled. At JHH and MSK, participants were recruited from the general metropolitan population of the greater Baltimore and the greater New York City areas respectively. The MC study participants were recruited from the patient population coming to the Mayo Clinic for an unrelated illness or for a general health examination. Potential candidates were excluded if they had a life expectancy of less than 5 years due to other disease, or if they were thought not able to tolerate pulmonary resection. They were also excluded if the initial sputum cytology, chest x-ray, or physical examination led to suspicion of lung cancer. Early in the study the high probability of lung cancer in these three populations was clearly established. Of the first twelve hundred men who died, 55% died of cardiovascular disease and 30% died of neoplasms, of which half (15%) were lung cancer.

Recruiting an adequate number of subjects proved to be a difficult and time-consuming task, a fact that cannot be overemphasized in considering clinical chemoprevention trials of lung cancer. The MC began recruiting in 1971, and did not complete their recruitment until 1976, with a total of 10,933 subjects. JHH began recruiting in 1973 and finished in 1978 with a total of 10,387 subjects. MSK recruitment began in 1974 and was completed in 1978 with 10,040 subjects. The total number of men recruited into the study from all three centers was 31,360. Follow-up was excellent at all three centers. At MSK only 39 of the 10,040 men recruited were lost to follow-up at the completion of the screening program. Thus, follow-up was 99.6% complete, and comparably excellent follow-up was obtained by both the MC and JHH groups.

The study design was essentially identical at JHH and MSK, but differed at MC. JHH and MSK study participants were randomized immediately into a group either receiving annual chest x-rays only, or a dual screening group receiving sputum cytology every four months in addition to the annual chest x-ray. The study design at the MC required sputum cytology, chest x-ray, and clinical examination of all potential candidates at the time of consideration for entry. Those who were suspected of lung cancer on any of these initial examinations were excluded from further study in the program. Those who were free of cancer by these criteria were then randomized into a screening group that was offered chest x-rays and sputum cytology every four months, or a control group that was contacted annually for follow-up but not requested to have any diagnostic or screening procedures.

LUNG CANCERS DETECTED

On their initial examination, 79 men were found to have lung cancer at JHH, 53 men at MSK, and 91 men at MC. This yielded prevalence rates of 7.6, 5.3, and 8.3 per thousand, respectively, at each of the above institutions. The MC patient population could potentially include some men seeking medical care because of symptoms attributable to lung cancer, perhaps accounting for their slightly higher prevalence rate. Subsequently, 366 lung cancers developed in the MC population, 405 in the JHH population, and 301 at MSK.

The results of the MSK study are available to us in greater detail and are summarized here; the MSK data are in substantial agreement with data from the two other centers. At MSK the overall screening study results were as follows: 190 lung cancers were detected by screening, 103 lung cancers were detected and diagnosed at other medical facilities during the screening period (interval cases), and 61 cases were diagnosed during a 2 year post-screening follow-up period. Thus, a total of 354 lung cancers were found among the 10,040 men during the 5 to 8 years of screening and two years post-screening. As will be discussed in more detail below, on the initial (prevalence) examination a greater number of lung cancers were detected in the dual screen group than in the x-ray only group. This was attributed to detection of radiologically occult lung cancers by sputum cytology. The lung cancer prevalence rate at MSK was 4.5 per thousand in the x-ray only screening group and 6.0 per thousand in the dual screening group. Incidence rates were 3.8 per thousand per year in the x-ray only group

and 3.7 per thousand per year in the dual screening group.

The incidence of lung cancer increased sharply with increasing age from less than 2 per thousand man-years under age 50, to 6 per thousand man-years at ages 65 to 70. Prevalence rates also increased rapidly with increasing age. Age is therefore an important factor in selecting a high risk population for chemoprevention trials.

Screening proved highly successful in detecting at least some lung cancers at an early stage. Of the total 190 cancers detected by screening, 100—more than half—were detected in Stage I, and of these, 93 were resected. By contrast, of the 103 lung cancers that developed and were diagnosed during the screening period but not detected by screening examination (interval cases), only 20 were found in Stage I, though 19 of these 20 were successfully resected. In the post screening period there were 61 lung cancers diagnosed; 12 were identified in Stage I and 11 were successfully resected. Thus, Stage I lung cancers constituted only 20% of the interval and post-screening cases, but more than half of the cases detected by screening (Table I). Of the entire 293 cases of lung cancer that developed during the screening period, including those not detected by screening but diagnosed elsewhere with or without symptoms, 41% (120 cases) were diagnosed in Stage I. This dropped to 20% during the post-screen period when these same men were receiving conventional medical care (Table I).

LUNG CANCER SURVIVAL

Over 90% of Stage I lung cancers could be resected and the survival of Stage I resected lung cancer is approximately 70% at 8 years. Resection rates for Stage II lung cancer were almost as high but survival at 5 years drops to 25%. The resection rate of Stage III carcinoma decreased sharply to 17% and the survival rate for those resected is less than 10% at 5 years (Fig. 1).

Since survival of the Stage I lung cancers is much better than that of higher stage lung cancers, even considering only those higher stage carcinomas that are resected, overall survival in the screened population exceeds that expected in the general population. Two criticisms have been brought against using favorable survival rates as an argument in favor of screening: first, that the better survival rate reflects length bias; and second, that early stage lung cancers may include cases that would not go on to cause death if left untreated. The length bias argument is countered by the fact that survival rates remain relatively constant after 5 or 6 years (Fig. 1). Most of the deaths that did occur after that time were due to second primary lung cancer. The question of over-diagnosis is addressed in Figure 2. The patients with Stage I T_1 and T_2 tumors could be divided into two groups, a group that was resected, and a somewhat smaller group that refused surgery or could not be operated on because of medical contra-indications. Since they were otherwise alike, the outcome would be the same in both groups except for the effect of surgical resection. Survival for the group whose tumors were resected was approximately 60% at 5 years and nearly identical in both the MSK and JHH patients whereas none of those who had no surgery survived for 5 years (Fig. 2). Since the hilar and mediastinal lymph node status was better known in the operated patients, and because this might create bias, the operated and non-operated groups were compared without regard to nodal status. We concluded that the patients with Stage I lung cancers who survived following resection would have died if left untreated, and that there is no over-diagnosis bias [11].

EVALUATION OF DETECTION METHODS

Lung cancer can be sub-categorized according to histology. Survival is most favorable for well-differentiated adenocarcinomas and epidermoid carcinomas. It is somewhat poorer for undifferentiated large cell carcinomas, and very poor for undifferentiated small cell or oat cell carcinomas. Only a single individual among 55 with oat cell carcinoma survived longer than 5 years.

Sputum cytology and the chest x-ray are complementary methods of detection. Early lung cancers diagnosed by cytology are almost all epidermoid carcinomas, whereas early stage adenocarcinomas are detected primarily by chest x-ray. Of the 147 lung cancers that developed in the population of 4,968 men randomized to the dual screening category at MSK, 27 were

TABLE I. Lung Cancer Detection Program at Memorial Sloan-Kettering

Stage	Number of Lung Cancers (Number Resected)			
	Detected by Screen	Interval	Post-Screen	Total
I	100 (93)	20 (19)	12 (11)	138 (123)
II	15 (13)	3 (3)	5 (4)	23 (20)
III	73 (18)	80 (8)	44 (7)	199 (33)
Total	190 (124)	103 (30)	61 (22)	354 (176)

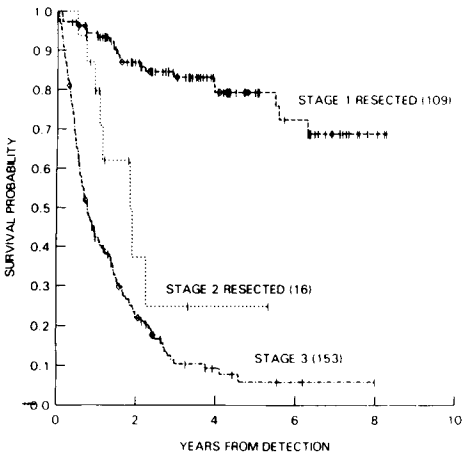

Fig. 1. Survival from lung cancer by stage. Three deaths from lung cancer after 5 years in the Stage I resected group were due to new primary lung cancers. From [17] with permission of the publisher.

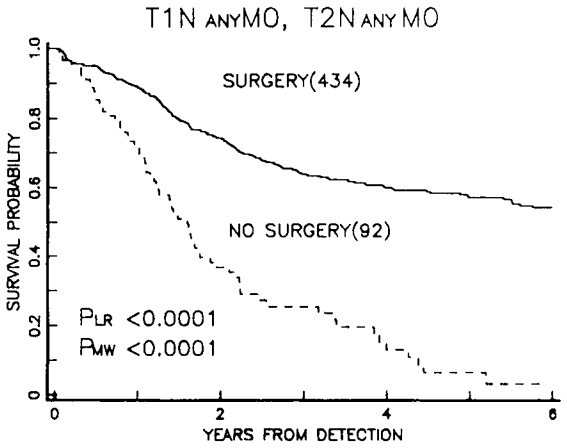

Fig. 2. Kaplan-Meier estimates of survival from resected versus unresected Stage I (T_1 and T_2) lung cancer. To avoid bias in comparing clinical staging (unresected cases) with pathologic staging (resected cases) the status of lymph nodes was ignored. Deaths are due to lung cancer; other deaths are treated as withdrawal. Significance is by log-rank (Plr) and modified Wilcoxon (Pmw) tests. From [11] with permission of the publisher.

detected by cytology and 20 of these were epidermoid. Of 60 lung cancers detected by chest x-ray, 44 were adenocarcinomas. It should be noted parenthetically that at all three centers, adenocarcinoma detected by chest x-rays was the most frequent tumor type, accounting for 47% of non-small cell lung carcinomas, compared to 35% for epidermoid carcinoma. Of the 46 interval lung cancers not detected by screening, twelve were small cell or oat cell carcinomas that are characteristically very rapidly growing and rapidly disseminating tumors. It is presumed that they developed between screening examinations (Table II).

In the initial or prevalence examination at MSK, 30 lung cancers were detected in the dual screen population compared with 23 in the x-ray only population. The difference was due to radiologically occult lung cancers detected by sputum cytology in the dual screen group. These were *in situ* and superficially invasive squamous carcinomas. Careful histologic study of these early squamous carcinomas by step sections of the entire bronchial tree from the resected lobectomy specimens demonstrated that most of these carcinomas took origin in segmental or sub-segmental bronchi [12]. It was not until the carcinomas developed into sub-

TABLE II. Method of Detection of Lung Cancer According to Cell Type in the MSK Dual Screen Population (4968 Men)

Cell Type	Method of Detection				
	Cytology	X-Ray	Both	Interval	Total
Epidermoid	20	8	8	10	46
Adenocarcinoma	5	44	3	21	73
Large cell cancer	1	3	0	2	6
Oat cell cancer	1	5	3	12	21
Carcinoid	0	0	0	1	1
Total	27	60	14	46	147

stantial tumors that the lobar and mainstem bronchi were involved.

Squamous metaplasia has been proposed as an intermediate marker in the development of squamous lung cancer. The most frequent sites of squamous metaplasia of the tracheo-bronchial tree are in the main stem and lobar bronchi, proximal to the usual sites of origin of squamous carcinoma and certainly far proximal to the peripheral parenchymal origin of most adenocarcinomas. The location of squamous metaplasia, differing from that of the site of origin of lung cancer, is a strong argument against using squamous metaplasia as an intermediate marker. Furthermore, squamous metaplasia is very common, particularly among cigarette smokers. It is probably a response to irritation from inhaled smoke or other respired gases or particles, not a reflection of early neoplastic change. Careful histologic examination of the cases of early lung cancer in this study revealed a number of instances in which carcinoma *in situ* was seen arising in otherwise unremarkable mucosa of segmental bronchi that did not show squamous metaplasia [12]. It seems clear that squamous metaplasia is not a necessary precursor of carcinoma. In the case of adenocarcinoma, which is now the most common lung cancer, no dysplasia, carcinoma *in situ*, or other change in adjacent bronchial epithelium has been identified as a potential precursor or intermediate marker of the carcinoma [13].

It could be argued that *in situ* and superficially invasive, radiologically occult squamous carcinomas represent overdiagnosis, and that if left alone would never progress to clinically apparent carcinoma. If this were true there would always be an excess of cases in the dual screen group because of the occult carcinomas detected by sputum cytology. By the end of the screening period, however, the total number of lung cancers in the two groups were almost identical. One hundred seventy-eight cancers were diagnosed in the x-ray only group and 176 in the dual screen group. Furthermore, survival from lung cancer was almost exactly the same in the two groups. We concluded that the squamous lung cancers detected by sputum cytology are slow growing and very slow to metastasize. At the time these carcinomas are first detectable by chest x-ray, they are still localized and still resectable and curable by lobectomy. We concluded that sputum cytology is of value in detecting radiologically occult lung cancers in patients at high risk who have only a single examination and are unlikely to remain under medical surveillance. In high risk populations examined annually by chest x-rays, sputum cytology has no added benefit.

ON THE VALUE OF SCREENING FOR LUNG CANCER

Is there any benefit from screening? To answer this in a statistically definitive manner would require randomizing subjects into screening and no-screening groups—a practical impossibility. Even if it were morally acceptable, it would be technically impossible to prohibit the control population from having chest x-rays.

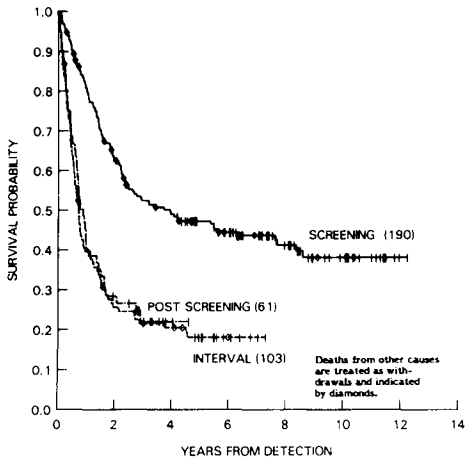

Fig. 3. Survival from lung cancer detected by screening compared to interval and post-screening cases. From [8] with permission of the publisher.

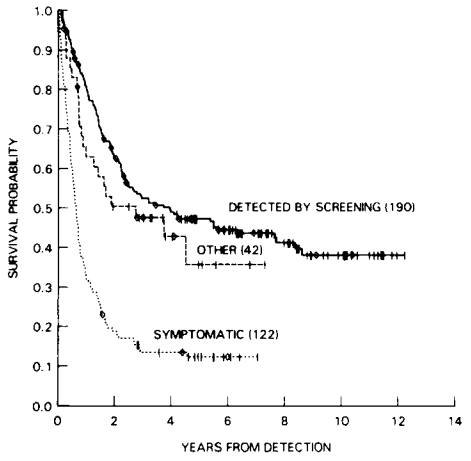

Fig. 4. Survival of lung cancer according to method of detection. The survival of patients with asymptomatic lung cancer detected by chest x-rays taken as part of a routine physical examination or incidental to hospitalization for unrelated illness (other) is essentially the same as for men with lung cancer detected by screening. Survival of patients with symptomatic lung cancer was comparable to overall survival from lung cancer in the United States. From [18] with permission of the publisher.

Conclusions about screening must be derived indirectly from the data. These data show that survival of patients whose lung cancers are detected by screening is about 40% at 10 years, whereas those who develop lung cancer not detected by screening have survival rates of approximately 15% at 5 to 6 years. Even more impressive, patients whose lung cancers developed and were diagnosed in the post-screening period had exactly the same survivial rates as interval patients who developed lung cancer during the screening period which was not detected by screening (Fig. 3). The patients in the post-screening period were, of course, receiving conventional medical care. Finally, it is worth noting that the majority of patients in the interval group and in the post-screening group with early stage lung cancer, *i.e.*, Stage I lung cancer, were still asymptomatic at the time of diagnosis. Their cancers were detected by chest x-rays taken routinely either as part of the admission examination on entry into the hospital for other illness, or as part of an examination by their family doctor. One can consider Stage I lung cancers diagnosed in this manner in the post-screening period and in intervals between screening examinations as having been detected by screening chest x-rays carried out elsewhere. If one compares survival of patients whose lung cancer was detected by our screening with survival of patients who had asymptomatic lung cancer detected by routine chest x-rays elsewhere, the survival rates are almost the same (Fig. 4). On the other hand, survival of patients with symptomatic lung cancer leading to diagnosis was very poor, in the range of 10 to 12% at 5 years, quite comparable to survival rates for lung cancer in general throughout the country.

In summary, lung cancer survival at the present time throughout the United States is approximately 13% at 5 years. In this screening program, 40% of all lung cancers were detected in Stage I. Two-thirds of those with Stage I lung cancer treated by resection did not die of their disease. Overall, 35% of the participants with lung cancer survived for 5 years, regardless of tumor stage and treatment. For patients with asymptomatic lung cancer detected by their personal physician, survival is a similar 35% at 7 years. For patients with symptomatic lung cancer diagnosed by their personal physician, survival is only 13% at 7 years. We conclude that symptomatic lung cancer is seldom curable, and that the decision not to screen for asymptomatic lung cancer is equivalent to a decision not to treat for cure. Since single site

screening programs similar to this one are very expensive, we recommend that screening for early lung cancer be carried out by chest x-rays included in the annual physical examination of asymptomatic high risk individuals. Sputum cytology is advisable only for individuals who are unlikely to return.

DURATION OF EARLY STAGE LUNG CANCER

Certain lung cancers behave in a more aggressive, and others in a more indolent fashion. Among the aggressive carcinomas is small cell or oat cell carcinoma. In general, well-differentiated adenocarcinomas or epidermoid carcinomas are the most favorable, but even among these there are subsets of carcinoma of similar histology with quite different growth rates. In a study of prior chest x-rays from patients in this program, Heelan [14] found that 51 of 78 patients had x-ray-visible lesions at least one year prior to the time their lung cancer was detected. The implication was that those with prior visible lesions had more slowly growing cancers. This was confirmed by their survival probability which was approximately 70% at 5 to 6 years. In contrast, the patients without a prior visible lesion had survival rates of slightly over 20% at 5 to 6 years. Thus, even among the carcinomas with similar histologic classification, there are distinct differences in growth rate and behavior.

Flehinger and Kimmel [15] have used the data derived from this lung cancer detection study to construct a mathematical model of lung cancer development. They conclude that for adenocarcinoma and large cell carcinoma of the lung: 1) the mean duration ranges upwards from 4 years; 2) the probability of detection by a single x-ray examination in early stage lung cancer ranges downwards from 16%; 3) the probability of surgical cure of early stage lung cancer is up to 52%; and 4) expected reduction in mortality by annual chest x-ray screening is up to 18% [16]. While these are not optimistic estimates, it should be recalled that 18% of the expected 168,000 new cases of lung cancer this year represent about 30,000 patients. The hope, of course, is that a more effective screening technique than the routine chest x-ray can eventually be developed.

MULTIPLE LUNG CANCERS

Do patients who have had one lung cancer and are now at high-risk of a second lung cancer represent a suitable population for chemoprevention? In a review of the collaborative early lung cancer detection program, the probability of a second carcinoma at each of the 3 centers was as follows: At MSK, 14 of 293 patients (4.8%); at JHH, 28 of 475 patients (5.9%); and at MC, 40 of 540 patients (7.4%) had second primary lung cancers. In total, 40 patients had synchronous second lung cancers, 37 had metachronous lung cancers, and 5 patients had both synchronous and metachronous carcinomas.

STATISTICAL CONSIDERATIONS FOR CLINICAL CHEMOPREVENTION TRIALS

One can calculate how large a population at risk would be needed to prove, with statistical confidence, that a given chemoprevention program was effective in preventing lung cancer. The following is assumed: 1) the population at risk is randomly divided into study and control groups, the former receiving chemoprevention beginning at age 50 and the latter receiving none; 2) based on data from the lung cancer study described above, and in the absence of preventive treatment, 5% will eventually develop squamous lung cancer based on data from the lung cancer study described above; 3) both study and control groups are examined annually by chest x-rays with detection probability of 0.3; and 4) the mean duration of early stage squamous lung cancer is 4 years. Table III indicates for a given reduction in incidence of lung cancer, the various population sizes and number of years in the study required to establish 0.05 significance. As indicated in the table, a chemoprevention program that reduces squamous lung cancer incidence by 25% would require a study of at least 12 years duration and involve 80,000 people at risk (adult male cigarette smokers). To confirm a 50% reduction would require 20,000 people for eleven years, or 80,000 people for 4 years. A study of this magnitude is not feasible at the present time, or even justified by preliminary data on chemoprevention agents, and since there are presently no good intermediate markers of developing lung cancer

TABLE III. Population Size and Study Durations Required to Prove A Significant (p = 0.05) Reduction in the Incidence Rates of Squamous Cell Lung Cancer

Incidence Reduction	Population Size	Years on Study	
		Power = 0.8	Power = 0.9
25%	20,000	Impossible	
	40,000	Impossible	
	80,000	12	15
50%	20,000	11	15
	40,000	6	7
	80,000	4	5
75%	20,000	3	5
	40,000	3	3
	80,000	2	2

that could shorten the observation period, we conclude that squamous lung cancer is not a suitable model for evaluating chemoprevention agents. A similar argument can be made with respect to adenocarcinomas and undifferentiated small cell carcinoma.

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