Cytopathological Analysis of Sputum in Patients with Airflow Obstruction and Significant Smoking Histories

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ABSTRACT

Advances in the understanding of lung cancer biology have led to observations that specific genetic changes occur in premalignant dysplasia. These observations have occurred predominantly in molecular studies of resected lung tumors and consequently, they may not be fully representative of those biological abnormalities characterizing premalignant lesions in individuals without overt lung cancer. Studies of premalignant epithelial cell biology and chemoprevention are needed in this patient subgroup. Such an initiative is now underway through the lung cancer Specialized Program of Research Excellence (SPORE) grant awarded to subgroup. Such an initiative is now underway through the lung cancer Specialized Program of Research Excellence (SPORE) grant awarded to the University of Colorado Cancer Center (and affiliated institutions) by the National Cancer Institute. To identify participants for the early detection and chemoprevention trials of the Colorado SPORE, we initiated a sputum cytology screening program targeting persons with chronic obstructive pulmonary disease and smoking histories of 40 or more pack-years. During the first 26 months after activation of the screening program, sputum samples from 632 participants were evaluated. Of these, 533 (84%) of the subjects submitted specimens deemed adequate for cytopathological interpretation; 99 (16%) provided sputum samples unsuitable for cytdiagnosis. Of those participants who submitted adequate samples, 48% had cytodiagnoses of mild dysplasia, 26% had moderate to severe dysplasia, and 2% presented with carcinoma in situ or invasive carcinoma. Logistic regression modeling was pursued to determine whether selected demographic and/or clinical status variables could be identified as statistically significant predictors of the specific cytological outcome to be expected (mild dysplasia, moderate dysplasia, and so forth). The only apparent associations found from both univariate and multivariate analyses were that the total number of pack-years of smoking history decreased with severity of cytodiagnosis and that those individuals with mild or moderate dysplasia were more likely to be ex-smokers than those with grades of regular metaplasia or lower. Based on the initial results of the Colorado SPORE sputum cytology screening program, we conclude that persons with chronic obstructive pulmonary disease and 40 or more pack-years of smoking history have a high prevalence of premalignant dysplasia detectable through sputum cytology and should be targeted for research programs focusing on lung cancer prevention, early detection, and exploratory biomarker studies.

INTRODUCTION

Lung cancer is now the leading cause of cancer death among both males and females in the United States (1). It is also one of the most lethal types of cancers to acquire, as reflected through an overall 5-year survival rate of 14% (1). In part, the poor prognosis of lung cancer is due to the late stage at which this disease is typically diagnosed; over 50% will have advanced-stage IIIb or IV disease at diagnosis, both of which are usually incurable by present therapy (2). Reasons for this phenomenon reside in the fact that symptoms of early lung cancer are often nonspecific, thus precluding many patients from being motivated to seek medical attention during a time interval wherein treatment could be advantageous (3, 4). Indeed, resectability and survival rates are better among those with early stage lung cancer (5–8). Such observations lend credence to the idea that a reduction in lung cancer mortality is achievable if this disease can be diagnosed and treated before metastatic spread.

The premise that early detection can produce a mortality benefit is not new and, in fact, has served as the impetus for several studies (9–18) over the past four decades to evaluate the efficacy of lung cancer screening by chest radiography and sputum cytology (the only tests of established value for detecting presymptomatic bronchogenic carcinoma). One of the most influential of these studies was the large, randomized, controlled trial sponsored by the National Cancer Institute in the early 1970s. Entitled the National Cancer Institute Cooperative Early Lung Cancer Detection Program, this cooperative trial was conducted at Johns Hopkins medical institutions, the Memorial Sloan-Kettering Cancer Center, and the Mayo Clinic. The approximately 30,000 participants were males ≥ 45 years of age who smoked 1 or more packs of cigarettes per day (or within 1 year of enrollment; Ref. 13). At the Johns Hopkins medical institutions and Memorial Sloan-Kettering Cancer Center, the study sample received annual chest radiographs plus sputum cytological evaluations every four months; the control sample received only yearly chest radiographs. In the Mayo Clinic trial, the study sample received both chest radiographs and sputum cytological tests every four months; the control group was simply advised that these two tests should be obtained annually. Regardless of differences in the experimental designs employed, these three trial centers uniformly failed to show a reduction in mortality as a consequence of periodic chest radiographs and sputum cytological examinations (14–17). This outcome prompted the National Cancer Institute and other health policy and research groups to conclude that large-scale radiological or cytological screening for early lung cancer was not efficacious.

The National Cancer Institute cooperative trial had a debilitating effect on early lung cancer detection research. In the 20 years since that trial was initiated, however, significant advances have occurred in the understanding of lung cancer biology, thereby renewing interest in this topic. Intensive study of the molecular genetics of colon carcinoma have buttressed the multistep theory of carcinogenesis (19) and suggest that invasive cancer of many types, including lung carcinoma (20), is the result of an accumulation of mutations in precursor cells. A corollary to this theory is the concept of “field cancerization.” In lung cancer, field cancerization embodies the contention that the entire respiratory epithelium is susceptible to carcinogens and that repeated exposures may translate into the independent development of precursor lesions with the potential for their progression at variable rates to cancer (21). Precursor lesions may be identified by genetic or...
phenotypical analysis and may be amenable to direct ablation or to regression by pharmacological treatment. However, before the new information regarding lung carcinogenesis can be applied to clinical settings, it is necessary to validate genetic hypotheses and the utility of genetic and other biomarker tests through their assessment in patient cohorts at high risk for lung cancer who have yet to develop overt malignancy. Such an initiative is now underway through the lung cancer SPORE grant that was awarded to University of Colorado Cancer Center (and affiliated institutions) by the National Cancer Institute in 1992.

The Colorado lung cancer SPORE is characterized by a number of prevention and early detection trials whose research aims are to establish intermediate biomarkers in premalignant lesions and assess the possible degree and time course of their reversion after treatment by either smoking cessation interventions or chemoprevention agents. To acquire subjects for these trials, a regional sputum cytology screening program has been established, targeting current and ex-smokers with COPD. Because previous studies have shown such individuals to have a significant risk for lung cancer (22–26), we hypothesized that a high yield of cytological abnormalities would be found in this population, thereby facilitating a large pool of candidates for the Colorado lung cancer prevention and early detection SPORE trials. This paper reviews the results of the screening program during its first 26 months of operation in terms of rates and predictors of abnormal cytology.

PATIENTS AND METHODS

Patient Eligibility Criteria and Recruitment. To initiate the sputum cytology screening program, a protocol was developed outlining the procedures for patient enrollments, sputum specimen processing and interpretation, and data management. This protocol was approved by the institutional review boards associated with all participating hospitals and clinics.

For the screening program, eligibility is limited to persons with the following attributes: (a) spirometry-confirmed diagnoses of COPD as defined by a FEV1 of less than 70% predicted and a ratio of FEV1/FVC of less than or equal to 70%; and (b) cigarette smoking histories of 40 or more pack-years. Excluded from enrollment are individuals with: (a) a diagnosis of cancer (excluding non-melanoma skin cancer) within five years from date considered for entry into the program; (b) a current respiratory infection; (c) insufficient mental capacity (as evaluated by the enrolling physician) to cooperate with the program’s conditions of participation; or (d) recent exposure to chemoprevention agents by serving as subjects in related research.

Individuals were screened for eligibility at 21 sites located in Colorado, Kansas, Wyoming, and Nebraska. Fifteen enrollment sites are offices of pulmonologists in private group practice. The remaining six sites are outpatient pulmonary and family practice clinics at the Denver Veterans Affairs Medical Center, the University of Colorado Health Sciences Center, the National Jewish Center for Immunology and Respiratory Medicine, Presbyterian/St. Luke’s Medical Center, Citizens Medical Center (Colby, Kansas), and Regional West Medical Center (Scottsbluff, Nebraska). To identify program candidates, medical records of patients scheduled for office visits at the various enrollment centers were reviewed daily by authorized on-site personnel and SPORE data managers assigned to provide supplemental staff support. At the time of their office visits, potential subjects were advised as to the nature and objectives of the screening program by their attending physician (or designee). After informed consent was obtained from patients, the coordinating institution of the screening program (the Lung Cancer Institute of Colorado) was immediately notified by telephone. At the time of notification, patient eligibility was reconfirmed by Lung Cancer Institute personnel and a unique SPORE identifier number assigned to that patient for specimen- and data-tracking purposes.

A compulsory component of the enrollment process was the collection of patient-specific information concerning various demographic and clinical status data such as gender, age, race, cigarette smoking habits, non-cigarette tobacco use, pulmonary function status, current respiratory illnesses, and cancer history. Such data were obtained through direct interviews with the participants as well as by referencing these individuals’ medical records.

Methods for Sputum Specimen Collection. The early morning spontaneous cough technique served as the primary method for acquisition of sputum specimens. To increase the probability that material of deep lung origin would be obtained, subjects received detailed verbal and written instructions on how to perform this technique. Included in these instructions was the directive that subjects provide two 3-day pooled sputum specimens across six consecutive days immediately after their enrollment date. Subjects were supplied with two postage-paid mailable containers (filled with fixative solution composed of 2% Carbowax and 50% alcohol) for the purpose of collecting the requested samples.

We selected the early morning spontaneous cough technique as the specimen collection method and determined the need for two (rather than one) pooled specimens due to findings from a pilot study. This study compared the success rate between induction and the early morning spontaneous cough technique in COPD patients with smoking histories of 40 or more pack-years. The results indicated that regardless of the sequence by which subjects performed these techniques (i.e., induction first followed by spontaneous cough technique or vice versa), the second sample obtained was superior in terms of producing an adequate sputum specimen. This finding prompted the decision to use the second 3-day pooled specimen for cytological interpretation; the first sputum sample provided by subjects is retained at the Colorado lung cancer SPORE tissue bank for possible future use in experimental biomarker studies.

Methods for Sputum Specimen Processing and Interpretation. The second 3-day pooled sputum samples were processed at the cytology laboratories of the following Colorado SPORE-affiliated institutions: Presbyterian/St. Luke’s Medical Center, the Denver Veterans Affairs Medical Center, and St. Mary’s Hospital and Medical Center. Specimens were blended at high speed (22,000 rpm) for several seconds. Test tubes with the blended specimen were then centrifuged at 1,500 rpm for 15 min and vortexed to resuspend the cell sample. Cell pellets were subsequently smeared onto four slides and allowed to dry fully before fixation with 95% alcohol. These smears were then stained using the Papanicolaou technique.

The four stained smears prepared from each specimen were examined by the SPORE team of cytotechnologists and cytopathologists. The objectives of these examinations were to evaluate specimen adequacy, inflammation severity, and degree of cellular dysplasia. Specimen adequacy was evaluated as being either optimal for interpretation, less than optimal for interpretation, or unsatisfactory. Inflammation severity was graded as either insignificant, mild, moderate, or severe. The results of cytopathological evaluations are categorized according to the following diagnostic scheme: (a) no significant epithelial abnormalities; (b) regular metaplasia; (c) mild dysplasia; (d) moderate dysplasia; (e) severe (marked) dysplasia; (f) carcinoma in situ; or (g) invasive carcinoma.

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Criteria to Assess Sputum Adequacy. The adequacy of a sputum sample was evaluated by the reviewer visually dividing the sputum smear into four equal quadrants. One quadrant of the slide was then selected that appeared to be representative of the entire smear. A less than optimal or unsatisfactory smear was judged by the number of empty fields observed in the slide quadrant chosen for evaluation using a ×100 microscope. The specific criteria used to assess adequacy are as follows: (a) satisfactory, 100 or more histocytes present in slide review quadrant or the presence of Curschmann’s spiral; (b) less than optimal, from 50–99 histocytes present in slide review quadrant and >5 empty

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3 The abbreviations used are: SPORE, Specialized Program of Research Excellence; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; N:C, nuclear:cytoplasmic; CR, cytological results.

fields in quadrant; and (c) unsatisfactory, less than 50 histocytes present in slide review quadrant and >5 empty fields in quadrant.

Criteria to Assess Inflammation Severity. Inflammation severity was evaluated to determine what, if any, portion of cells was being obscured. Based on the clinical judgment of the reviewing cytopathologist, collection of another sputum specimen may be requested if the degree of inflammation obscured a sufficient number of cells to preclude a definitive diagnosis. The criteria used for grading inflammation severity are as follows: (a) insignificant, less than 5% of cells obscured; (b) mild, 5–25% of cells obscured; (c) moderate, 25–75% of cells obscured; and (d) severe, more than 75% of cells obscured.

Criteria to Assign Cellular Dysplasia Grade. The grades of cellular dysplasia and the criteria used to assign them are as follows: (a) no significant epithelial abnormalities (basophilic, ciliated epithelial cells admixed with macrophages frequently containing pigment and other inflammatory cells; round nuclei of epithelium were basally oriented; evenly dispersed chromatin; inconspicuous nuclear membranes; inconspicuous nucleoli; and no metaplastic or dysplastic cells were present); (b) squamous metaplasia without dysplasia (clumps of basophilic cells without cilia; uniform cells and nuclear size; low N:C ratio; nuclear chromatin was finely granular; and small rounded nucleoli, usually single, may have been present); (c) mild dysplasia (cells varied slightly in size; nuclei varied slightly in size, and the N:C ratio may have varied slightly; nuclei were round to oval, and the halves of the nucleus were mirror images; cytoplasm may have been acidophilic; and the distinct cytoplasmic border had a "cookie cutter sharp" appearance); (d) moderate dysplasia (cells varied moderately in size, and may have been somewhat smaller than those found in mild atypia; nuclei varied in size with variation in the N:C ratio; nuclear lobulations, crevices, and nodules were present; variation from cell to cell in size and shape; cytoplasm was dense, and acidophilia predominated; nuclear material may have shown hyperchromasia with more stippled-like chromatin pattern; increased number of atypical cells; and the nucleus had unequal halves (not mirror images)); (e) severe (marked) dysplasia (cells varied markedly in size and shape; nuclear pleomorphism, and coarse chromatin was hyperchromatic; the N:C ratio varied, with extremes; hyperchromasia may have been present with chromatin condensation along the nuclear envelope; acidophilic cytoplasm predominated; single cells predominated; and the nucleus may have followed the shape of the cytoplasm); (f) carcinoma in situ (clumps or single cells were present; cells varied markedly in size and shape; the N:C ratio may have been higher or lower than normal; chromatin was coarsely clumped, especially along the nuclear membrane, with large chromocenters; mitoses may have been present; multinucleated cells and individual cell degeneration may have been present; and cytoplasm was predominantly acidophilic, but atypical basophilic cells may also have been present); and (g) invasive carcinoma (cells were larger and may have been very pleomorphic; often single cells but clusters may have been found; chromatin was coarsely clumped, especially along the nuclear membrane; nucleoli were large and acidophilic; cannibalism and multinucleation were common; cytoplasm was acidophilic or basophilic; and necrotic debris was common).

The smear examination protocol entailed independent reviews of each set of four smears by an assigned cytotechnologist and cytopathologist. Results of these reviews were recorded and subsequently compared for agreement. When interpretation discrepancies occurred, the cytotechnologist and cytopathologist met to achieve a consensus opinion on specimen adequacy, level of inflammation, and diagnosis. A quality assurance system has also been established to maintain the integrity of the screening program's sputum cytology component. This system operates through the random selection of, at minimum, 10% of the initially evaluated smear sets for the purpose of a second blinded examination by a SPORE cytopathologist panel member. Interpretation differences between the quality control and initial cytological evaluations are discussed at periodic meetings held by panel members. These meetings are held strictly for educational purposes to enhance uniformity of cytology smear readings across reviewers; the initial cytological results were not changed when disagreements were observed with correlated quality control readings.

Statistical Methods. Because this report presents initial data from what is expected to be an ongoing program, the methods employed were predominately descriptive relative to the demographic, clinical status, and cytopathological information collected on subjects. Means, variances, ranges, and proportions contained in various categorizations were measured as appropriate. In addition, selected exploratory multivariate logistic regression modeling was performed.

Analyses were also conducted on the level of agreement between results of the initial and second blinded cytological evaluations made of those sputum smears selected for quality control evaluations. Agreement was measured descriptively by concordance (percentage of agreement) and discordance (percentage of disagreement). Statistical analysis was performed applying χ² statistics, which are agreement-corrected for chance. Values of χ² greater than 0.75 represent excellent agreement beyond chance; values between 0.40 and 0.75 represent fair to good agreement beyond chance (31). Statistical significance was assumed for P < .05 (two-tailed test). These agreement measurements were calculated for all the cytopathologists as a whole and for each of the three cytology laboratory sites participating in the Colorado SPORE program.

RESULTS

During the first 26 months of the screening program (February 1993–April 1995), samples from 632 participants were examined. A total of 533 (84%) subjects provided specimens viable for cytopathological interpretation. Viable samples were defined as those graded as being "adequate" or "less than optimal" for cytodiagnosis. Of the 533 subjects with diagnostically viable samples, 403 (76%) had adequate and 130 (24%) had less than optimal specimens. A total of 99 (16%) of the 632 participants provided sputum samples inadequate for cytodiagnosis. In Table 1, selected demographic and clinical characteristics are presented for the 533 participants who had sputum samples that yielded a cytodiagnosis (defined as the CR subgroup).

As reflected in Table 1, a majority (72%) of the CR subgroup were males. The mean age of these subjects was 67 years. Approximately 80% of the CR subgroup was between 60–80 years of age; 4% were 80 years of age or older. The predominance of older subjects was attributed to the entrance criterion mandating that participants have smoking histories of 40 or more pack-years.

Racial distribution was heavily skewed to white subjects of non-Hispanic origin (95%). The proportions of blacks and Hispanics were equal. Less than 1% of the CR subgroup was Asian.

Data collected on smoking history included smoking status, daily

Table 1 - Demographic and smoking history characteristics of patients with adequate sputum samples collected by the Colorado SPORE sputum screening program

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<th>Age</th>
<th>Type</th>
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<td>33–49</td>
<td>21 (4)</td>
<td>White</td>
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<td>50–59</td>
<td>66 (12)</td>
<td>Black</td>
<td>50–99</td>
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<td>60–69</td>
<td>233 (44)</td>
<td>Hispanic</td>
<td>70–99</td>
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<td>70–79</td>
<td>190 (36)</td>
<td>Asian or Pacific Islander</td>
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<td>80–90</td>
<td>23 (4)</td>
<td>American Indian</td>
<td>Other</td>
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* The number of current smokers was 164 (31%), and the number of ex-smokers was 369 (69%).
* Mean age, 67; range, 33–90; SD = 8.44.
* Mean pack years, 70.6; range, 40–207; SD = 30.4.
cigarette consumption, and the number of years in which these individuals engaged in this habit. With these data, the number of pack-years of smoking was estimated per participant. In the CR subgroup, the mean number of pack-years was approximately 7.1, with a range of 7—70; SD, 14.0). The mean ratio of the FEV1:FVC measurements was 4(6, range, 21—70, SD, 11.4). These data reflect a significantly obstructed study sample, as expected.

Presented in Table 3 is the breakdown of cytopathological results of the CR subgroup overall and by smoking status (ex-smoker or current smoker). A majority (76%) of all subjects represented in the sample were diagnosed with mild or greater dysplasia. The most prevalent cytdiagnosis was mild dysplasia (48%); moderate dysplasia was the second-most frequent cytdiagnostic interpretation, with 25% of the subjects presenting with this diagnosis. Approximately 3% of the CR subgroup had cytdiagnoses of severe (marked) dysplasia, carcinoma in situ, or invasive carcinoma. (All patients with lung carcinoma had cytdiagnoses of squamous cell carcinoma.) Comparisons between ex-smokers and current smokers showed that participants with mild to moderate dysplasia were more likely to be ex-smokers than those with less severe cytology (P = 0.03, one-tailed t test).

Table 4 provides data on the mean number of years since ex-smokers quit smoking by cytdiagnosis. Across diagnostic categories 0–3 (no significant abnormalities, regular metaplasia, mild dysplasia, and moderate dysplasia), the mean number of smoking cessation years was very similar, ranging between 7.89—8.42. Cytdiagnostic categories 4–6 (severe dysplasia, carcinoma in situ, and invasive carcinoma) showed a downward trend in mean years of smoking cessation (mean range, 2.50—6.50). Although the number of observations (8) were small, these 3 remaining cytological grades reflected early and frank cancer stages and as such, a comparison of means between the diagnostic categories was considered warranted. This analysis was conducted by first combining categories 4–6 into one group and then performing variance analysis. ANOVA for unbalanced data showed no statistically significant difference in mean years of smoking cessation among the groups (P = .72; Ref. 32).

Cytdiagnoses of the CR subgroup were evaluated for integrity by assessing concordance, discordance, and percentage agreement correct for chance (measured by K statistics) in 86 patient cases that underwent an initial blinded quality control evaluation. Table 5 presents the results of these analyses for all participating pathologists as a whole and for each cytdiagnostic laboratory site (Presbyterian/St. Luke’s Medical Center, site 1; St. Mary’s Hospital and Medical Center, site 2; and the Denver Veterans Affairs Medical Center, site 3). Overall agreement was 84.9%; disagreement was 15.1%. Agreement by site ranged between 78.6% (site 1) and 100% (site 2). Agreement by K statistics was considered excellent (31) and statistically significant overall and for sites 2 and 3 (κ > 0.75 and P < 0.001 for each). Agreement was good and statistically significant for site 1 (κ = .71; P = <.001).

Additional analyses were conducted to individually examine the association between age, pulmonary function status, and pack-years of smoking history, respectively, with the degree of dysplasia found in study subjects. Table 6 presents these results.

The mean values and SE calculated for age, predicted FEV1 percentage, and FEV1:FVC ratio revealed no statistically significant gradient or pattern across cytdiagnostic categories. However, an apparent downward trend was observed over the first four diagnostic grades (no significant abnormalities, regular metaplasia, mild dysplasia, and moderate dysplasia) for mean pack-years smoked. The slope of a line fitted over that range was found to be significantly different from zero (P = 0.02; two-tailed t test). Cytdiagnostic categories 4–6 (severe dysplasia, carcinoma in situ, and invasive carcinoma) were omitted because they contained only 13 observations.

Although most of the variables that could potentially influence
cytodiagnostic outcome showed no apparent association individually, the possibility existed that, when taken collectively, patterns of association could emerge. Consequently, exploratory multivariate analyses of this data set were attempted.

Collapsing cytodiagnostic categories 0 and 1 (no significant abnormalities and regular metaplasia) and 2 and 3 (mild dysplasia and moderate dysplasia), a step-down logistic regression model was fit with the following as potential independent variables: age, sex, years smoked, pack year history, current smoking status, presence of symptoms of chronic respiratory disease linked with the effects of long-term smoking, and percent of pack-years of smoking history decreases by severity of cytological atypia. This result suggests our study population represents a subclass of current and ex-smokers with moderate to severe atypia who were more likely to have quit smoking than those with normal sputum cytology results. Definitive explanations for these anticipated findings are not feasible at this time due to the relatively small study sample size and limitations in the types of data that were collected. A potentially important data omission was information on symptomology. Many individuals either quit smoking or reduced their cigarette consumption rate after the onset of chronic respiratory symptoms linked with the effects of long-term smoking on the bronchial airways (cough, wheezing, dyspnea, and sputum production). Accordingly, there may have been a higher prevalence of such symptoms in those study participants who were ex-smokers or who had fewer pack-years of smoking history. Such symptoms, in turn, could have been influencing variables on cytological outcome. Future studies may be warranted on this issue.

DISCUSSION

Initial results of the Colorado SPORE sputum cytology screening program did reveal high rates of cytological abnormalities in our study sample of patients with COPD and smoking histories of 40 or more pack-years. A finding of particular interest was the proportion of participants who presented with moderate to severe dysplasia (26%). Because former studies have reported that individuals with these cytodiagnoses are at high risk for the development of lung cancer (33-36), this result suggests our study population represents a subclass of current and ex-smokers who could ultimately benefit from routine cytomorphologically based screening for this disease. Certainly, the National Cancer Institute Cooperative Early Lung Cancer Detection Program (discussed earlier) demonstrated that persons diagnosed with lung cancer by sputum cytology alone had an extremely favorable outcome in terms of survival (17). Similar findings have also been reported in more recent studies to assess survival rates in patients with radiologically occult lung cancer who were diagnosed by sputum cytology (37, 38). Our efforts to longitudinally follow participants of the Colorado SPORE screening program by means of annual sputum examinations should elucidate more definitive answers on this subject.

Both univariate and multivariate analysis suggest that the total number of pack-years of smoking history decreases by severity of cytological diagnosis and those individuals with mild to moderate atypia were more likely to have quit smoking than those with normal sputum cytology results. Definitive explanations for these anticipated findings are not feasible at this time due to the relatively small study sample size and limitations in the types of data that were collected. A potentially important data omission was information on symptomology. Many individuals either quit smoking or reduced their cigarette consumption rate after the onset of chronic respiratory symptoms linked with the effects of long-term smoking on the bronchial airways (cough, wheezing, dyspnea, and sputum production). Accordingly, there may have been a higher prevalence of such symptoms in those study participants who were ex-smokers or who had fewer pack-years of smoking history. Such symptoms, in turn, could have been influencing variables on cytological outcome.

Future studies may be warranted on this issue.

As stated above, participants of the screening program are being offered annual sputum cytological examinations as well as being monitored for changes in clinical status. Moreover, screening program participants with cytodiagnoses of moderate to severe (marked) dysplasia and carcinoma in situ are being entered (after consent) into the Colorado SPORE’s various lung cancer prevention and early detection trials, most of which require serial collections of urine, serum, sputum, bronchial biopsy material and brushings, and tumor tissue (when relevant). Collectively, the data that will emerge from these interrelated initiatives should provide new information on the sequence and prognostic significance of cytological and histological changes as well as biomarker expression patterns that occur in pre- and early lung neoplasia. Due to the high yield of abnormal cytology found in our study sample of current and ex-smokers with COPD and smoking histories of 40 or more pack-years, we recommend that such individuals be considered as excellent candidates for research investigations focusing on lung cancer prevention and early detection.
REFERENCES


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