A mathematical model of the progression kinetics of lung cancer was described and used to shed light on the natural history of adenocarcinoma and large cell carcinoma of lung from data collected in screening studies of male smokers by the Memorial Sloan-Kettering Cancer Center and The Johns Hopkins Medical Institutions. In both programs, estimates of the mean duration of early-stage adenocarcinoma or large cell carcinoma of lung ranged upward from 4 years, and estimates of the probability of detecting it in early-stage disease ranged downward from .16. The probabilities of curing early-stage disease through surgical treatment were found to be at most .52 and .13 in the New York and Baltimore studies, respectively. These estimates led to the conclusion that expected reduction in mortality from adenocarcinoma and large cell carcinoma of lung as due to annual x-ray screening from age 45 to 80 years is not greater than 18% in New York and 5% in Baltimore. [J Natl Cancer Inst 1988;80:337-344]

Currently, lung cancer is the most common cause of cancer death in the United States. Cure rates are low because, in the majority of cases, metastasis to regional lymph nodes or distant sites occurs before symptoms lead the patient to medical attention. Earlier diagnosis would require detection by screening asymptomatic high-risk individuals (e.g., smokers over the age of 45 yr), and only two such screening techniques are presently available: the chest x-ray and sputum cytology. Several clinical studies undertaken before 1970 failed to demonstrate any impact on lung cancer mortality attributable to annual or semiannual screening with chest radiographs (1-3). Thus early in the 1970s the National Cancer Institute organized three cooperating studies intended to answer the following questions (4). (a) Can detection of lung cancer be improved by adding modern sputum cytologic screening techniques to yearly conventional x-ray examinations? (b) Will the mortality from lung cancer be reduced by this type of screening program, newer localizing methods, and prompt appropriate treatment?

Randomized clinical trials were conducted in three centers: at the Mayo Clinic (5) in Rochester, MN, The Johns Hopkins Medical Institutions (6) in Baltimore, MD, and the Memorial Sloan-Kettering Cancer Center (7,8) in New York, NY. The Hopkins and Sloan-Kettering programs were both initiated in 1974 and lasted for 10 years. Their designs were identical and focused on a comparison of 4-monthly sputum cytology combined with annual chest x-rays as opposed to annual chest x-rays alone. The Mayo program ran from 1971 to 1984 with a completely different design in which all participants were initially screened by x-ray and cytology, and only those without suspicion of lung cancer were randomized into two groups; one group was offered chest x-rays plus sputum examinations every 4 months, and the other group had no further programmed screening at all. In all three centers, the lung cancers were treated promptly by surgical resection whenever possible. None of the programs demonstrated a significant decrease in mortality from lung cancer attributable to differences in the screening programs (9). The Hopkins and Sloan-Kettering studies directly addressed only the value of sputum cytology; x-ray screening, which was identical in both study and control groups, was not assessed.

Data collected in these trials have now been made available for study and analysis. This paper makes use of a mathematical model of the natural history of lung can-

Abbreviations Used: AJC = American Joint Committee on Cancer; ALCa = adenocarcinoma-large cell carcinoma of lung; PA = posteroanterior.
cancer in the presence of a screening program to analyze the Sloan-Kettering and Hopkins data. A description of the model, mathematical details, and statistical analysis of Sloan-Kettering data were described previously (9). We now review assumptions on which the model is based, analyze the Hopkins data, and compare conclusions derived from the New York and Baltimore studies.

In each of the two centers, approximately 10,000 male volunteers >45 years of age, each of whom smoked at least 20 cigarettes per day, were randomly assigned to one of two screening schedules. The "x-ray only" group were offered PA and lateral chest x-rays at enrollment and annually thereafter; the "dual screen" group were asked to submit sputum specimens every 4 months in addition to the annual radiographic examinations. Active screening was continued until all participants had been enrolled for at least 5 years. Any positive or suspicious findings were carefully investigated, and surgery was offered whenever resection of lung cancer seemed feasible. Follow-up staffs in both centers urged all participants to follow their assigned screening schedules, and all enrollees were followed through 1984 to determine their survival and cancer status, even if they failed to comply with the screening schedules. Approximately 0.5% were lost to follow-up at the end of 10 years. All deaths in the study population were individually reviewed by a Mortality Review Committee consisting of pulmonary physicians, pathologists, and biostatisticians from the cooperating institutions to determine whether death was due to lung cancer. The data used in this modeling effort consist of the following.

(a) Age at first screen for all participants. (The age distribution was almost identical in the two institutions.)

(b) Number of years in the screening program for each participant (varying from 5 to 8 yr in both studies: totals of 61,961 man-yr at Sloan-Kettering and 64,737 at Hopkins).

(c) Date and cause of every death. (From all causes, there were 879 deaths during the study period in the Sloan-Kettering program and 1,207 in the Hopkins program: rates of 14/1,000/yr at Sloan-Kettering and 19/1,000/yr at Hopkins.)

(d) Characterization of each detected cancer by (1) cell type, (2) whether or not detected by routine screening x-ray, (3) age at detection, (4) screening year at detection, (5) stage, and (6) survival after detection. AJC stage I cancers are called "early;" AJC stages II and III are called "advanced" (10).

(e) For Sloan-Kettering cases detected by x-ray after the initial screen, retrospective evidence of the presence or absence of cancer in the previous year's radiograph (11).

During the screening period, 423 and 293 lung cancers were diagnosed in the Hopkins and Sloan-Kettering studies, respectively (rates of 6.5 and 4.7/1,000/yr). A brief summary of their characteristics is presented in table 1.

We note first that in both the Sloan-Kettering and Hopkins studies more than half the lung cancers found were adenocarcinomas or undifferentiated large cell carcinomas. The difference in proportion of large cell carcinomas at Sloan-Kettering and Hopkins is attributed to a difference in diagnostic criteria used by the pathologists in the two institutions. Some cases classified as large cell carcinoma of lung at Hopkins would have been considered poorly differentiated adenocarcinoma at Sloan-Kettering; thus, for the purposes of this analysis, adenocarcinoma and large cell carcinoma of lung are grouped together and are jointly named "ALCa." In each institution, 83% (59/71 and 73/88) of the early cases of ALCa were diagnosed in the Hopkins and Sloan-Kettering studies more than half the lung cancers found were adenocarcinomas or undifferentiated large cell carcinomas.

### Table 1. Lung cancers confirmed during screening period classified by cell type, early vs. advanced stage, and whether detected by routine x-ray screening*

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Detected by x-ray screening</th>
<th>Not detected by x-ray screening</th>
<th>Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Advanced</td>
<td>Total</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>56</td>
<td>44</td>
<td>100</td>
</tr>
<tr>
<td>Large cell</td>
<td>3</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Squamous cell</td>
<td>17</td>
<td>24</td>
<td>41</td>
</tr>
<tr>
<td>Oat cell</td>
<td>2</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>78</td>
<td>85</td>
<td>163</td>
</tr>
</tbody>
</table>

**Notes:**
- Counts refer to lung cancers found by any method between the date of enrollment and its anniversary date in 1982. Early cancers are AJC stage I; advanced are AJC stages II and III (10). Cancers "Not detected by x-ray screening" were found by sputum cytology, symptoms, or x-rays taken elsewhere, outside of routine screening procedures. — = <0.5%.

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Figure 1 depicts Kaplan-Meier estimates of the survival probability of all cases of ALCa in the Sloan-Kettering and Hopkins studies, in which 5-year survivals were .40 and .25, respectively. Figure 2 depicts the survival of early and advanced cases of ALCa in (A) the Sloan-Kettering study and (B) the Hopkins study. The 5-year survivals of early cases in New York and Baltimore were .73 and .55, respectively, while the advanced cases had corresponding survival probabilities of .14 and .07. Early cases constituted 45% and 41% of all the ALCa found in the two studies. These percentages and the associated survivals of early cases are much better than the statistics reported for the United States as a whole, in which 5-year survival from lung cancer is estimated currently to be .13 for all cell types (12).

It is very important to determine whether these apparent improvements represent true advantages to early detection, treatment, and cure or whether they are artifacts of the well-known biases introduced by screening programs, i.e., length-biased sampling, lead-time bias, and over-diagnosis bias. The basic question concerns the men who had ALCa detected by chest x-ray in early stage and promptly resected and who are alive and well many years later. Had they not been screened radiographically, would their cancers have progressed to advanced stage, symptoms, and death or would these men still harbor and be unaware of their disease? Since in the Sloan-Kettering and Hopkins studies all participants were offered the same chest x-ray procedures, we have no direct evidence with which to answer this question. Therefore, we have developed a mathematical model to represent the natural history of ALCa: we have estimated the essential parameters of the model and have used it to draw inferences about the possible long-term benefits associated with screening.
Assumptions

Our model is based on the simplest set of assumptions that we considered capable of approximating the complexity of the incidence and development of ALCa in the presence of a periodic program of x-ray examinations, surgical treatment, and follow-up. The model is illustrated in figure 3.

(a) In the high-risk population volunteering for screening, a subgroup of the participants are susceptible to ALCa. The probability that an individual belongs to this subgroup is designated susceptibility, \( p \).

(b) In the absence of screening and treatment, ALCa, after its onset, progresses through two stages: early and advanced, followed by cancer death.

(c) Age of onset and durations of the early and advanced stages are random variables. Age of onset is characterized by a distribution with increasing hazard, and stage durations are exponentially distributed with mean values \( \mu_1 \) and \( \mu_2 \).

(d) A screening program consists of periodic examinations intended to detect the cancer. If an early case of ALCa is present, a single examination detects it with probability \( p_1 \). Since compliance with the screen is not perfect, \( p_1 \) must be interpreted as the probability that the examination is carried out when scheduled and that the cancer is detected. Advanced ALCa may be brought to medical attention as a result of screening detection or symptoms.

(e) When ALCa is detected, screening is aborted and the patient is treated. The probability of "cure" for early stage is equal to \( c_1 \); advanced ALCa cannot be cured. Cure is defined pragmatically in terms of the patient's survival after detection: if the patient is cured, his survival distribution is the same as if he had never had ALCa; if he is not cured, his survival distribution is the same as if his cancer had not been detected through screening.

(f) Members of the population are subject to the competing risk of death from ALCa or death from other causes. Onset of ALCa and death from ALCa can occur only if not preceded by death from other causes.

The key parameters in this model are the susceptibility, \( p \); the mean duration of the early stage, \( \mu_1 \); the detectability of the early stage, \( p_1 \); and the cure probability of the early stage, \( c_1 \). We must recognize that none of these quantities can be directly observed. It is impossible to determine whether an individual is susceptible to ALCa if he does not develop the disease. Furthermore, even for a patient who is diagnosed with ALCa, there is no direct way of knowing the length of time between onset and date of detection. If early-stage disease is not detected by chest x-ray or sputum cytology, there is generally no method of ascertaining its presence. Therefore, \( p_1 \) cannot be estimated as the number of detected cases divided by the total number of early-stage cases. Finally, if a patient survives many years after treatment for ALCa, we cannot know how long he would have survived in the absence of treatment, so that \( c_1 \) cannot be estimated directly as the proportion of patients surviving treatment.

In this study, parameter estimation consists primarily of determining those values of susceptibility, mean duration of early stage, early-stage detectability, and early-stage cure probability that are consistent with observed data in the context of our model. The critical observed data are survival probabilities of early and advanced ALCa, total number of early cases, and age-dependent cancer mortality rates.

All the key parameters of the model, \( p, \mu_1, p_1, \) and \( c_1 \), depend strongly on the population being screened, on the techniques of carrying out the chest x-ray examinations, and on the methods of treatment, in addition to the natural history of the disease. Therefore, estimates of these parameters from the Hopkins data may differ from those based on the Sloan-Kettering data. The two populations differed in the following important ways: (a) race—8% of the Sloan-Kettering and 13% of the Hopkins participants were black; (b) reported exposure to potential occupational and environmental carcinogens—Sloan-Kettering, 11%, and Hopkins, 25%; and (c) reported smoking habits—median number of cigarettes per day—Sloan-Kettering, 31.2, and Hopkins, 28.5. Methods of recruitment were almost identical, but results were quite different. The majority of the Hopkins participants were recruited from a list of motor vehicle license holders. The Sloan-Kettering group included large numbers of subscribers to a group health plan; New York City policemen; and respondents to newspaper, radio, and television publicity; as well as motor vehicle license holders. The age distributions of the two populations were almost identical. For whatever reason, the overall death rate from all causes was much higher in the Hopkins than in the Sloan-Kettering population (19/1,000/yr at Hopkins and 14/1,000/yr at Sloan-Kettering).

In both institutions the chest x-rays were PA and lateral views taken with the use of 36 × 43-cm films at 140 kV at a distance of 1.8 m or more. They were interpreted separately by two professionals. At Hopkins both were Board-certified radiologists, while at Sloan-Kettering the first reading was by a specially trained radiologic technologist and the second was by a Board-certified radiologist. Each institution used another Board-certified radiologist to review suspicious findings and arbitrate conflicting interpretations.

In both institutions, the recommended treatment of stage I cases consisted of surgical resection. At Hopkins, mediastinoscopy preceded surgery in many cases (d), but mediastinal lymph node dissection was not routinely carried out.
with the resection of the lung tumor, at Sloan-Kettering, mediastinoscopy was not performed and the mediastinal lymph nodes were dissected as part of the surgical procedure (7). Thus there may be differences in the postsurgical (pathologic) staging, as well as in the treatment, so that the early cancers in the two institutions may not be identically defined. Moreover, surgical treatment of advanced cases, particularly those with mediastinal lymph node involvement, tended to be more aggressive at Sloan-Kettering.

Thus we have identified a number of differences in populations and procedures that may induce differences in parameter estimates and conclusions about the value of screening.

Parameter Estimation

We developed, based on the assumptions of our model, a set of equations to express observable quantities in terms of nonobservable model parameters. We then carried out a set of calculations to eliminate those values of the parameters for which the observed data would be very improbable. (This is the accepted philosophy behind confidence interval estimation.) The details of this procedure are fully discussed in (9). This process proceeds through the following steps:

(a) The mean duration of the advanced stage, \( \mu_2 \), is estimated by maximum likelihood from survival data of advanced cases.

(b) The maximum likelihood estimate, \( \hat{c}_1 \), of the cure probability, \( c_1 \), is expressed as a regression on the mean duration of early stage, \( \mu_1 \) (taking into account the above estimate of \( \mu_2 \)) from survival data of early cases.

(c) A maximum likelihood estimate of susceptibility, \( p \), is found, conditional on \( \mu_1 \) and \( p_1 \), from the total number of early cases detected over the course of the study.

(d) A joint confidence region for \( \mu_1 \) and \( p_1 \), using the estimate of \( \mu_2 \) and the relationship of \( \hat{c}_1 \) to \( \mu_1 \), is determined by least-squares fitting of age-dependent ALCa mortality rates.

(e) For Sloan-Kettering data, the \( (\mu_1, p_1) \) region is restricted by inference from data on retrospective evidence of presence or absence of cancer in radiographs taken a year before the detection of a tumor.

(f) Parameter values contained in the confidence regions developed above are used to calculate the expected number of ALCa deaths in the study period; the regions are further restricted to match these expectations with observed mortality.

The results of this estimation follow.

(a) On the basis of survival data, the mean duration of the advanced stage of ALCa, \( \mu_2 \), is estimated to be 2.21 years in the Sloan-Kettering study and 1.41 years in the Hopkins study.

(b) In both studies, the estimated cure probability, \( \hat{c}_1 \), decreases almost linearly with \( \mu_1 \), the mean time in early stage. To explain this relationship, we recall assumption e in which it is postulated that the patient who is not cured survives as if his cancer had not been detected through screening. Thus the estimated cure probability \( \hat{c}_1 \) is roughly equivalent to the proportion of patients who lived longer than might have been predicted based on a mean survival of \( \mu_1 + \mu_2 \). The larger the value of \( \mu_1 \), the smaller is this estimate. The regressions with their 95% confidence limits are exhibited in figure 4.

(c) The 95% confidence regions for \( (\mu_1, p_1) \) based on agedependent ALCa mortality are exhibited in figure 5. The Sloan-Kettering estimate of \( \hat{c}_1 \) decreases from .72 to 0 as \( \mu_1 \) increases from 0 to 12 years, while the corresponding Hopkins estimate goes from .49 at 0 year to 0 at 5 years.

(d) The 95% confidence regions for \( (\mu_1, p_1) \) based on age-dependent ALCa mortality are exhibited in figure 5. The Sloan-Kettering estimate of \( \hat{c}_1 \) decreases from .72 to 0 as \( \mu_1 \) increases from 0 to 12 years, while the corresponding Hopkins estimate goes from .49 at 0 year to 0 at 5 years.
(e) In the Sloan-Kettering study, a special investigation related to the radiographs of patients whose cancers were detected by screening after their initial screen (11). Previous negative radiographs, when available, were re-evaluated in light of the findings at detection. It was found that 80% of those with ALCa detected in the early stage exhibited evidence of disease on their previous x-rays. With the methods described in the previous paper, this piece of information was used to restrict the \((\mu_1, P_1)\) confidence region with the curve represented by a dashed line in figure 5A, after which \(\hat{\mu}_1\) ranges up from 3 years and \(\hat{P}_1\), down from .20, very similar to the Hopkins confidence region.

(f) The bold-type curves in figure 5 represent the parameter values for which the expected numbers of ALCa deaths in the study period exactly match the actual numbers. In the Sloan-Kettering study, there were 72 deaths due to ALCa, while in the Hopkins study there were 133. To match these numbers, the Sloan-Kettering values of \(\mu_1\) range up from 4 years and \(\hat{P}_1\), down from .16; the Hopkins values of \(\mu_1\), up from 4 years and \(\hat{P}_1\), down from .15.

In table 2(A), we display typical values of \(\hat{\beta}\) and \(\hat{c}_1\) corresponding to these estimates of \(P_1\) and \(\mu_1\). The Sloan-Kettering values of susceptibility range from .10 to .14, while the Hopkins values are .16 and .19. The estimates of cure probability for Sloan-Kettering are .52 at \(\mu_1 = 4\) years, .33 at \(\mu_1 = 7\), and .07 at \(\mu_1 = 11\); the Hopkins values of \(\hat{c}_1\) are .13 at \(\mu_1 = 4\) and 0 at \(\mu_1 = 7\). Note that the \((\mu_1, P_1)\) confidence regions are almost identical for the two institutions, while the corresponding values of cure probability and susceptibility are markedly different.

The difference in susceptibility to ALCa of subjects enrolled at Sloan-Kettering and Hopkins cannot be attributed to differences in race or reported exposure to carcinogens since the characteristics of ALCa patients in both studies were not substantially different from those of the populations as a whole. For example, the proportion of blacks among the ALCa patients is 8% at Sloan-Kettering and 16% at Hopkins, while the population proportions are 8% and 13%. The proportions of ALCa patients reporting exposure to carcinogens are 11% and 24%, respectively, compared to population proportions of 11% and 25%. Some other environmental or sociologic factor must account for the greater susceptibility of the Baltimore group.

With respect to the estimated cure probabilities, four pos-

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**Table 2. Expected mortality in population screened from 45 years to 80 years of age***

<table>
<thead>
<tr>
<th>Model parameter</th>
<th>Estimates</th>
<th>Expected mortality</th>
<th>Percent difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\mu_1) (p_1)</td>
<td>(\hat{\beta}) (\hat{c}_1)</td>
<td>No screen</td>
<td>Screening</td>
</tr>
<tr>
<td>-----------------</td>
<td>-----------</td>
<td>--------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering</td>
<td>4 .16</td>
<td>.10 .52</td>
<td>52</td>
</tr>
<tr>
<td>7 .09</td>
<td>.12 .33</td>
<td>50</td>
<td>45</td>
</tr>
<tr>
<td>11 .06</td>
<td>.14 .07</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>Johns Hopkins</td>
<td>4 .15</td>
<td>.16 .13</td>
<td>78</td>
</tr>
<tr>
<td>7 .08</td>
<td>.19</td>
<td>79</td>
<td>79</td>
</tr>
</tbody>
</table>

**(A) From ALCa (per 1,000)**

| Memorial Sloan-Kettering | 4 .18 | .09 .48 | 44 | 36 | 18 |
| 7 .10 | .10 .27 | 42 | 39 | 9 |
| 11 .06 | .12 | 43 | 43 | 0 |
| Johns Hopkins | 4 .20 | .08 .21 | 40 | 37 | 8 |
| 7 .11 | .10 | 39 | 39 | 0 |

**(B) From adenocarcinoma of lung (per 1,000)**

*\(\mu_1\) = mean duration of early stage, \(p_1\) = probability of detecting early-stage cancer at a single radiographic examination, \(\hat{\beta}\) = estimated susceptibility, \(\hat{c}_1\) = estimated cure probability of early stage.
Possible differences between the studies might contribute to the large difference between Sloan-Kettering and Hopkins. First, mediastinal node dissection or other differences in treatment at Sloan-Kettering may improve survival. Second, some cases characterized as early at Hopkins might have hidden nodal metastases that would be found through mediastinal node dissection at Sloan-Kettering, where they would be classified advanced. Shifting the least favorable early cases to the advanced group would make survival in both groups appear better in statistical analysis [the Will Rogers effect (13)].

Third, the pathologic criteria for selecting the group of adenocarcinoma plus large cell carcinoma patients may not be identical in the two institutions. Fourth, the natural history of ALCa may be different in the New York and Baltimore populations because of differences in racial mix and exposure to carcinogens, among other factors.

We have wherever possible tried to estimate the maximum conceivable effect of each of these four explanations on estimated survival probabilities. First, we found that, of those 15 ALCa patients classified stage III only because of mediastinal lymph node involvement in the Sloan-Kettering study, only 4 are currently alive. Thus, unless we can attribute benefit to the removal of lymph nodes in which no cancer is detected by pathologic examination, we must conclude that lymph node dissection alone contributes little to the probability of cure. We are unable to evaluate other possible differences in surgical procedure, since the computer-based files obtained from the National Cancer Institute had no information about treatment in the Hopkins study.

Second, we estimated the maximum Will Rogers effect by shifting the same 15 Sloan-Kettering patients from the advanced to the early case group and by recalculating the survival of both groups. This shift reduced the 5-year survival of the early group from .73 to .66 and the 2-year survival of the advanced group from .33 to .26. These effects are small compared to the differences between those of Sloan-Kettering and Hopkins.

Third, it seems unlikely that pathologic criteria can be responsible for a major difference, since the proportion of patients with ALCa is nearly identical in the two studies (see table 1).

Fourth, no significant mortality differences could be found, within either the Sloan-Kettering or Hopkins population, attributable to race or reported exposure to carcinogens. Thus any difference in the natural history of ALCa between the two populations must be ascribed to some factors that are not recorded in the study data base, such as poverty levels or environmental pollution. For some reason, the general level of health in the Baltimore study population was poorer than in New York, as reflected by the fact that the total number of deaths from all causes was 879 in the Sloan-Kettering program and 1,207 in the Hopkins program.

Effect of Screening on Mortality

An important purpose of this modeling effort has been to investigate the possible benefit of annual radiographic screening of populations at high risk for lung cancer, i.e., heavy smokers similar to those enrolled in the Sloan-Kettering and Hopkins studies. Therefore, we have calculated the expected number of deaths due to ALCA in a population screened annually from 45 years to 80 years of age on the basis of those model parameters estimated in the previous section. For comparison, the expected mortality in the absence of any routine x-ray screening was also calculated, and the percent decrease in mortality attributable to screening is considered the expected benefit. The results of this calculation are displayed in table 2(A). For the Sloan-Kettering population, it is possible that the reduction in ALCa mortality might be as great as 18%. For Hopkins, however, the maximum benefit consistent with the data is 5%. Repeating all the above steps for data on adenocarcinoma alone leads to table 2(B), in which it is shown that the maximum benefit at Sloan-Kettering would be 18% and at Hopkins, 8%.

Conclusions

Certain characteristics of the ALCa in screening programs in New York and Baltimore may be summarized from direct observation. These are: the total number of cases—159 at Sloan-Kettering, 215 at Hopkins; stage distribution—45% for stage 1 at Sloan-Kettering, 41% at Hopkins; number of ALCa-caused deaths—72 at Sloan-Kettering, 133 at Hopkins; ALCa death rates—1.2 per 1,000 per year at Sloan-Kettering, 2.1 per 1,000 per year at Hopkins; 5-year survival of all cases—.40 at Sloan-Kettering, .25 at Hopkins; stage I cases—.73 at Sloan-Kettering, .55 at Hopkins.

However, we have no direct observation of the essential characteristics of the progression kinetics of the disease in the presence of a screening program. These include the probability that a high-risk individual will eventually contract the disease; the duration of early, localized ALCa; the detectability of early disease by readily available screening techniques; and the cure probability of the early ALCa if it is detected. This modeling effort was intended to produce an understanding of the range of these quantities consistent with the observed data in both the Sloan-Kettering and Hopkins studies. It is believed that this understanding will help to identify avenues through which lung cancer mortality might be reduced and to determine whether periodic screening might confer any benefit.

The major conclusions of this research may be summarized as follows.

(a) A large proportion of heavy smokers will, if they live long enough, eventually contract ALCa—10% to 14% of the New York population, 16% to 19% of the Baltimore group.

(b) The mean duration of the early stage of this disease is at least 4 years and may be considerably longer. This is true of both populations. This fact must be taken into account when evaluating the importance of the favorable survival curves observed for stage 1 ALCa. Long survival may be attributed, possibly in part, to the slow course of early-stage disease rather than to the favorable effects of treatment.

(c) The probability of detecting early-stage ALCa by a single PA and lateral chest x-ray examination is less than .16 based on data in both studies. This is a serious deficiency in a screening program and points clearly to the need for new and more effective imaging techniques or other modes of early detection.

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(d) The estimated cure probabilities associated with surgical treatment of early-stage ALCa are markedly different in the Sloan-Kettering and Hopkins studies. If the mean duration of early stage were as short as 4 years, then the Sloan-Kettering estimate of cure probability would be .52 while the Hopkins would be .13. At 7 years, the corresponding estimates are .33 and 0. This difference is attributable to several possible sources discussed in the Parameter Estimation section.

(e) Finally, we consider the possible impact of annual screening with present chest roentgenographic techniques for subjects, starting at 45 years of age; here again, the Sloan-Kettering and Hopkins data lead to different conclusions. From the Sloan-Kettering data, one might conclude that ALCa mortality reduction associated with screening and surgical treatment could be as great as 18%, while the Hopkins study leads to the conclusion that 5% is an upper bound. A greater reduction in mortality would require either more effective detection or more effective treatment of early-stage lung cancer.

References

Cancer Among Medical Diagnostic X-Ray Workers in China\(^1,2\)

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Cancer incidence among 27,011 diagnostic x-ray workers was compared to that of 25,782 other medical specialists employed between 1950 and 1980 in China. X-ray workers had a 50\% higher risk of developing cancer than the other specialists (relative risk (RR) = 1.5; 95\% CI = 1.3-1.7). Leukemia was strongly linked to radiation work (RR = 3.5, \(n = 30\)). Cancers of the breast (RR = 1.4, \(n = 11\)), thyroid (RR = 2.1, \(n = 7\)), and skin (RR = 1.5, \(n = 6\)) were increased among x-ray workers employed for 10 or more years. High risks of cancers of the esophagus (RR = 3.5, \(n = 15\)) and liver (RR = 2.4, \(n = 48\)) were not consistent with a radiation effect since risk did not vary by duration of employment. This finding suggested that some differences might exist between groups of hospital workers in social class, alcohol intake, dietary habits, and other risk factors. No excess lung cancer (RR = 0.9, \(n = 22\)) or multiple myeloma (\(n = 0\)) was observed. Significant excesses of leukemia and cancers of the breast and thyroid occurred among x-ray workers first employed prior to 1960 when radiation exposures in China were high. In fact, it was not uncommon for employees to be given time off from x-ray work because their WBC count was severely depressed. These data indicated that repeated exposure to x-rays over many years can increase the risk of leukemia and several other tumors but apparently not that of lung cancer. [J Natl Cancer Inst 1988;80:344-350]

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\(^{2}\)This work represents an analysis of data collected by the National Coordinating Research Group of Dose-Effect Relationships in Medical Diagnostic X-Ray Workers in China.
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