The University of Texas Southwestern Medical Center

Harold C. Simmons Comprehensive Cancer Center

LUNG CANCER: TO SCREEN OR NOT TO SCREEN

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INTRODUCTION:

Lung cancer is one of the most common malignancies in men and women combined and it represents a major cause of morbidity and mortality in the USA. Together with prostate, breast and colorectal cancers, lung cancer is among the most common cancers and it is the leading cause of cancer death in the USA. The American Cancer Society estimates that for the year 2001, there will be 169,500 new lung cancer diagnoses and 157,400 deaths from lung cancer (1); Table 1.

Table 1: TEN MOST COMMON NEW CANCER DIAGNOSES AND CAUSES OF CANCER DEATH FOR YEAR 2001

	New Cancer Diagnosis	Cancer Deaths
Cancer Sites	**Number**	**Number**
Prostate	198,100	31,500
Breast	193,700	40,600
Lung	**169,500**	**157,400**
Colorectal	135,400	56,700
Lymphoma	63,600	27,600
Bladder	54,300	12,400
Melanoma	51,400	7,800
Uterine corpus	38,300	6,600
Leukemia	31,500	21,500
Pancreas	29,200	28,900

Lung cancer usually presents in an advanced stage as only 20% of consecutive lung cancer patients are potentially resectable at diagnosis (2). Since surgical resection of the tumor is the most effective therapy for lung cancer, the inability to apply this therapy to the majority of patients is reflected in the poor survival of patients. Only 14% of all lung cancer patients are expected to be alive and disease free after 5 years (1).

Lung cancer is a group of heterogeneous histologies though most of them have aggressive behavior. The most common histologic forms of lung cancer include: adenocarcinoma (40%), epidermoid carcinoma (25%), undifferentiated large cell carcinoma (15%) and small cell lung cancer (20%). The bronchoalveolar form of lung cancer is an infrequent form of adenocarcinoma and represents approximately 2% of lung cancers. Most forms of lung cancer involve the central structures of the lung and mediastinum. Some, particularly the adenocarcinomas, present in the periphery of the lung (2).

Eighty-five percent of lung cancers are smoking-related (3-6). The frequency and the mortality from lung cancer are directly related to the intensity of cigarette smoking (3). Therefore, lung cancer is a potentially preventable disease if smoking could be eradicated

from our culture. Adenocarcinomas are less often associated with smoking than other forms of lung cancer.

The survival of lung cancer patients is influenced by its clinical or surgical staging at diagnosis. Thus, patients presenting with early stages of disease have a better prognosis than those with more advanced stages of disease. This is, therefore, the reason behind efforts toward the early detection of lung cancer. This presentation examines the issues around the screening for lung cancer and puts them into perspective in view of new technologic advances in radiology and molecular biology.

IMPORTANCE OF DISEASE STAGE AT DIAGNOSIS:

Table 2 describes the different criteria used to stage lung cancer according to the American Joint Committee on Cancer and the Union Internationale Contre le Cancer. The primary tumor is divided into four categories (T1-T4) depending on size, site, and local involvement. Lymph node spread has been subdivided into bronchopulmonary or hilar (N1), ipsilateral mediastinal (N2), and contralateral mediastinal or supraclavicular disease (N3). The absence (M0) or presence (M1) of distant metastasis is also recognized by this staging system. Four stages of lung cancer have been identified, with significant differences found in 5-year survival, depending on the stage of disease at diagnosis. Several authors have confirmed the accuracy of this staging system (7,8).

Table 2: TUMOR, NODE, METASTASIS (TNM) STAGING SYSTEM FOR LUNG CANCER

PRIMARY TUMOR:

TX	Positive malignant cell; no lesion seen
T1	< 3 cm diameter
T2	> 3 cm diameter Distal atelectasis
T3	Extension to parietal pleura, chest wall, diaphragm, or pericardium < 2 cm from carina or total atelectasis
T4	Invasion of mediastinal organs Malignant pleural effusion

REGIONAL LYMPH NODE INVOLVEMENT:

N0	No nodal involvement
N1	Ipsilateral bronchopulmonary or hilar
N2	Ipsilateral or subcarinal mediastinal Ipsilateral supraclavicular nodes
N3	Contralateral mediastinal, hilum or supraclavicular

METASTATIC INVOLVEMENT:

M0 No metastasis
M1 Metastases present

NEW LUNG CANCER STAGING		5-YEAR SURVIVAL (%)
Ia	T1, NO, MO	> 70
Ib	T2, NO, MO	60
IIa	T1, N1, MO	50
IIb	T2, N1, MO	30
	T3, NO-1, MO	40
IIIa	T1-3, N2, MO	10-30
IIIb	Any T4, any N3, MO	< 5-10
IV	Any M1	< 2

The TNM staging of lung cancer includes clinical, surgical and pathologic subsets. The surgical and pathologic staging are the most accurate since there could be up to 30% under-staging with clinical tools alone.

Patients with smaller lesions and those without evidence of loco-regional lymph node involvement or distant metastasis have better prognosis. This is shown in Table 3 below, reflecting the experience of Naruke with 2055 lung cancer patients operated on for cure (9). Patients with early T and N lesions have better 5-year survival.

Table 3: LUNG CANCER 5-YEAR SURVIVAL BY TUMOR (T) AND NODAL (N) STATUS

Tumor	No.	% Survival	Node	No.	% Survival
T1	562	67	N0	967	63
T2	902	41	N1	454	42
T3	405	30	N2	546	17
T4	160	12	N3	88	2

The limited 5-year survival of resected patients, even at Stages I and II (70-30% respectively), is explained in part by the findings of Matthews and Mountain suggesting early dissemination of disease (10,11). Matthews found that among patients who died within one month from potentially curative surgery, 14% to 63% of patients had evidence of distant metastasis (17% epidermoid, 40% adenocarcinoma, 14% large cell, and 63% small cell (10). Mountain, on the other hand, reported that among patients who underwent potentially curative operations for lung cancer, over 70% of them relapsed systemically first regardless of tumor histology and surgical staging at presentation (11). These observations point to the fact that in a significant number of patients lung cancer disseminates at early stages.

SCREENING FOR LUNG CANCER --THE EARLY AMERICAN EXPERIENCE:

In the late 60s and early 70s, the National Cancer Institute (NCI) embarked into a program of early detection of lung cancer at three major institutions: the Mayo Clinic, Memorial Sloan Kettering, and Johns Hopkins. A major ingredient at that time was the success obtained with implementation of the Papanicolaou test in reducing mortality from cervical carcinoma and the promising findings of early detection of lung cancer by sputum cytology by Saccomano (12).

The NCI program called for the accrual of over 10,000 male cigarette smokers older than 45 years of age at each institution. At Johns Hopkins and at Memorial Sloan Kettering, the enrollees were randomized into two groups. One group, the study group, was to have an annual chest x-ray and quarterly sputum cytology. The control group was to have an annual chest x-ray. The Mayo Project had quarterly sputum cytology and chest x-rays in the study group versus a usual care control group (13).

These studies demonstrated that sputum cytology and chest x-rays did not reduce the mortality from lung cancer among male cigarettes smokers when compared to an annual chest x-ray (Memorial Sloan Kettering and Johns Hopkins) or usual care (Mayo Clinic) groups. These studies did not evaluate the role of chest x-ray alone in lung cancer mortality. However, the survival of patients who were resected in the screen groups was superior to that of controls and three-fold better than the NCI Surveillance, Epidemiology, and End Results (SEER) for men diagnosed with lung cancer at that time (14). Screened patients had a larger proportion of resectable patients than in unscreened groups. Tables 4 and 5 summarize two of these trials.

Table 4: MEMORIAL SLOAN KETTERING CANCER CENTER LUNG PROJECT: FINAL RESULTS

	Chest x-ray + Sputum cytology	**Chest x-ray Alone**	**p**
Population	5072	4968	
Incidence rate	144	144	NS
No. Stage I	59 (41%)	58 (40%)	
No. Stage II	7 (5%)	11 (8%)	NS
No. Stage III or IV	78 (54%)	75 (52%)	
No. Resectable	73 (51%)	77 (53%)	NS
Actuarial 5-yr Survival	37%	33%	NS
Morbidity	63%	64%	NS
Mortality	90	92	NS

NS = not significant

The Memorial Sloan Kettering study did not demonstrate any significant difference in mortality or any other end point by the addition of sputum cytology to annual chest x-ray. The results of the Johns Hopkins study were similar (15,16).

Table 5: MAYO CLINIC PROJECT FINAL RESULTS
(9-YEARS AFTER STUDY ENTRY)

	Screened	Control	p
Population	4618	4593	
Incidence rate	206	160	0.016
No. Stage I or II	99 (48%)	51 (32%)	NR
No. Stage III or IV	107 (52%)	109 (68%)	0.0019
No. Resectable	94 (46%)	51 (32%)	0.0096
Actuarial 5-year Survival	33%	15%	NR
Morbidity	59%	72%	0.016
Mortality	122	155	0.72

NR = not reported

The Mayo Lung Project included a 6-year average period of screening and 3 additional years of observation. Even though there were larger number of lung cancers diagnosed in the screened group and that such cancers were more often resectable, there was no difference in overall lung cancer mortality (17). An update of the Mayo Lung Project through 1996 confirms the lack of effect on lung cancer mortality (18). Eddy has suggested that the Mayo Clinic Lung Project detected malignant lesions by screening that were not clinically significant and most likely would not have become clinically evident during the trial's follow up period (19). Similar results were reported by the Czek Lung Cancer Screening Study (20,21).

Lead-Time, Length Bias and Overdiagnosis Bias

The lack of beneficial effect of screening for lung cancer on the absolute mortality due to lung cancer, in spite of detecting more early lesions by screening, has been explained as resulting from lead-time bias, length-bias and overdiagnosis bias (22-24).

In lead time bias, the assumption is made that the early detection of the disease does not change the disease's clinical course or natural history. The time of diagnosis is moved forward by screening, so that, even if the time of death is not altered, the observed survival will be longer in a case detected by screening than otherwise would have been detected. This early diagnosis is a prerequisite for effective screening, and, in the absence of any benefit from treatment, it also results in a longer period of observed morbidity for a patient with screen-detected disease. Lead-time bias predicts an excess of cases due to screening. Assuming that all cases are clinically significant lesions that eventually will become life-threatening if not treated, after screening is discontinued, the number of control cases should catch up. This, however, did not occur at the Mayo Lung Project in which both groups were observed during a post experimental period and in the Czeck study, in which both groups underwent annual chest x-ray screening. Accordingly, lead-time bias can not explain the persistent discrepancies in the incidence rate observed in the two trials.

In length-bias, the rate of development of cancer is variable, and, therefore tumors would have a variable length of time in a preclinical, screen-detectable phase. When screening is applied regularly to a population, cases detected by screening will include a disproportionate number of slower growing tumors, which remain longer in the preclinical, screen-detectable phase. Length-bias arises because these cases would have a better prognosis than faster growing tumors. Some, however, would argue that detection of these tumors is beneficial if advantages in stage distribution translate into improvement in long-term survival and cure. This concept could be further tested by examining the difference between the prevalence cases and those detected at subsequent screening. In the Mayo Lung Project, for example, there were 4 times as many incidence cases as prevalence cases (366 cases vs. 91 cases). The 5-year survival rates were only slightly better among prevalence cases than among incidence cases in the experimental group (40% vs. 33%). These observations suggest that the length bias effect in the Mayo Lung Project was small.

Overdiagnosis-bias is a subcategory of length-bias. It means that some of the slowly growing cancers never would have been diagnosed in the absence of screening and that individuals died from other causes without their sub-clinical cancer being recognized. It also can be the result of "pseudo disease" which would have never progressed to clinical disease. Although this concept may have some foundation for prostate cancer (25), this is not substantiated by epidemiologic or clinical experience. Lung cancer is one of the deadliest malignancies as only 12-14% can be cured today (1,26). The majority of those derived from patients who undergo surgical resections of their disease. By contrast, the survival of patients with early disease who do not undergo surgical resection is rather poor (Table 6) (27).

Table 6: 5-YEAR SURVIVAL FOR STAGE I PATIENTS WHO DID NOT UNDERGO SURGERY

Study	No. Not Resected	No. Survivors	Percent
Memorial Sloan Kettering	5	0	0
Johns Hopkins	29	1	3.4
Mayo Clinic	11	1	9.1
Japan Screening Group	69	7	10.1
Turku Hospital	15	0	0
TOTAL	129	9	7

Therefore, epidemiologic research would support the conclusion that lung cancer is a rather poor candidate for overdiagnosis through screening.

Autopsy studies suggest that overdiagnosis might be present in prostate cancer. It has been demonstrated that 33% of men over 50 years old and 67% of men over 60 years who die of unrelated causes have evidence of latent prostate cancer at autopsy (25). For lung cancer, the frequency of incidental lung cancer at autopsy has ranged between 15% in Malmo, Sweden, to 3% and to 0.8% in the USA (28-30).

Clinically, there is little evidence of lung cancer patients surviving their disease untreated (31-33). Survival for untreated patients, ranging between two and five years, has been reported for 7% to 0.7% of patients respectively (31). Most series report the dismal prognosis of untreated lung cancer patients with average survival between 6 to 9 months (31-33). Data from 492 lung cancer patients collected from seven screening studies in which treatment did not include surgical resection demonstrate that only 21 patients (4%) were alive 5-years after diagnosis. Furthermore, 90% died from lung cancer and not from co-morbid conditions (27). This is in marked contrast to reports in breast and prostate cancers. Among 250 patients seen between 1805 and 1933 at Middlesex Hospital, the median survival and five year survival rates for untreated breast cancer patients were 2.7 years and 18% respectively (34). In another series of untreated breast cancer patients in Boston, the 5-year survival rate was 23% (35). A meta-analysis including 828 prostate cancer patients from six studies who were treated with initial observation demonstrated that the disease specific 10-year survival rate was 87% for men with low grade tumors (36). This data raises the possibility that prostate specific antigen (PSA) might be overdiagnosing prostate cancer.

Therefore, epidemiologic, autopsy and clinical data do not substantiate the several biases attributed to the potential gains from lung cancer screening.

COMPUTED TOMOGRAPHY SCREENING

The development of low dose spiral CT has increased our ability to detect smaller peripheral lung lesions, at lower radiation dose, and potentially at a more cost- effective output. Initial work by Ohmatsu (37) and Mori (38-39) evaluated the appropriate conditions for CT screening. Their results established the following scanning parameters: 120 KVp, 50 mA, 10-mm collimation, 1 rotation of the x-ray tube per second, and table speed of 20mm/second. A 30-cm area is scanned, beginning at a point 2cm superior to the apex and ending at the diaphragm during a single breath hold of 15 seconds. The parameters were defined and validated to permit the detection of nodules > 5 mm in size while reconstructing images every 1 cm. Muramatsu demonstrated that the radiation exposure using these parameters is approximately ten times higher than that of plain chest x-rays, but it is less than one-sixth that of conventional CT and only 1.3 times that of fluoroscopy as applied for mass screening of the gastrointestinal tract (40).

There have been several studies of low dose spiral CT for lung cancer screening in Japan (41-43), though the Anti-Lung Cancer Association (ALCA) study was among the first to utilize this methodology as a prospective initial screening method (42). The ALCA is a for-profit organization created in 1975 for lung cancer screening. Members pay dues and are entitled to biannual screening. Initial screening consisted on chest x-ray, frontal and lateral views, and sputum cytology. CT screening was added in September 1993. Members are usually men, and 92% of them are heavy smokers. Table 7 shows the results of screening before and after the introduction of CT screening. The rate of lung cancer detection has doubled since the introduction of CT screening. Similarly, the percent of adenocarcinomas has increased. The size of the detected lesions has decreased

from an average of 29.5 mm before CT to that of 15 mm after the introduction of CT. The 5-year survival of screened patients has improved from approximately 55% before the introduction of screening CT to 83% after it (p= 0.015).

Table 7: LUNG CANCER CASES DETECTED BY THE ANTI-LUNG CANCER ASSOCIATION SCREENING PROGRAM

	Before CT (Sept.1975-Aug 1993)	After CT Introduction (Sep 1993-Dec 1998) Total	Without CT	CT Alone
No. examined	26,338	9993		
Cases detected (%)	43 (0.16)	36 (0.36)	12 (0.12)	24 (0.24)
Location (%)				
Hilar	7 (16.3)	5 (13.9)	5 (41.6)	--
Periphery	36 (83.7)	31 (86.1)	7 (58.4)	24 (100)
Histologic type (%)				
Adenocarcinoma	21 (48.9)	24 (66.7)	2 (16.7)	22 (91.6)
Squamous cell	15 (34.9)	11 (30.6)	9 (75)	2 (84)
Small cell	5 (11.6)	1 (2.8)	1 (8.3)	--
Others	2 (4.6)	--	--	--
Stage (%)				
IA	18 (41.9)	28 (77.8)	6 (50)	22 (91.6)
IB	5 (11.6)	1 (2.8)	1 (8.3)	--
IIA	3 (7)	1 (2.8)	1 (8.3)	--
IIB				

Watanabe has reported the histologic pattern of recently detected peripheral adenocarcinomas by CT screening in Japan (44). By far, the most common cancers are adenocarcinomas (table 8)

Table 8: RECENTLY DIAGNOSED PERIPHERAL LUNG CANCERS IN JAPAN

Adenocarcinoma	142 (81.6%)
Squamous Cell	18 (10.3%)
Adenosquamous	5 (2.9%)
Large Cell	5 (2.9%)
Carcinoid	3 (1.7%)
Adenoid Cystic	1 (0.6%)
TOTAL	174

Noguchi has further studied this issue and reported that among resected adenocarcinomas detected by low dose spiral CT, there are six potential sub groupings with different clinical behaviors (45). He recognized Type A or localized bronchoalveolar carcinoma; Type B or localized bronchoalveolar carcinoma with foci of collapse of alveolar structure; Type C or bronchoalveolar carcinoma with foci of active fibroblastic proliferation; Type D or poorly differentiated adenocarcinoma; Type E or tubular

adenocarcinoma, and Type F or papillary adenocarcinoma with compressive and destructive growth.

Table 9 illustrates the survival relationships of the subtyping of adenocarcinomas as reported by Watanabe (44).

Table 9: SURVIVAL EFFECTS OF HISTOLOGIC SUBTYPING OF ADENOCARCINOMAS

Type	Number	% 5-Year Survival
A	19	100
B	5	100
C	70	73.6
D	19	56.2
F	16	77.5
OVERALL	129	86.8

The pioneer work of the Japanese with CT lung cancer screening has led the way to other investigations of CT lung cancer screening. In the USA, Henschke has reported her experience with CT lung cancer screening through the Early Lung Cancer Action Project (ELCAP) (46, 47). The ELCAP was limited to asymptomatic volunteers, 60 years of age or older who had a history of at least 10 pack/years of cigarette smoking and no history of cancer (other than non-melanotic skin cancer). Accrual started in 1993 and was completed in 1998. One thousand volunteer smokers participated in the ELCAP study. There were 54% males; 91% were white, their median age was 67 years, and their median number of pack/years of smoking was 45. There were 559 nodules found by low dose CT. Of these, 35% had benign calcifications and were therefore considered benign. There were 196 nodules found by chest x-ray. Of these, 60% had calcifications. CT identified 233 subjects with 1-6 non-calcified nodules. Only 33 of them had these nodules also apparent by chest x-rays. Twenty-seven (12%) were malignant. Chest x-ray detected 68 subjects with 1-6 non-calcified nodules, among whom 33 actually had non-calcified nodules on low dose CT. Seven (10%) were malignant. The remaining 35 subjects had false positive chest x-rays. The size of the nodules detected by low dose CT was in general half of those detected by chest x-ray. The distribution of the 27 malignancies detected by low dose CT relative to their size, their clinical staging, and their corresponding appearance by chest x-ray is shown in Table 10, below.

The overall frequency of malignancy was four times greater on low dose CT than on chest x-rays (2.7% vs. 0.7%). Stage I malignancies were detected six times as frequently with low dose CT as on chest x-ray. Pathologically, among the 27 malignancies, there were 18 adenocarcinomas, 3 bronchoalveolar carcinomas, 3 mixed squamous-adenocarcinomas, 1 squamous cell carcinoma, 1 atypical carcinoid and 1 person with two tumors, 1 adeno-squamous and 1 bronchoalveolar carcinoma. The long-term survival of these patients is not available.

Table 10: DISTRIBUTION OF MALIGNANCIES BY SIZE AND STAGE*

	Nodule size (in mm) on low dose CT				
Stage	**2-5**	**6-10**	**11-20**	**21-45**	**Total**
IA	1	12 (1)	8 (2)	1 (1)	22 (4)
IB	0	0	0	1	1
IIA	0	1 (1)	0	0	1 (1)
IIB	0	0	0	0	0
IIIA	0	0	0	2 (2)	2 (2)
IIIB	0	1	0	0	1
Total	1	14 (2)	8 (2)	4 (3)	27 (7)

*Numbers in parentheses are those detected by chest x-ray

The long-term effectiveness of low dose CT screening in general is still under study. Among the major challenges ahead are the appropriate selection of subjects who might benefit best from early lung cancer screening, determination of the biologic significance of the lesions being detected, determination of the resulting benefit/risks associated with their surgical resection, the cost-effectiveness associated with this technology and who should cover these costs. Although all of these issues need further evaluation, Okamoto in Japan (48) and Miettinen in Canada (49) suggest that low dose CT will prove cost-effective. Miettinen even questions whether or not this technology should be subject to prospective randomized studies for the early detection of lung cancer.

WHO IS HIGH-RISK FOR LUNG CANCER?

Present lung cancer screening projects would be more successful if they would apply to subjects at highest risk for lung cancer. A Mayo Clinic study reported the development of second primary lung cancer in patients with resected lung cancer at a rate of 2.6 patients per 100 patient years from the first through the fifth year following surgery, then decreasing to 0.8 patients per 100 patient years in the sixth and subsequent years (50). In addition, other factors make subjects more susceptible to this disease. Included is the linear relationship of lung cancer incidence to cigarette smoking and to the degree of pulmonary damage resulting from chronic inflammation (51). These factors are briefly reviewed below.

Smoking: It has been estimated that 80% of lung cancer deaths among men and 75% of lung cancer deaths among women are attributable to smoking (4). There is clear evidence of a dose-response relationship between smoking and lung cancer. The risk of lung cancer increases with the number of cigarettes smoked, years of smoking duration, earlier age of onset of smoking, degree of inhalation, tar and nicotine content, the use of unfiltered cigarettes and passive smoking, and it decreases in proportion to the number of years after smoking cessation (3,6).

Occupation: Lung cancer risk increases with exposure to carcinogens such as asbestos, radon, bis (chloromethyl) ether polycyclic aromatic hydrocarbons, chromium, nickel, and

inorganic arsenic compounds (52-59). The association with occupational exposure to these agents appears to be independent of cigarette smoking.

Chronic Pulmonary Disease: There is increasing evidence that pulmonary fibrosis resulting from chronic pulmonary inflammation is a significant risk factor for lung cancer. Among patients with chronic obstructive pulmonary disease, Tockman reported that the risk of developing lung cancer was associated with high entry values for age, smoking, and ventilatory status by linear, proportional hazard, and log-linear adjustment techniques. Among cigarette smokers, the presence of airway obstruction was more of an indicator for the subsequent development of lung cancer than was age or the level of smoking. The risk of lung cancer also increased in proportion to the degree of airway obstruction. Furthermore, he reported that smokers with ventilatory obstruction are at greater risk for lung cancer than are smokers without obstruction (51)

Genetic predisposition: The genetic and molecular events underlying the pathogenesis of lung cancer are an area of active investigation. To date, there is limited evidence that genetic factors contribute to lung cancer risk. Variations in the metabolism of carcinogens have been implicated (60). The pathways to create these toxic metabolites are genetically determined.

Diet: Dietary antioxidant micronutrients have an important role in scavenging free radicals produced endogenously and exogenously by tobacco smoke, solvents and pollutants. Carotenoids and vitamins C and E trap free radicals and reactive oxygen molecules, whereas selenium is a component of antioxidant enzymes (61). Unfortunately, chemoprevention studies with some of these agents to date have failed to have an impact on lung cancer incidence (62-68).

MOLECULAR DIAGNOSIS OF LUNG CANCER

There are a number of abnormal molecules found present in lung cancers, their surrounding "normal lung" and in sputum (4, 69-72). Most of the recent work is being done in NSCLC. The most common abnormalities are deregulation of tumor suppressor gene p53, aberrant expression of the epidermal growth factor receptor (EGFR) and one of its ligands, and the presence of K-ras abnormalities in adenocarcinomas (69-72). Other areas of investigation include:

Heterogenous Ribonucleoprotein A2 (hn RNP-A2): It regulates mRNA's shuttling, splicing and polyadenylation. hn RNP-A2 has been found to be expressed up to two years before the clinical diagnosis of lung cancer. It has also been shown to have an accuracy of 73% in predicting the development of lung cancer in Yunnan tin miners who are at a have risk for lung cancer (73).

Repair of Tobacco Carcinogens Induced DNA Adducts: Wei has reported that lung cancer patients have a significantly lower capacity to repair tobacco carcinogens induced DNA damage compared to controls and that such impairment associates with a greater than two-fold risk for lung cancer ($p < 0.001$) (74).

Abnormal DNA Methylation: Alterations of the pattern of DNA methylation are thought to have important implications for abnormalities of gene expression, chromosome structure, timing of DNA replication, and chromatin organization. This abnormality targets cytosine rich sequences (CpG islands) in promoter regions of many genes. Methylation of CpG islands prevents expression of a gene and effectively "deletes" such a gene. This abnormality can be detected in serum and sputum and can serve as a preclinical marker of cancer (75-76).

The following is a list of aberrant promoter methylation of multiple NSCLC genes:

- Retinoic Acid Receptor β-2 (RARβ)
- Tissue Inhibitor of Metalloproteinase 3 (TIMP-3)
- p16ink4a
- 06-methylguanine-DNA-methyltransferase (MGMT)
- Death-associated Protein Kinase (DAPK)
- E-cadherin (ECAD)
- p14arf
- Glutathione S-transferase P1 (GSTP1)

Palmisano et al studied a group of individuals who were smokers and exposed to radon through a uranium mining company in Colorado (77). They reported that among 10 patients with established lung cancer, abnormal methylation of p16 was found in 8 out of 8 patients, and methylation of MGMT gene in 4 out of 6 tumors. They extended these studies to 11 high-risk individuals who ultimately developed lung cancer. Sputum samples of these 11 individuals were abnormal for the presence of aberrant promoter methylation of p16 as far back as 35 months before diagnosis of cancer. Furthermore, they found a 90% concordance between p16 methylation in the primary tumor and paired sputum samples. Seven of the 11 samples had abnormal methylation of the MGMT gene with a 78% concordance between findings in the primary tumor and in sputum samples.

At UT Southwestern, we have started a lung cancer screening program for individuals who have at least a ten-year-pack history of cigarette smoking. Included as well are individuals who had a prior resection for lung cancer. Subjects undergo a baseline evaluation that includes a chest x-ray, pulmonary functions tests, sputum cytology, a spiral CT of the chest and determination of hn RNP-A2/B1, K-ras mutation, her-2-neu, p53 abnormalities, DNA methylation in sputum as well as DNA methylation studies in blood. The studies of molecular markers at UT Southwestern are being supported by the SPORE (Specialized Program of Research Excellence) grant, Dr. John Minna, PI. These studies are being conducted by Drs. Minna and Adi Gazdar, and some of their results are reflected below.

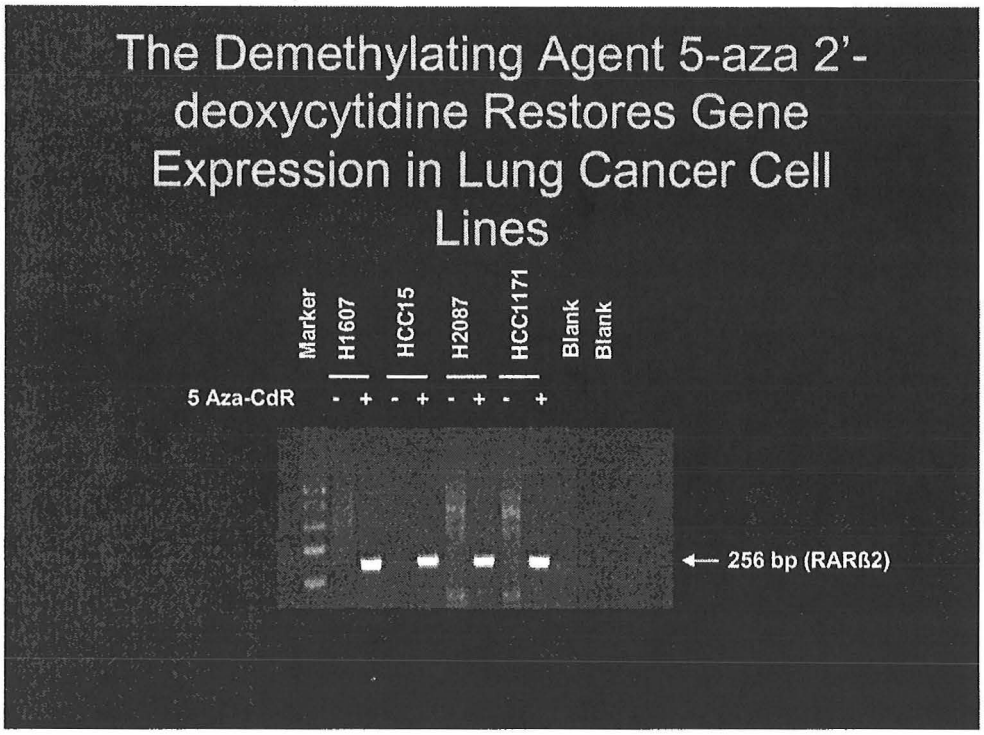
Zöchbauer-Müller et al reported results of studies of aberrant promoter methylation of a number of genes in 107 resected primary NSCLC and in 104 corresponding nonmalignant lung tisues by methylation-specific PCR as indicated in Table 11 below (76). A total of 82% of the NSCLCs had methylation of at least one of these genes, 37%

had one gene methylated, 22% had two genes methylated, 13% had three genes methylated, and 8% had four genes methylated. In comparing the methylation patterns of tumors and nonmalignant tissues, there were many discordances where the genes methylated in nonmalignant tissues were not methylated in the corresponding tumors. This observation suggests the possibility that methylation was occurring as a preneoplastic change in nonmalignant tissues.

Table 11: PERCENT METHYLATION IN 107 NSCLC AND 104 NORMAL LUNG TISSUES

Gene	Tumor	Normal Tissue
RARβ	40	14
TIMP-3	26	8
p16ink4a	25	0
MGMT	21	0
DAPT	19	6
E-cadherin	18	0
P14ARF	8	5
GSTP1	7	0

Virmani, Minna and Gazdar investigated if methylation of the P2 promoter of RARβ2 and RARβ4 might silence the RARβ gene in human lung cancer and lung cancer cell lines (78). P2 promoter was methylated in 63 of 87 (72%) SCLC, in 52 of 127 (41%) NSCLC and lung cancer cell lines ($p<0.001$), and in 1 of 58 (2%) control samples. They also found that four lung cancer cell lines with methylated promoter regions lacked expression of RARβ2 and RARβ4 genes and that exposure of these cell lines to 5-aza 2'-deoxycytidine restored their expression. This observation raises the possibility that treatment of affected cells with 5-aza 2'deoxycytidine or other demethylating agents could serve as chemoprevention agents of lung cancer.



CONCLUSIONS:

Lung cancer remains as the most lethal form of cancer in the USA and throughout the world. Since it is to a great extent smoking related, lung cancer represents a potentially preventable disease. This cancer is usually silent as 70-80% of the time presents already advanced and beyond the possibility for surgical resection and possible cure. Disease at early stages has greater possibility for cure, and this is the reason for attempts at early diagnosis through programs of lung cancer screening in high-risk individuals. The screening programs of the early 1970s utilizing chest x-rays and sputum cytology were successful in detecting earlier disease though they failed to improve overall lung cancer related mortality. Several explanations for this outcome have been given, however, they were all speculative. Included is the possibility of lead-time bias, length bias, and overdiagnosis. New and improved radiologic techniques such as low-dose spiral CT appear promising. Low dose spiral CT is at least three times more successful than chest x-rays in the detection of smaller, peripherally located lung cancers. Japanese and American investigators have demonstrated its feasibility, and the initial survival data resulting from resection of these lesions appears beneficial. The biologic significance of these findings relative to previous lung cancer screening efforts remains unknown. The introduction of complementary studies of molecular markers in sputum and blood as well as in resected tumors has the potential to improve our understanding of this issue. Lung cancer screening remains an important area for further clinical and laboratory investigations.

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