Screening, Early Detection, and Early Intervention Strategies for Lung Cancer

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Screening for lung cancer has been utilized for several decades without demonstrating overall survival benefit. However, recent advances in treatment of lung cancer, improvements in our biologic understanding of lung cancer development, and an increasing population of healthy ex-smokers provide cause for optimism. Several chemoprevention trials suggest that it may be possible to intervene in the oncologic process prior to the development of invasive malignancy, resulting in a delay or reversal of these changes.

If discoursing on a difficult problem were like carrying weights, when many horses can carry more sacks of grain than a single horse, I would agree that many discourses would do more than a single one; but discoursing is like courting, not like carrying, and one Barbary courser can go faster than a hundred Frieslands.


Introduction

Lung cancer is the most frequent cause of cancer death in both men and women. While the incidence of lung cancer appears to have decreased in white men, it continues to rise in nonwhite men and women. Most lung cancer is caused by cigarette smoking, but strategies to prevent or reduce this addiction have met with only modest success to date.[1] Smokers who quit remain at an increased though gradually declining risk of lung cancer over at least the next decade.[2] For these individuals, early detection and treatment of the cancers that they may still develop remains the best hope of further reducing their risk of death from lung cancer.

Strategies for dealing with early lung cancer fall into three themes: true screening programs for the evaluation of asymptomatic individuals believed to be at high risk for lung cancer; early detection programs for the evaluation of patients presenting with ambiguous symptoms; and early intervention programs aimed at stopping or reversing the processes involved in lung carcinogenesis before the development of invasive malignancy.

Since approximately 90% of lung cancer develops in individuals with a history of cigarette smoking, many of whom have chronic respiratory symptoms, the distinction between screening and early detection is blurred. Individuals who participate in "screening" programs may be motivated by subtle changes in their baseline cough or sputum production (or by a family member's prodding that such a change has occurred) and thus may not truly represent the larger population of smokers and ex-smokers from whom they are drawn.

Lung Cancer Presentation, Staging, and Treatment Outcome

Table 1 shows the stage distribution of 170,000 cases of lung cancer diagnosed in the United States in 1993. While a few patients with stage III disease (those with minimal weight loss and good performance status) may be cured by aggressive multimodality therapy, only those patients with stage I or II disease are classically considered to be resectable with high probability of cure. If only those patients with T1N0 disease are considered as truly early presentations, more than 85% of patients with lung cancer currently present with more advanced disease.

<table>
<thead>
<tr>
<th>Stage and Clinical Operability Group (U.S.)</th>
<th>Cases per Year</th>
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<tbody>
<tr>
<td>T1NO</td>
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<tr>
<td>T1N1, T2N0, T2N1</td>
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</tr>
<tr>
<td>IIIA resectable</td>
<td>10,500</td>
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<tr>
<td>IIIA partially resectable</td>
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<tr>
<td>Total</td>
<td>170,000</td>
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Radiographically detectable lung cancer is hardly early disease. To be seen on routine chest radiograph, in the favorable circumstance of a peripheral nodule that does not overlie shadows of rib or mediastinal structures, a lesion has to be approximately 1 cm in diameter. Such a mass will typically contain 10 to the 9th tumor cells, representing about 30 doublings under an ideal condition of no cell loss. Such conditions never occur in human tumors; a comparison of actual and potential doubling times suggests that cell loss factors in the range of 80% to 90% are common.[3] At this point, the "early" tumor has undergone most of its life span. This long preclinical history for even the smallest radiographically detectable tumors gives ample opportunity for the mutational appearance and clonal selection of phenotypes capable of invasion, metastasis, and drug resistance.

The TNM staging system, while reasonably applicable to patients with non-small cell lung cancer (NSCLC), generally is not used for patients with small cell lung cancer (SCLC). The distinction between "limited" and "extensive" SCLC then reduces to a reflection of the sensitivity of the imaging and other technology used to search for it. The
Shifts of stage distribution due to earlier diagnosis should not be confused with the shifts in staging classification.[5] In the case of changes in diagnostic sensitivity, clinicians are intervening in the disease process at an earlier time, which may result in either a real therapeutic gain (if effective therapies are available) or an apparent gain (from the lead time gained in time from diagnosis to time of death). In contrast, shifting patients from one stage to another by the use of more sensitive imaging techniques for staging but not changing the time of initial diagnosis simply changes the way in which the same set of clinical events are categorized and has no effect on the survival of the entire population with the disease, but may improve the outcome for each of its subgroups.

Figures taken from the clinical data on which the new International Staging System was based represent that which can be obtained with good standards of practice in staging and treatment.[6] They do not reflect the modest improvements in survival now being reported for the use of adjuvant chemotherapy in combination with either surgical resection or definitive radiation therapy for locally advanced disease.[7] In selected series with meticulous surgical staging of the mediastinum, survival for patients with T1N0M0 disease is up to 80% higher in the series of the Lung Cancer Study Group.[8] Survival for patients with T1N0M0 lung cancer is comparable to survival of patients with T1N0M0 breast cancer, but only a small percentage of patients with lung cancer are detected at this stage. It is a reasonable hypothesis that detection of patients with lung cancer prior to the development of nodal metastases would significantly improve survival. Patients with treated lung cancer who relapse generally do so within the first three years; true late failures are uncommon. Second primary tumors of the lung, esophagus, and head and neck sites are problematic, however, and in aggregate have an incidence of approximately 2% to 3% per year.[9] Thus, the impact of screening and early detection programs ought to be demonstrable with relatively short follow-up.

**Lung Cancer Causation and Epidemiology**

At the beginning of this century, lung cancer was a rare disease. The present global epidemic, with over 2 million deaths estimated for the year 2000, is the direct result of governmentally sanctioned production and aggressive marketing of addictive tobacco products, primarily cigarettes.[10] While an effective strategy for lung cancer treatment and control will include a broad spectrum of activities, it is unarguable that the greatest long-term reduction in lung cancer mortality will come from a decrease in the number of smokers.

In the United States, lung cancer is most commonly diagnosed in the seventh decade of life. A generation ago, lung cancer was predominantly a disease of men. Much early clinical research in lung cancer, including the three large prospective trials of radiographic and cytologic screening conducted in the US, was limited to men who smoked.

While the increase in prevalence of lung cancer smoking by women starting in the 1940s changed this situation dramatically. Deaths from lung cancer overtook those of breast cancer for US women in the 1980s. Current US data show a decline in smoking prevalence among white men, but smoking has continued to increase among women, and recent data have suggested a leveling off or even reversal in the tendency to decrease smoking in young women.[1]

At present, approximately 25% of the adult population of the United States are smokers, and an additional 40 to 50 million are former smokers.[1] The American Cancer Society Cancer Prevention Study II has demonstrated that, while the risk of subsequent development of lung cancer declines for both men and women regardless of the age at which they quit smoking, the greatest gains are seen for those quitting at an earlier age, and that this difference is significant even when correcting for the number of years smoked.[2,11]

**Lung Cancer Biology**

The lung is anatomically and physiologically at least three separate organs. The trachea and main bronchi are normally lined by ciliated, pseudostratified columnar epithelium and also contain neuroendocrine cells. The predominant types of tumors arising in large central airways are squamous cell and small cell carcinomas. The thickness of the lining epithelium gradually declines as the airways become smaller. The pseudostratified, ciliated columnar cells gradually give way to ciliated columnar and finally ciliated cuboidal cells in the terminal bronchioles. Epithelial mucous cells are interspersed throughout the conducting airway. Interspersed among the cuboidal cells of the terminal and respiratory bronchioles are Clara cells, thought to produce the mucus covering for these small airways. The predominant histology seen in peripherally arising lung cancers is adenocarcinoma, which morphologically can be divided into solid and bronchoalveolar types. At the cellular level, these tumors arise from type II pneumocytes that normally produce surfactant. The bronchoalveolar carcinomas are believed to arise from Clara cells that are involved in xenobiotic metabolism. Each of these cell types has associated characteristic differentiation markers that may form the basis for both detection and therapeutic strategies (Table 2).[12]

### Table 2. – Markers of Lung Cancer Differentiation

<table>
<thead>
<tr>
<th>Adenomatous</th>
<th>Neuroendocrine</th>
<th>Squamous</th>
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<tbody>
<tr>
<td>Clara 10-kD protein</td>
<td>Chromogranin A</td>
<td>Cytokeratin</td>
</tr>
<tr>
<td>Surfactant-associated protein Leu 7</td>
<td>Involucrin</td>
<td></td>
</tr>
<tr>
<td>Carcinoembryonic antigen</td>
<td>Neuron-specific enolase</td>
<td>Epidermal growth factor receptor</td>
</tr>
<tr>
<td>ras oncogene activation</td>
<td>Dopa decarboxylase</td>
<td>Transblutaminase</td>
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Approximately one fifth of lung carcinomas are large cell undifferentiated tumors that cannot be assigned to one of the above lineages. All histologic types can be found admixed within a single tumor, consistent with a model of their development from a common stem cell of variable differentiation potential. The usual anatomic distribution of the different tumor histologies may derive from the normal distribution of partially committed cell lineages, from variable penetration of different carcinogenic components of cigarette smoke to different regions of the lung, and possibly from differences in local metabolic transformation of procarcinogens and effects of the extracellular matrix and paracrine growth factors on carcinogenesis.[12]

These distributions of normal cell and tumor types are typical rather than absolute. Lung cancers of all cell types may be found in any location in the tracheobronchial tree and lung. This classification implies that, while there may be some very early events common to the development of all types of lung cancer, further preneoplastic and neoplastic development can follow along several divergent lines, and screening strategies should be able to detect each of these. The observation that there has been a shift in the proportion of lung cancers of the various histologic types over the past several decades, with the predominant cell type changing from squamous cell to adenocarcinoma, should be considered in a proper theory of lung cancer initiation and promotion.[13]

**Historical Screening Studies**

In the 1950s, several nonrandomized trials of lung cancer screening were conducted in the United States and Europe. Trials in Philadelphia[14] and London[15,16] used chest photofluorograms obtained at six-month intervals. These studies found that approximately one half of the cancers detected in these populations were found by the screening examinations, and the remainder was identified on interval chest radiographs obtained for evaluation of symptoms. While the resectability rate of the cases detected on the screening examinations was approximately 30%, the overall resectability for all cases was only 20%, which did not appear different from historical results in unscreened patients.

### Table 3. Prospective Trials of Screening for Lung Cancer
In an attempt to clarify questions raised by these nonrandomized studies, the US National Cancer Institute sponsored lung cancer screening trials that were conducted in the 1970s in three institutions — Johns Hopkins University (The Johns Hopkins Lung Project [JHLP]), the Mayo Clinic (Mayo Lung Project [MLP]), and Memorial Sloan-Kettering Cancer Center (MSKLP).[17-19] In addition to these three US studies, a randomized trial had been conducted in Czechoslovakia,[20] and several recent carefully conducted case-control studies have taken place in Europe and Japan. The individual trials differed somewhat in their design and study population (Table 3).

The JHLP and the MSKLP trials were designed to evaluate the incremental benefit of adding sputum examination to chest radiography (CXR). In both the JHLP and MSKLP trials, the control groups were offered annual CXR. The dual screen group was offered an annual cytological examination of induced sputum plus examination of spontaneously produced sputum at four months and eight months. The comparison, therefore, was whether the addition of regular sputum cytology examinations to annual radiographic screening led to a reduction of lung cancer mortality compared with annual radiographic screening alone. Of the US studies, only the MLP trial was designed to compare unscreened management with a policy of intensive dual screening with both CXR and sputum cytology examinations every four months. The unscreened group, however, was advised to obtain annual CXR and sputum cytology as part of “routine medical care,” but these individuals were not reminded to comply with this initial recommendation. Thus, this study can be seen as comparing two different frequencies of recommended screening and compliance.

The outcomes of these studies have been presented in several formats: results of the initial prevalence examinations in the cohorts to be screened, the follow-up of the patients detected during the screening period, and overall pooled results of the three trials. The general observations and conclusions of the three trials are clear, but their interpretation has been controversial. There was agreement that “within the trials there was no advantage in terms of mortality reduction to the group offered intensive screening in the Mayo study, with four monthly sputum cytology and chest radiology, while in the Johns Hopkins and Memorial Sloan-Kettering studies, there was no advantage to the group that received sputum cytology in addition to annual chest radiograph examinations.”[21] However, the trials as designed did not address or resolve the question of whether any pattern of surveillance CXR was better for high-risk populations than a policy of obtaining such studies only when patients presented with symptoms.

These studies led to a conclusion that while the screening approaches available at that time could lead to the detection of presymptomatic lung cancer, particularly squamous cell carcinoma, at an earlier stage than in the control group, the overall survival for the screened population was no longer than that of the controls. This led to adoption of policies discouraging routine CXR and sputum screening and provided an unwarranted nihilism regarding all aspects of lung cancer detection and treatment.

None of the US randomized trials compared a policy of screening vs no intervention in the absence of symptoms. The Czechoslovak trial most closely approached this design; all enrolled men underwent an initial prevalence examination, after which the control group had no other planned intervention for three years. Screened individuals underwent CXR and cytology every six months. In the initial three years of the study, 36 lung cancers were detected in the study group vs 19 in the control group, and survival of these patients with lung cancer was superior in the intervention group compared with that in the control group, but the overall death rate from lung cancer was greater (although not significantly -- 28 vs 18 cases) in the study group (P=0.18). At three years, CXR and sputum cytology were performed for both groups, followed by annual CXR. At six-year follow-up, the mortality rate was the same for the two groups.

The studies of issues and populations in these trials, which were designed in the late 1960s and conducted in the early 1970s, are not entirely pertinent for the mid-1990s. The screened populations were all men, most smokers, and often afflicted with other tobacco-related illnesses that led to a high frequency of interval CXRs in addition to the screening examinations. The present candidate for screening is more likely to be a man or woman 40 to 59 years of age, a former smoker with a history of 15 to 25 pack years, and often without illnesses requiring close medical attention. In addition to this shift in demographics, a change in the dominant histology of newly diagnosed lung cancer has emerged. During the period of the US collaborative trial, most cases in both the screened and unscreened groups were squamous cell carcinoma.[19,22] This pattern has changed in the past decade, for unclear reasons, to one in which adenocarcinoma is the predominant histology in trials of patients with both resectable and resectable disease. In the past, adenocarcinomas of the lung have been more common in women, but they have now become the predominant histology for both sexes in the US.[13] European series continue to report higher incidence of squamous cell carcinoma.

### Use of Molecular Markers in Screening

An ideal marker of genetic change should appear early in the carcinogenic process, yet be specific for malignancy or for a commitment to subsequent malignant development. It should be detectable in body tissues that are easily and repeatedly obtainable by relatively noninvasive and inexpensive procedures, such as exfoliated cells or peripheral blood rather than bronchosopic biopsies. The genetic change should be readily detectable by automated or semiautomated methods, and structural changes in coding regions of a gene sequence may be better targets than changes that alter gene regulation. Finally, situations in which a limited number of genetic changes account for the majority of tumors are appealing in that they limit the number of mutant sequences to be screened.

For these reasons, genetic changes in the ras oncogene have been an appealing target. Mutational activation of ras occurs in approximately 30% of lung adenocarcinomas, as well as in high frequency in adenocarcinomas of the bowel and pancreas. Activation almost always involves point mutation at codons 12,13, or 61.[23] Presence of ras mutations in lung adenocarcinoma is closely linked with prior cigarette smoking and appears to be an adverse prognostic factor independent of stage.

Sidranski et al[24] first demonstrated that ras mutations could be identified in exfoliated cells present in the stool of patients with resectable and potentially curable colon cancer. Subsequently, Tobi et al[25] were able to detect ras mutations at codon 12 in exfoliated colonic mucosa in 40% of clinically normal individuals at high risk for developing colorectal cancer because of strong family history or a personal history of adenomas. Others have reported detection of mutant ras in gastric aspirates and stool specimens of patients with pancreatic cancer.[26,27] Several recent reports extend these data to lung cancer. Kelly et al[28] have demonstrated the feasibility of detecting ras mutations in cells obtained by sputum cytology in patients with known lung cancer. Mills et al[29] have described using a sensitive assay for K-ras codon 12 mutations in individuals suspected of having lung carcinoma. They studied 87 specimens of bronchoalveolar lavage fluid that had been obtained from 86 patients, 35 of whom underwent subsequent diagnostic bronchoscopy. Of 52 patients with diagnosed lung cancer, 16 had bronchoalveolar lavage with K-ras 12 codon mutations, including 14 of 25 patients with adenocarcinoma, 1 of 3 with bronchoalveolar...
In an extension of this methodology to patients without diagnosed malignancy but at risk, Mao et al[30] examined sputa that had been obtained during the JHLP with a percentage of patients having gone on to develop adenocarcinoma. Of 15 patients so identified, analysis of the resected tumor specimen showed mutated ras or p53 in 10 patients. In eight of these 10, the same mutation could be demonstrated in sputum samples that had been obtained at least one year prior to clinical diagnosis[30].

Healthy individuals as well as those with cancer have small amounts of soluble DNA fragments in their circulation; Sorenson et al[31] have taken advantage of this fact and developed a polymerase chain reaction assay to look for ras mutations (codon 12) in patients with lung cancer. They have reported preliminary findings indicating the feasibility of such detection in patients with known lung cancer and are extending the methodology to study high-risk individuals.

These are all preliminary studies of limited numbers of patients, and most have used detection of ras mutations which are present in only approximately 30% of lung cancers. Ras mutations are not seen in SCLC, so other strategies will have to be developed for their screening. Substantial technical issues remain to be resolved before they can be more widely implemented[32] These or similar tests will not be available on the internist’s laboratory order sheet in the near future. As noted above, these genetic changes are seen in both invasive tumors and preneoplastic epithelium. Substantial questions as to their interpretation will arise, and initial caution is in order.[33]

In determining the various genetic and phenotypic differences between normal and malignant lung tissue, several questions should be considered: Which genetic events are causative and which are bystander? Is there an oblique sequence of genetic events (ie, early vs late events) or is the cumulative mutational burden the relevant causative factor? If there is a required or usual sequence, can early events be used as early detection markers? Are some later events (eg, mdr amplification, ras activation) prognostic markers independent of stage and histology? Can an understanding of early events lead to chemoprevention strategies?

These considerations, as well as the increasing understanding of carcinogenesisis as a process comprising multiple genetic changes occurring over years rather than a single instantaneous change, raise the question of whether screening programs should be directed toward the process of carcinogenesisis or the end result of cancer. The answer will depend in part on the frequency with which early events in carcinogenesisis (eg, loss of normal p53 function, loss of mutation repair capacity) result in invasive malignancy and the toxicity of therapy used to treat them.

Circulating Tumor Markers

Several tumor markers have been proposed either to follow disease status or for screening of lung cancer. Both carcinoembryonic antigen and neuron-specific enolase blood levels are commonly elevated in lung cancer (the former in all histologies, the latter primarily in SCLC) but have not been reliably elevated in patients with minimal disease to allow for early detection either de novo or of relapse in patients who have undergone surgical resection or had complete response to chemotherapy.[34]

Newer approaches to the development of serum techniques for early tumor detection have focused on detection of growth factors produced by tumors. Most small cell carcinomas and approximately 15% of non-small cell carcinomas are under autocrine growth stimulation mediated by gastrin-releasing peptide (GRP). Early studies that attempted to use this as a marker were not successful, due in part to its very short serum half-life. The pro-hormone (Pro-GRP) has a longer half-life. Miyake et al[35] have shown that the ratio of Pro-GRP:GRP in tumor tissue is 1:2, but the ratio in blood is 76:1. Using a cutoff of 40 pg/mL, these investigators reported elevations in 0.5% of normal controls, 0.8% of patients with nonmalignant pulmonary disease, and 67% of patients with SCLC, with similar results for pure and mixed histologies.

Whether this test will show sufficient specificity and sensitivity for screening remains to be determined. Initial mass screening studies in Japan have reported a detection rate of approximately 0.04%. Agus and et al[36] reported that in smokers, bronchial washing and urine ProGRP levels are elevated but serum levels are not.

Identification of High-Risk Groups

If screening tests had no cost and absolute specificity, there would be little need to limit them to high-risk populations. Since these conditions are not met by any present test, identification of groups of individuals at a higher risk of developing lung cancer than the general population is important for developing screening techniques for reasons of efficiency, feasibility and predictive value.

Approaches taken to identify high-risk individuals and groups have classically included demographic factors (male gender, age), smoking history, and occupational history (exposure to asbestos, uranium, and chloroethyl ether). The observation that lung cancer develops in only approximately 10% to 15% of smokers has prompted the search for additional risk factors. In addition to exposure to other carcinogens, a further potential source of variability in risk derives from differences in the metabolic conversion of procarcinogens to active carcinogens, or the degradation and/or excretion of active carcinogens. During the past decade, interest focused on members of the cytochrome P450 group of enzymes. There is considerable individual phenotypic variability in the activity of this system, which may be assessed either functionally, by rates of metabolism of test substances such as debrisoquine, or by immunoquantitation of enzyme isotypes. While initial reports suggested that slow debrisoquine metabolizers were at significantly altered risk,[37] more recent larger studies have not confirmed these and fail to establish this specific metabolic phenotyping as a valid indicator of risk.[38] The more general concept of individual variability of risk based on differences in procarcinogen metabolism may be valid and simply require better ways of measuring carcinogen exposure at the molecular level. This may be done either at the level of assay of the appropriate enzymes involved in the metabolism of key carcinogens or by looking more directly at such DNA damage as adduct formation or production of double minute chromosomes. Spitz et al[39] have recently reported that patients with curatively treated upper aerodigestive cancers whose peripheral lymphocytes were hypersensitive to in vitro mutation induction by bleomycin had a significantly higher incidence of synchronous or metachronous second primary malignancies than those with lower mutagen sensitivity. Mutagen sensitivity did not correlate with age, sex, smoking status, or tumor stage. It will be important to verify this finding and extend such studies to prospective monitoring of populations at high risk of developing their first malignancy. The ability to use an easily obtained and renewable tissue such as peripheral lymphocytes facilitates tests of this sort for both the individual patient and the longitudinal studies should there be concern about changes in mutagen sensitivity over time.[40]

A further approach to defining individuals at high risk will be to identify those genetic changes that may facilitate the occurrence, retention, or repair of somatic mutations independently from exposure to exogenous mutagens. The delineation of the mutator phenotype and its role in the development of human colorectal adenocarcinoma, as well as evidence that the frequency of occurrence and the efficiency of repair of various types of p53 mutations are important in their transforming ability, suggest that this may be a useful approach. Such changes may antedate more specific changes in the activation of oncogenes or tumor suppressor gene inactivation and may provide a simpler unitary point of intervention for prevention strategies.

Prospects for New Screening Approaches

The large trials of screening by CXR and morphologic examination of exfoliated cells were not only criticized in terms of their lack of statistical power to detect small differences in mortality, but also hampered by technologies that could detect cancers late in the biologic history of the disease. Biologic markers of earlier disease are required.

<table>
<thead>
<tr>
<th></th>
<th>Assay Technical Status</th>
<th>Assay Result</th>
<th>Subsequent Lung Cancer</th>
<th>No Subsequent Lung Cancer</th>
<th>Total</th>
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<tr>
<td>Satisfactory</td>
<td>Positive</td>
<td>20</td>
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<tr>
<td></td>
<td>Negative</td>
<td>2</td>
<td>35</td>
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</table>
Immunostaining of Sputum Specimens

One approach to improving the sensitivity of analysis of examination of exfoliated cells is immunostaining of sputum. Tockman et al[41] reported that immunostaining of cytologically atypical sputa obtained and archived in the JHLP was able to predict which patients would go on to develop invasive carcinoma, with a lead of approximately 20 months prior to clinical diagnosis.[41] These investigators used a pair of monoclonal antibodies, one raised against a squamous cell line and the other raised against a small cell cancer line, to examine preserved sputa from 26 patients who were known to have subsequently developed lung cancer and specimens from 43 participants who did not develop cancer (Table 4).[42] This dual antibody panel was able to detect both small cell and non-small cell histologies. The likelihood that a premalignant specimen from a patient (from this population of patients with cytologic atypia) who subsequently developed invasive cancer would stain positively with one or both of the antibodies was highly significant (P=.0001).

This finding requires both validation and evidence that earlier detection will be therapeutically beneficial. To facilitate these studies, the Lung Cancer Early Detection Working Group has begun a prospective trial of evaluation of patients with previously resected T1-2N0M0 NSCLC. This group is at high risk (approximately 3% per year) of developing second lung cancers (as well as other aerodigestive tumors), which will reduce the number of cases required for validation of this concept.[42,43] Patients are being evaluated by annual induced sputum that is investigated both by conventional cytopathologic analysis as well as immunostaining. As of December 1995, this trial had accrued 956 of a planned 1260, with completion of accrual expected early in 1997. A correlative study is collecting bronchoalveolar lavage fluid from these patients for analysis of tumor growth factors, analysis of oncogene mutations in exfoliated cells, and other possible early tumor markers.

Fluorescence Bronchoscopy

A variety of substances will preferentially accumulate in neoplastic and preneoplastic tissues. Several fluorescent porphyrins derivatives show such selectivity. Hung et al[44] observed differences in the intensity and wavelength of the intrinsic fluorescence of normal and atypical bronchial mucosa. They have developed a fluorescence bronchoscope that allows real-time video display of false color images based on ratios of fluorescence at two different wavelengths. This allows for the localization and biopsy of areas of bronchial epithelium that appear normal under conventional white-light bronchoscopy but which display abnormal fluorescence characteristics (Figure). In preliminary studies of 53 patients and 41 volunteers, white-light and fluorescence bronchoscopy had similar specificity of 94%, while the sensitivity of the fluorescence bronchoscopy was 72% compared with 48% for white-light bronchoscopy.[45] Several questions need to be addressed before fluorescence bronchoscopy can be widely adopted. While it appears that the technique can identify areas of epithelial abnormality not seen on conventional bronchoscopy, the true sensitivity (compared to biopsy) is unknown. Prospective correlation of fluorescence bronchoscopy and biopsy with examination of the entire bronchial tree removed in patients undergoing resection would be a valuable way to ascertain such sensitivity information. Although the technique has been useful in the experience of its developers, its more general applicability with both pulmonologists and pathologists less committed to development of such new methodologies is uncertain.

**Intervention Strategies in High-Risk Populations**

There is emerging consensus that carcinogenesis, rather than cancer, is the appropriate target for the major focus of our clinical strategies. In the past, scientists have concentrated on the end result (eg, tumor, lump, shadow on CXR) rather than on the molecular or cellular processes that underlie and antedate it. Such a developmental and preventive approach is particularly appealing in the setting of a carcinogenic process that involves a broad field of tissue, such as the respiratory epithelium, and where multifocal disease (either synchronous or metachronous) is common, since approximately 3% of patients who survive their first lung cancer develop a second one each year. [9,46]

Retinoids have key roles in facilitating normal differentiation of squamous epithelia and in reversing premalignant changes. Pioneering studies in head and neck cancer[47] have demonstrated both a reversal of leukoplakia and a reduction in the risk of second malignancies in patients given high doses of 13-cis retinoic acid. Current confirmatory trials in head and neck cancer are being conducted with drug doses that are somewhat lower and better tolerated.

A similar strategy in lung cancer is rational, and preliminary data are encouraging. Pastorino et al[48] randomized 307 patients who had undergone curative resection for stage I NSCLC to observation or treatment with daily oral retinyl palmitate for one to two years. After a median follow-up of 46 months, 48% of the control patients and 37% of the treated group developed recurrence or a second primary tumor. Looking only at second primary tumors in the "field of prevention" (lung, head and neck, bladder), the treated group experienced a significant reduction in events from 25 to 13. Neither local recurrence nor distant metastasis was significantly reduced by treatment. These encouraging results were achieved with modest toxicity; approximately 10% of patients discontinued treatment due to objective or subjective toxicity.

These results should not be interpreted as mandating the routine use of chemopreventive agents. Two recent reports[49,50] suggest caution in our approach to implementing chemoprevention strategies based on our present understandings and agents.

Retrospective studies of dietary habits of smokers who did or did not develop lung cancer suggested a protective effect from consumption of carotenoids and, to a smaller extent, alpha-tocopherol. In 1985, a joint United States-Finnish trial was designed to prospectively evaluate the effects of dietary supplementation with beta-carotene, alpha-tocopherol, or both, in male smokers 50 to 69 years of age.[49] Using a two-way randomization design, 29,133 patients were entered. In 1994, a total of 876 new cases of lung cancer were reported. No reduction in incidence was seen in the men receiving alpha-tocopherol (change in incidence = -2%; 95% CI, -14% to +12%). An increased incidence of lung cancer was seen in the men who received beta-carotene (change in incidence 18%; 95% CI, 3% to 36%). Overall mortality also was also higher in the men receiving beta-carotene (95% CI, 1% to 16%, P<0.02). The increased incidence and mortality were surprising and contrasted with results from animal data, with other human trials using beta-carotene, and with results of retrospective studies correlating dietary intake with risk of lung cancer. Although the apparent harmful effects seen in this study may have been due to chance, it is unlikely that a strong protective effect was missed.
Lee et al.[50] have recently reported a prospective trial of the use of isotretinoin in a population of heavy smokers. This was an attempt to replicate in a controlled trial the earlier uncontrolled European trials that use of the retinoid etretinate led to reductions in squamous metaplasia. Patients were randomized to treatment with isotretinoin (1.0 mg/kg) or placebo for six months and were evaluated by regular bronchoscopy with biopsies taken from multiple sites. The major study endpoint was change in bronchial metaplasia. The overall metaplasia index decreased over time for both the treatment and control groups, although the change was significant only for the control group, and the difference in the change in metaplasia index for the two groups was not significant.[50] Significant reductions in dysplasia were seen in 54.3% of the isotretinoin subjects and in 58.8% of controls. A confounding factor was the cessation of smoking by a large number of members of both the treatment and control groups; significant reductions in metaplasia were seen only in those subjects who continued to smoke. It is unclear from this trial whether the use of the metaplasia index as an intermediate marker was an unfortunate choice or the pharmacologic intervention was ineffective. Changes in smoking (and possibly dietary) behaviors that may accompany participation in trials of chemopreventive agents may alter the processes of carcinogenesis and need to be carefully analyzed in phase III trials.

The message from these two "negative" trials is not that chemoprevention has failed, but rather that it remains an area warranting increased laboratory and clinical investigation.

Cautions in the Application of New Screening Methods for Preneoplasia

The rapid development of highly specific and sensitive tools for detection of genetic changes in respiratory epithelium must be applied with both speed and caution in the clinic. There is little if anything in biology with absolute specificity. Cancer represents a maladaptive (to the individual organism, although not necessarily to the species) choreography of the usual repertoire of cellular responses and processes. Even structurally abnormal oncogene products (eg, mutated ras gene product) work their harm by performing a normal function (signaling for cell growth) in improper circumstances (the absence of an activating ligand or for a growth factor receptor). The line between malignancy and premalignancy is likely to be ill marked and may shift over time. Benefit is likely to be seen not only in approaches that aim for early detection and intervention in what is clearly malignant, but also in detection and interference with the process of carcinogenesis; however, a clarity as to which of these processes we are dealing with is essential. Acceptable costs, both social and individual, are likely to be different for the two approaches.

The high incidence and lethality of lung cancer have prompted a variety of therapeutic and diagnostic approaches to reduce this appalling toll. Primary prevention through the reduction of cigarette smoking is likely to be the most successful strategy in achieving this goal. However, we were all current smokers in the United States to quit today, we would still face more than a million cases of lung cancer developing over the next decade from cigarettes already smoked.

Conclusions

No screening strategy has yet been shown in a prospective trial to reduce lung cancer mortality, although screening of a high-risk group of male smokers 45 years of age or older would provide a shift to earlier stage at diagnosis and greater resectability for the screened cases. These gains, which are consistent with the shifts that would be seen from lead-time bias and length biased sampling, did not translate to consistent benefit either in survival of the detected cases or in a reduction in mortality for the population as a whole.

On a general health policy level, present data do not support the implementation of screening policies based on regular CXR and sputum cytology in older male smokers. This should not lead primary physicians to believe that an indolent approach to symptoms consistent with lung cancer can be neglected or indifferently evaluated in the patient at risk. Past studies may not apply to the present situation. We have different populations to screen, with an increasing number of former rather than current smokers. Some progress in the treatment of lung cancer has been realized, and our understanding of the early molecular and cellular events in lung cancer development is providing us with tools that can detect preneoplastic or early neoplastic changes at a time when the tumor burden is several logs less than with present radiographic detection. A key step from early detection to prevention will be made as methods are developed to arrest or reverse some of these molecular events. The potential for application of these new technologies to today's clinical trials and tomorrow's clinical practice should leave us with realistic optimism for the role of screening and early intervention in lung cancer.

References


