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The Early Detection of Second Primary Lung Cancers by Sputum Immunostaining*

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Study objective: **To determine whether monoclonal antibody (Mab) detection of tumor-associated antigen expressed on sputum epithelial cells precedes clinical presentation of second primary lung cancer.**

Design Setting/Participants: **Eleven oncology centers collaborate in the accrual of 1,000 patients with stage I non-small cell lung cancer (NSCLC) who had undergone resection. The Mabs examined in this study (624H12, 703D4) detect two promising *oncofetal/differentiation markers* (ie, a difucosylated Lewis X and a 31-Kd glycoprotein antigen).**

Interventions: **Induced sputum specimens are evaluated for quality, then are Papanicolaou and immunostained by independent central laboratories at enrollment and annually thereafter. The predictive value of Mab markers is compared with routine morphologic study for detection of second primary lung cancer during an anticipated 3 years of accrual and 1 year of follow-up.**

Measurements and results: **Five hundred eighty of an anticipated 1,000 patients have been accrued on schedule. Patients are primarily white (88.6%), former smokers (75.9%), men (55.6%), with a median age of 66.7, and joined the study at an average of 3.7 years following resection of a stage 1 NSCLC (34.4% squamous, 43.6% adenocarcinoma). Central laboratories found less dysplasia and more unsatisfactory specimens (27.3%) than do the accrual institution laboratories. Immunostaining identifies more suspicious cells than does morphologic study. However, only two second primary lung cancers (eight total deaths) have occurred to date.**

Conclusions: **Halfway through the accrual, we describe the study design and preliminary observations. This study illustrates rational selection of carcinogenesis markers by linkage of marker expression on preneoplastic specimens with subsequent expression on tumor tissue.**

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The current epidemic of lung cancer remains a vexing clinical problem. Only 13% of the 160,000 estimated new cases in the United States each year can be cured by available treatment modalities. Although some progress is being made in reducing the US incidence and prevalence of cigarette smoking,[1] the problem of latent lung cancers in recent smokers will remain a major public health problem well into the next century.

Through the 1980s, substantial effort was expended on attempts to detect lung cancer earlier, under the assumption that earlier detection would lead to diagnosis at an earlier stage, more amenable to potentially curative surgical therapy. However, the three clinical trials sponsored by the National Cancer Institute (NCI) (at Johns Hopkins University, Memorial Sloan-Kettering Hospital, and the Mayo Clinic) demonstrated among 30,000 high-risk participants that while chest radiography and sputum cell morphologic study can detect presymptomatic, earlier-stage carcinoma, particularly carcinoma of the squamous cell type,[2-5] higher resectability and survival rates among the study groups than in the controls did not translate, into lowered (overall) lung cancer mortality.[6-10] Consequently, it is widely held that screening for early lung cancer is a futile exercise and the American Cancer Society does not include annual chest radiograph or sputum cell morphologic examinations in its guidelines for detecting lung cancer at early stages.[11]

Through the time of the NCI collaborative trial, the only clinical marker available to detect pulmonary neoplastic changes was the recognition of dysplastic morphologic features in exfoliated epithelial cells by light microscopy.[12] We now know that cytomorphologic criteria alone are not sufficiently sensitive for lung cancer screening. Less than 10% of lung cancers in the NCI early lung cancer detection trials were detectable only by routine sputum cell morphologic study. More than half of the patients with lung cancer presented clinically in the interval between annual screenings. Length-biased sampling, lead-time bias, and misclassification, in addition to failures of detection and of therapy, contributed to the lack of improvement in mortality rates.[13-16]

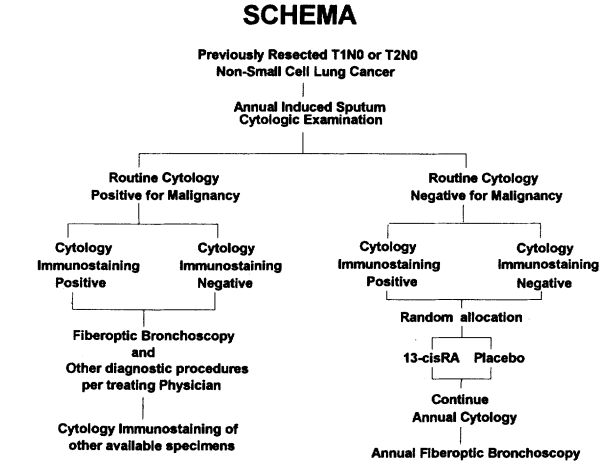

FIGURE 2. Projected and actual accrual for patients with stage I resected NSCLC by the Lung Cancer Early Detection Working Group (LCEDWG).

Our recent report[17] suggests the possibility of overcoming these challenges to the early diagnosis of lung cancer and forms the conceptual basis for this trial. Using two monoclonal antibodies (Mabs) originally developed against small cell and non-small cell lung cancer,[18,19] we reexamined archived specimens from the NCI-Johns Hopkins study and found that in subjects with moderate atypical metaplasia, these antibodies could predict the later development of lung cancer at least 2 years prior to clinical recognition with a sensitivity of 91% and a specificity of 88%.[17] The present study seeks to validate the use of Mabs to detect the process of carcinogenesis by determining whether immunostaining of annually induced sputum specimens can improve the sensitivity/specificity of routine (Papanicolaou-stained) sputum cell morphology to detect second primary lung cancer during 3 years of accrual and a year of follow-up clinical surveillance.

Methods

Study Design

The schema presented in Figure 1 shows the design for this study. All patients with previously resected stage I non-small cell lung cancer (NSCLC) who meet enrollment criteria receive an annual examination of their sputum produced during a hypertonic saline solution induction. If morphologic examination of this specimen at the accrual institution shows the presence of frankly neoplastic cells, the patient undergoes a diagnostic workup for lung cancer at the direction of the treating physician. All specimens are sent to the Frost Center Laboratory at Johns Hopkins where the study cytopathologist (Y.S.E.) interprets the morphologic features. An aliquot of each specimen, regardless of morphology, is sent to the study immunocytopathologist (P.G.) at the University of Pennsylvania. The double-blind results of sputum morphology and immunocytochemistry, are compared with the incidence of second primary lung cancer at the end of 3 years of accrual and 1 year of follow-up. Second primary lung cancer is defined as lung cancer, which if it appears up to 2 years following resection of the index lung cancer, is of a different histologic cell type, and if it appears after 2 years following resection of the index lung cancer, may be of the same cell type, provided that it has the characteristics of a primary lung cancer and it arises in a different lobe.

Participants are asked to undergo fiberoptic bronchoscopy and washings annually to see if this enhances diagnostic accuracy. Patients will be requested to undergo bronchoscopy regardless of whether their sputum specimen immunostains positive or negative. They may of course refuse. Refusal of bronchoscopy does not invalidate participation in the remainder of the study.

Study Population

Investigators at institutions that had formerly participated in the NCI's Lung Cancer Study Group (LCSG)[20-23] plus other institutions with active surgical oncology programs have formed the collaborative Lung Cancer Early Detection Working Group (LCEDWG) to accrue for this study 1,000 patients with stage I NSCLC who had undergone resection. The lifetime incidence of second primaries, strictly defined as a second lung cancer of different histologic features, is over 10% in these patients with an annual incidence of 1 to 5% depending on the subgroup.[24] This is a significantly higher rate than even the heaviest smoking populations and offers a unique laboratory for the study of early detection and chemoprevention. That all of these patients are in active follow-up promises success both for initial recruitment and for the likelihood of obtaining serial specimens.

There are no exclusions by age, sex, or ethnic background. Any patient currently in follow-up 6 months or more after surgical resection, chemotherapy, or radiotherapy, who has not developed either recurrence or a second primary and meets the following criteria is eligible: (1) All patients must have had prior documentation of NSCLC. (2) The patient's condition has been staged at surgery and the extent of disease documented. A biopsy specimen must have been taken from at least one mediastinal node station, and all biopsy specimens from mediastinal nodes must have been found to be negative. There are no known or suspected metastases beyond the mediastinum. (3) The patient has T1N0, T2N0, or T1N1 disease. (4) The surgeon has completed a total resection of the tumor.

Central Laboratory Procedures

Unlike well-standardized diagnostic tests, the successful collection of specimens for sputum immunoassays by the accrual centers requires close cooperation with the central laboratories. Prior to placing patients on trial, each LCEDWG institution established its sputum induction facility, and underwent a specimen collection training/approval process conducted by a Frost Center Laboratory cytotechnologist from the Johns Hopkins School of Hygiene. Each patient performs an annual sputum induction consisting of a 15-min inhalation of hypertonic saline solution before a laminar-flow hood. Fresh sputum is smeared on glass slides for Papanicolaou staining and interpretation. The remaining sputum is homogenized, concentrated, and placed in Saccomanno's preservative solution using standard techniques.[25]

Monthly feedback is provided to the accrual centers regarding specimen quality. Specifically, from the slides and a Saccomanno slurry received for each patient, Frost Center cytotechnologists review a minimum of four Papanicolaou-stained slides (two fresh smears, wet-fixed, and two preserved) for each patient's induced specimen, and two similarly prepared slides of the 3-day, postinduction preserved material. A single cytopathologist (Y.S.E.) reviews all slides that show moderate (or more severe) atypical metaplasia, as well as a sample of the negatives and lesser metaplasias. The Frost Center Laboratory sends an aliquot of each sputum specimen to the study immunocytopathologist (P.G.) at the University of Pennsylvania for immunostaining and interpretation.

The Division of Cytopathology and Cytometry at the University of Pennsylvania is responsible for preparing, immunostaining, and interpreting a minimum of four slides (two for each antibody) from each patient's combined induced and postinduction specimens plus positive and negative control slides using the double-bridge ABC method of Gupta et al.[26] Immunostained slides are received back at the Frost Center where they undergo optical/electronic quantitation.[27,28] Interpretations of Papanicolaou-stained slides, immunostained slides, and optical/electronic quantitation are entered onto the database maintained by the Coordinating Center at Johns Hopkins Oncology Biostatistics. Finally, the Frost Center Laboratory stores all slides and prepares and banks an aliquot of the sputum specimens.

Results

Patient accrual was begun in January 1992 with a 3-year goal of recruiting 1,000 patients whose stage I lung cancer had been completely resected. After 18 months, 580 patients (58% of the accrual goal) have been registered onto this study (Fig 2). This figure illustrates that the observed accrual closely follows the accrual rate expected if the 3-year goal of 1,000 patients is to be met.

Sufficient registration data are available to report on 545 (93%) of the 580 patients. As seen in Table 1, the patients are primarily white (88.6%) and male (55.6%). While 90%

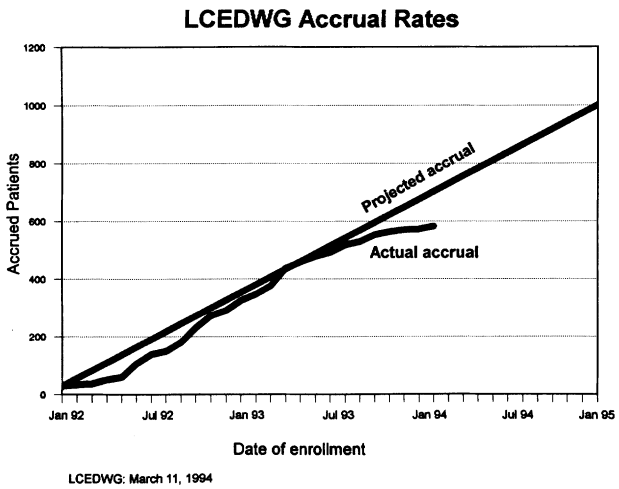

FIGURE 1. Schema for the early detection of second primary lung cancers by sputum immunostaining.

had smoked in the past (just 10.2% had never smoked), only 13.9% were current smokers at the time of registration, and three fourths of the patients now considered themselves former smokers. The average age at enrollment was 66.7 years (range, 33.7 to 89.0 years), the average age at the time of primary lung cancer diagnosis was 62.8 years (range, 32.2 to 85.8 years), and the average interval between primary lung cancer resection and enrollment in the present study was 3.7 years (range, 0.1 to 16.2 years). The good health of the patients at the time of their primary resection is attested to by their average Karnofsky score of 95.1 (range, 50 to 100).

Adenocarcinoma is the most commonly resected primary tumor cell type (43.6%); and, if supplemented by the bronchoalveolar subtype (11.7%), adenocarcinoma constitutes 55.3% of the resected primary tumors. About one third of the resected primary tumors are squamous cell type.

While 66.1% of the 333 sputum specimens reviewed by the central laboratory are negative, there is no significant association between the extent of cytomorphologic abnormality and the cell type of the resected primary tumor (Table 2, $p>0.9$). Twenty-seven percent of the sputum specimens are considered unsatisfactory by the central laboratory. This interpretation usually follows an insufficient number of alveolar macrophages observed in the smear, indicating a lack of adequate pulmonary material. The central laboratories find less dysplasia (6.6% vs 13.2%) and more unsatisfactory specimens (27.3% vs 13.2%) than do the accrual institution laboratories (Table 3, $p=0.006$). Table 4 suggests that current smokers more often produce satisfactory sputum cytologic specimens than do former smokers or never-smokers. However, this association fails to reach statistical significance ($p=0.13$).

When the number of cells that take up either of the Mabs is compared with the degree of morphologic abnormality (Table 5), the typical specimen with slight metaplasia exhibited eight to nine immunostained cells, although the intensity of the staining was weak (1.1+ or less). More than two immunostaining cells might be found on a slide of the typical specimen with moderately atypical metaplasia.

Projecting an annual follow-up visit 1 year after registration leads to an expected 340 follow-up visits. Observed follow-up is clearly lagging, and only 145 (43%) of the ex-

Table 1—*Characteristics of Population Enrolled as of March 11, 1994

Characteristic	n	%	p Value†
Race			
White	483	88.6	0.001
Nonwhite	62	11.4	
Sex			
Male	303	55.6	0.1
Female	242	44.4	
Smoking status			
Current	75	13.9	0.11
Former	410	75.9	
Never	55	10.2	
Histology of resected 1°			
Squamous	183	34.4	<0.0001
Large Cell	38	7.1	
Adenocarcinoma	232	43.6	
Bronchoalveolar	62	11.7	
Mixed	10	1.9	
Other	7	1.3	

				Range		
Characteristic	n	Mean	SD	Min	Max	p Value†
Time from surgery to enrollment, yr	540	3.7	3.3	0.1	16.2	<0.0001
Age at enrollment, yr	540	66.7	9.3	33.7	89.0	<0.0001
Age at diagnosis, yr	531	62.8	9.5	32.2	85.8	<0.0001
Karnofsky score	544	95.1	10.2	50	100	<0.0001

*Demographic data are presented for the 545 accrued patients for whom registration data are available.
†Testing for differences among clinical centers.
1°=primary tumor.

Table 2—*Frequency of Cytomorphology by Primary Cell Type

	Primary Cell Type				
Morphology	Squ (n=104), %	Lrg (n=25) %	Adn (n=140) %	Br-alv (n=43) %	Tot (n=333) %
Uns	34.6	12	27.9	27.9	27.3
Neg	57.7	80	64.3	69.8	66.1
Sli	6.7	8	7.9	2.3	6.3
Mod	1	0	0	0	0.3

*Cytologic interpretation is presented for the on-study sputum specimens for the first 333 accrued patients, classified by the cell type of the patients' resected primary cancer. There is no significant association.
*Seven specimens were of mixed or other primary cell type.
**Fourteen specimens have missing cell type.
‖Squ=squamous cell carcinoma; Lrg=large cell undifferentiated; Adn=adenocarcinoma; Br-alv=bronchiola alveolor carcinoma; Uns=unsatisfactory; Neg=negative; Sli=slight atypical metaplasia; Mod=moderate atypical metaplasia.

Table 3—*Cytomorphologic Distributions at First Screening**

Morphology	Central Laboratory Interpretation (n=333) %	Accrual Laboratory Interpretation (n=333) %
Neg	66.1	71.8
Sli	6.3	12
Mod	0.3	1.2
Gra	0	0.9
Can	0	0.9
Uns	27.3	13.2

*A significant difference is observed between the cytologic interpretation of the central laboratory and the accrual laboratory for the first 333 accrued patients.

‖ Neg=negative; Sli=slight atypical metaplasia; Mod=moderate atypical metaplasia; Gra=grave atypical metaplasia; Can=cancer; Uns=unsatisfactory.

pected follow-up visits have been reported to the coordinating center. Similarly, projecting the second primary lung cancer incidence rate at 3% per year from the LCSG experience leads to an expected 10 end-point events. Compared with the 10 events expected by this time, only two have been reported.

Discussion

With the explosive interest in tumor biology, new tools and new organizational strategies have emerged with a greater potential to identify markers of neoplasia in the sputum well in advance of the clinical diagnosis of cancer. Monoclonal antibody recognition of tumor-associated antigens has progressed furthest toward application as a lung cancer biomarker. By closely following the biology of neoplastic transformation, other rationally developed diagnostic tools can potentially detect the carcinogenesis process before the clinical onset of cancer. A wealth of published information, including our own experience,[15,18,19,29] is relevant in attempting to understand and organize the complex issues involved in bringing a biomarker into applications for preventative approaches to lung cancer. Monoclonal antibodies that recognize differentiation or tumor-associated antigens may be particularly useful in an early detection strategy to discriminate epithelial cells that have been transformed, but are not yet

Table 4—*Cytomorphology by Smoking Status**

	Current (n=51) %	Former (n=239) %	Never (n=37) %
Uns	19.6	28.9	37.8
Neg	72.6	63.6	59.5
Sli	5.9	7.5	2.7
Mod	2	0	0

*Although the frequency of unsatisfactory specimens increases with former and current smoking, this association does not reach statistical significance. p=0.13.

†Six specimens have missing smoking history.

‖ Uns=unsatisfactory; Neg=negative; Sli=slight atypical metaplasia; Mod=moderate atypical metaplasia.

Table 5—*Quantity and Intensity of Immunostained Cells by Cytomorphology**

Morphology	Mean No. of Cells Stained 703D4	Mean No. of Cells Stained 624H12	Mean Intensity of Stained Cells 703D4	Mean Intensity of Stained Cells 624H12
Slight	7.8	9.3	0.9	1.1
Moderate	2.2	2.7	0.1	0.2
Marked	0	0	0	0
Cancer	0	0	0	0

*Among the 60 cases immunostained at the University of Pennsylvania, immunostaining is observed by cells interpreted only slightly and moderately atypical on routine morphologic interpretation at Johns Hopkins.

overtly malignant, from cells of similar morphologic features due to "benign" injury. The potential for detection of early phenotypic markers of oncogene activation and their potential for reversal after intervention (*eg*, retinoid) therapies make the present studies an important first step in the determination of reproducible lung cancer intermediate end points.

The recent NCI/DCPC Workshop on the Primary and Secondary Prevention of Lung Cancer in Potomac, Md, highlighted the burgeoning potential for early detection and chemoprevention of **all** epithelial cancers. The markers of epithelial carcinogenesis described at that workshop are described in exfoliated cells or biopsy specimens of virtually all the major epithelial tumors. Lung cancer may offer a paradigm for progress against other epithelial cancers.

The present study emphasizes a collaborative matrix among the accrual centers and the laboratories conducting marker/intermediate end-point assays who maintain the specimen banks. The central laboratories responsible for the assays must interact closely with investigators conducting the accrual to assure that appropriate specimens are collected and preserved with standardized techniques appropriate to the assay. Similarly, the central laboratories must assure that the specimens from each accrued patient can be stored in a bank such that marker expression on tumor and preneoplastic specimens of the same patient can be compared. Specimen banks of tumor and premalignant tissue (or exfoliated cells) linked to the same patient are fundamental to successful selection of markers for early detection or intermediate end points.

The population with resected stage I lung cancer is uniquely appropriate for early detection and chemoprevention trials. These unique features include the following:

High risk: The **annual** incidence of second primary lung cancer (all four major cell types) is 3 to 5% in this population.[24] This is an order of magnitude greater than the incidence experienced by the middle-aged, heavy smokers in the NCI (Hopkins, Mayo, Memorial) ELC trial a decade ago. This 10-fold greater incidence translates into a 10-fold reduction in required sample size for lung cancer end points.

High motivation: Postsurgical survivors of lung cancer have had high rates of participation and compliance in the adjuvant trials completed through the LCSG. They have

willingly accepted the possibility of side effects in those trials and would likely feel similar enthusiasm for chemoprevention trials in the future.

Committed investigators: Successful accrual is a function of the enthusiasm and commitment of the investigators at the individual accrual centers. Standardization of specimen collection, drug administration, and clinical evaluation techniques will put a premium on those centers that can accrue large numbers of patients with stage I disease who have undergone resections. The LCEDWG investigators responsible for the present early detection trials have demonstrated their ability to accrue large numbers of these patients.

The large numbers of potential carcinogenesis markers and potential chemopreventive agents that await evaluation merit a concerted attempt to continuously accrue patients with stage I disease who have undergone resections into trials; beginning enrollment in trials of newer chemopreventive agents/markers as existing trials are filled. It is important to understand that there is no evidence that a single molecular defect underlies all lung cancer and will be detected by the Mabs under investigation. It is far more likely that during the process of malignant transformation, several possible point mutations, missense mutations, and allelic deletions take place, leading to the production of moieties as the Lewis X glycoprotein and the 31-Kd targets recognized by our Mab markers. The existence of these targets in exfoliated cells could indicate either an epithelium in the process of carcinogenesis or the presence of cancer. These Mab markers might be considered a sieve or a screen to identify patients who should undergo further testing. For example, patients who immunostain positive might undergo examination for oncogene mutations in endoscopic washings or in sputum as we are currently investigating.[30] Further, as the triage of markers is refined and validated in further trials, marker modulation by chemopreventive agents (*eg*, 13-cis retinoic acid) may become a useful intermediate end point and prognostic index for the efficacy of potential pharmacologic prevention and treatment.

The characteristics of the population accrued to the present study reflect the patients who undergo "curative" lung cancer surgery. The high proportion of female patients (44%) probably reflects the biology of resectable, isolated, peripheral lesions, *ie*, adenocarcinomas. More than half (55.3%) of the resected primary lung cancers in this series were of this cell type.

The lack of association between cytomorphology and cell type of primary tumor is preliminary, but interesting. In our earlier report,[17] we demonstrated that individuals with no more than moderate metaplasia in their sputum ultimately went on to develop all four major lung cancer cell types with approximately the frequency found in the population. In contrast, individuals who exhibited grave dysplasia developed only non-small cell types of lung cancer, while those with frankly malignant cytomorphologic features were found to have lung cancer, almost always of the epidermoid type.

The appearance of immunostained cells among the specimens considered morphologically negative (slightly and moderately metaplastic) is also of interest. Of all the lung cancer cases screened by cytology in the NCI-Johns Hopkins study, only 36.9% showed sputum epithelial cell metaplasia, dysplasia, or neoplasia in advance of their tumor. If glycopeptide markers are expressed by premalignant cells that do not show morphologic changes, then the potential for early detection is greatly enhanced.

Finally, the importance of banking the carefully obtained serial premalignant specimens from a high-risk population along with specimens of the subsequent tumors cannot be overstated. The genetic instability of cells undergoing malignant transformation leads to a plethora of mutational events. Those events that arise early in carcinogenesis and are preserved in the final tumor have the greatest potential as early detection biomarkers. If only the tumor were available to provide mutational clues, arbitrary selection of possibly late-developing events could lead to misdirected efforts at screening. The Mabs under study were developed from cell lines of human lung tumor. The Mabs were then tested on banked premalignant sputum specimens before their preliminary validation in our earlier report.[17] That prospective nonconcurrent study was conducted with a blinded analysis of sputum specimens selected from different time periods of the precancer screening. Because there were serial specimens available and long-term outcome on all the participants was known, the actual diagnostic precision of the two Mabs as early lung cancer detection markers could be discerned. This rational approach is a powerful method for selection and validation of potential early detection markers. A serially acquired archive of precancer specimens from a defined clinical cohort, when paired with demographic data, clinical follow-up, and tumor specimens, should have broad utility for many epithelial cancers.

Conclusions

Previous reports suggest that two Mabs can, with reasonable accuracy, detect changes in sputum samples 2 or more years before routine clinical lung cancer detection. We are presently halfway through the accrual in a trial designed to validate those earlier observations. However, this validation trial has been designed with the detection of lung cancer development as its end point. During the trial, the results of immunostaining will not modify therapy and thus, this trial cannot be the definitive study of the efficacy of this early detection technique for lung cancer mortality reduction.

Yet, these observations are of potentially enormous significance. An increase in lead time of 2 or more years might be sufficient to make widespread screening feasible and warranted even if patients with lung cancer without atypical metaplasia remained undetected by this technique. If this study demonstrates that the one third of patients with lung cancer with metaplasia or dysplasia can reliably be recognized 2 years prior to sputum cell morphologic study or clinical evidence of cancer, and if any of the remaining patients without atypia can have their conditions diagnosed, it will be a powerful argument for reconsidering formal trials of the efficacy of early detection and intervention for lung cancer mortality reduction. The availability of valid intermediate end points for lung cancer would be a significant resource for efficacy studies of

chemoprevention or early surgical intervention.

The Lung Cancer Early Detection Working Group (LCEDWG) Investigators (with their affiliations listed in parentheses) include the following: R.M. Bukowski, MD (The Cleveland Clinic Foundation); T. Lad, MD (Illinois Cancer Council/Comprehensive Cancer Center); D.S. Ettinger, MD (The Johns Hopkins Oncology Center); J. Deslauriers, MD (Le Centre de Pneumologie de Laval [Quebec]); R. Ginsberg, MD (Memorial Sloan-Kettering Cancer Center); K. Kelly, MD (University of Colorado/Health Sciences Center); E.C. Holmes, MD (University of California–Los Angeles); F. Muggia, MD (University of Southern California); J.A. Roth, MD (University of Texas/M.D. Anderson Cancer Center); M. Johnston, MD/M.F. McKneally, MD (University of Toronto); and J.D. Ruckdeschel, MD (H. Lee Moffitt Cancer Center [University of South Florida]).

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References

1 US Department of Health and Human Services. Volume Appendix: National trends in smoking cessation. In: The Health Benefits of Smoking Cessation. US DHHS, PHS, CDC, Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. DHHS publication No. (CDC) 90-8416, 1990; 579-628

2 Frost JK, Ball WC Jr, Levin ML, et al. Final report: lung cancer control, detection and therapy, phase II. NCI publication No. (PHS) N01-CN-45037. Washington, DC: NCI,1984

3 Tockman MS, Levin ML, Frost JK, et al. Screening and detection of lung cancer. In: Aisner J, ed. Lung cancer. New York: Churchill Livingstone, 1985; 25-40

4 Stitik FP, Tockman, MS, Khoury NF. Chest radiology. In: Miller AB, ed. Screening for cancer. San Diego: Academic Press, 1985; 163-99

5 Flehinger BJ, Melamed MD, Zaman MB, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Memorial Sloan-Kettering study. Am Rev Respir Dis 1984; 130:555-60

6 Berlin NI, Buncher CR, Fontana RS, et al. The National Cancer Institute Cooperative Early Lung Cancer Detection Program: results of the initial screen (prevalence): early lung cancer detection: introduction. Am Rev Respir Dis 1984; 130:545-49

7 Frost JK, Ball WC Jr, Levin ML, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Johns Hopkins study. Am Rev Respir Dis 1984; 130:549-54

8 Flehinger BJ, Melamed MD, Zaman MB, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Memorial Sloan-Kettering study. Am Rev Respir Dis 1984; 130:555-60

9 Fontana RS, Sanderson DR, Taylor WF, et al. Early lung cancer detection: results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic study. Am Rev Respir Dis 1984; 130:561-65

10 Frost JK, Fontana RS, Melamed MD, et al. Early lung cancer detection: summary and conclusions. Am Rev Respir Dis 1984; 130:565-70

11 Guidelines for the cancer-related check up: recommendations and rationale. CA 1980; 30:191-240

12 Saccomanno G, Archer VE, Auerbach O, et al. Development of carcinoma of the lung as reflected in exfoliated cells. Cancer 1974; 33:256-70

13 Frost JK, Ball WC Jr, Levin ML, et al. Sputum cytopathology: use and potential in monitoring the workplace environment by screening for biological effects of exposure. J Occup Med 1986; 28:692-703

14 Tockman MS. Survival and mortality from lung cancer in a screened population—the Johns Hopkins Study. Chest 1986; 89:324S-325S

15 Mulshine JL, Tockman MS, Smart CR. Considerations in the development of lung cancer screening tools. J Natl Cancer Inst 1989; 81:900-06

16 Prorok PC, Connor RJ. Screening for the early detection of cancer. Cancer Invest 1986; 4:225-38

17 Tockman MS, Gupta PK, Myers JD, et al. Sensitive and specific monoclonal antibody recognition of human lung cancer antigen on preserved sputum cells: a new approach to early lung cancer detection. J Clin Oncol 1988; 6:1685-93

18 Mulshine JL, Cuttitta F, Bibro M, et al. Monoclonal antibodies that distinguish non-small cell from small cell lung cancer. J Immunol 1983; 131:497-502

19 Rosen ST, Mulshine JL, Cuttitta F, et al. Analysis of human small cell lung cancer differentiation antigens using a panel of rat monoclonal antibodies. Cancer Res 1984; 44:2052-61

20 Piantadosi S. Long term follow-up of surgically resected T1N0 non-small cell lung cancer patients. Lung Cancer 1988; 4 (suppl):A82

21 Feld R, Rubinstein LV, Weisenberg TH, et al. Sites of recurrence in resected stage I non-small cell lung cancer: a guide for future studies. J Clin Oncol 1984; 2:1352-58

22 Ginsberg RJ. Limited resection for peripheral T1N0 tumors. Lung Cancer 1988; 4(suppl):A80

23 Thomas P, Feld R. Preliminary report of clinical trial comparing post-resection adjuvant chemotherapy versus no therapy for T1N1, T2N0 non-small cell lung cancer. Lung Cancer 1988; 4(suppl):A160

24 Grover FL, Piantadosi S. Recurrence and survival following resection of bronchioloalveolar carcinoma of the lung—The Lung Cancer Study Group experience. Ann Surg 1989; 209: 779-90

25 Saccomanno G, Saunders RP, Ellis H, et al. Concentration of carcinoma or atypical cells in sputum. Acta Cytol 1963; 7: 305-10

26 Gupta PK, Myers JD, Baylin SB, et al. Improved antigen detection in ethanol-fixed cytologic specimens: a modified avidin-biotin-peroxidase complex (ABC) method. Diagn Cytopathol 1985; 1:133-36

27 Tockman MS, Gupta PK, Pressman NJ, et al. Considerations in bringing a cancer biomarker to clinical application. Cancer Res 1992; 52(suppl):2711S-18S

28 Tockman MS, Gupta PK, Pressman NJ, et al. Cytometric validation of immunocytochemical observations in developing lung cancer. Diagn Cytopathol 1993; 9:615-22

29 Mulshine JL, Linnoila RI, Jensen SM, et al. Rational targets for the early detection of lung cancer. J Natl Cancer Inst Monogr 1992; 13:183-90

30 Mao L, Hruban RH, Boyle JO, et al. Detection of oncogene mutations in sputum precedes diagnosis of lung cancer. Cancer Res 1994; 54:1634-37