Lung Cancer and Chronic Obstructive Pulmonary Disease: Needs and Opportunities for Integrated Research
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Lung cancer and chronic obstructive pulmonary disease (COPD) are leading causes of morbidity and mortality in the United States and worldwide. They share a common environmental risk factor in cigarette smoke exposure and a genetic predisposition represented by the incidence of these diseases in only a fraction of smokers. The presence of COPD increases the risk of lung cancer up to 4.5-fold. To investigate commonalities in disease mechanisms and perspectives for disease chemoprevention, the National Heart, Lung, and Blood Institute (NHLBI) and the National Cancer Institute (NCI) held a workshop. The participants identified four research objectives: 1) clarify common epidemiological characteristics of lung cancer and COPD; 2) identify shared genetic and epigenetic risk factors; 3) identify and validate biomarkers, molecular signatures, and imaging-derived measurements of each disease; and 4) determine common and disparate pathogenetic mechanisms. These objectives should be reached via four research approaches: 1) identify, publicize, and enable the evaluation and analysis of existing datasets and repositories of biospecimens; 2) obtain phenotypic and outcome data and biospecimens from large studies of subjects with and/or at risk for COPD and lung cancer; 3) develop and use animal and other preclinical models to investigate pathogenetic links between the diseases; and 4) conduct early-phase clinical trials of potential chemopreventive agents. To foster much needed research interactions, two final recommendations were made by the participants: 1) incorporate baseline phenotyping and outcome measures for both diseases in future longitudinal studies of each disease and 2) expand collaborative efforts between the NCI and NHLBI.


Lung Cancer and Chronic Obstructive Pulmonary Disease: Environmental and Epidemiological Commonalities
Since the release of the 1964 Surgeon General’s Report on Smoking and Health, there has been a general decline of smoking rates in the US population, and fewer Americans are smoking today (1). Consequently, there has been a modest reduction in both lung cancer and chronic obstructive pulmonary disease (COPD) deaths as reflected in the decrease of the adjusted mortality rates per 100,000 from 156.1 to 149.9 for lung cancer and from 123.9 to 112.8 for COPD during the period 1999–2004 (2). Although these data are encouraging, their value is diminished by five major factors: 1) in 2004, 23% of males and 18% of females older than 25 years were still current smokers; 2) although smoking cessation reduces lung cancer and COPD incidence, the risks for these diseases in ex-smokers remain elevated for many years after quitting when compared with never smokers; 3) lung cancer incidence is declining in men but not in women, and COPD deaths have been steadily higher in women than in men since the late 1990s; 4) success in prevention of cardiovascular disease or acute infections is increasing the prevalence of lung cancer and COPD; and 5) in contrast to other common diseases, such as cardiovascular disease or infections, available treatments for COPD and lung cancer have limited benefits to those with advanced disease. The survival of lung cancer patients has changed little in the past 30 years (1,3–7).

The unrelenting incidence of lung cancer and COPD represents a major medical challenge that deserves concerted attention from both the pulmonary and the cancer research communities because several lines of evidence indicate a connection between COPD and lung cancer. The role of environmental smoke exposure in the development of chronic lung disease and lung cancer was underscored by the 2004 Surgeon General’s Report on the Health Consequences of Smoking (8). Similar to COPD, lung cancer is more likely to occur in the poor and in the less educated (9). Low lung function is an established risk factor for lung cancer, and among smokers, those with airflow obstruction have the greatest risk of developing lung cancer. Several studies (3,10–12) have shown that having moderate-to-severe COPD increases the risk of developing lung cancer up to 4.5-fold. Interestingly, recent data (13) also demonstrate that the presence of emphysema is associated with poor prognosis in those with lung cancer. Complementary to this is the observation that the incidence of lung cancer is associated with specific stages of COPD severity. Lung cancer is assigned

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as the cause of death in 33% of patients with mild-to-moderate COPD and in 14% of patients with more severe disease (14,15).

The majority of smokers with COPD have airway epithelial dysplasia, although this condition is not associated with the severity of airflow obstruction and may reflect the cumulative exposure to tobacco smoke (16). The prevalence of preinvasive lung cancer lesions is associated with COPD in 56% of men and 44% of women (5). These trends in incidence in females may be due in part to the fact that women tend to smoke fewer cigarettes than men, but also may reflect complex genetic interactions, including those related to sex, involved in the development of both diseases (5,17,18). Increased lung cancer risk is associated with emphysema even in lifelong nonsmokers, perhaps due to passive cigarette smoke or occupational exposures, underscoring the likely importance of genetic and epigenetic interactions (19).

Commonalities in Genetics and Epigenetics

Inhalation of the more than 6000 compounds present in cigarette smoke (20) is a common factor in both diseases, but only a fraction of smokers (10%–15%) develop COPD and/or lung cancer (21–23). The observation of familial aggregation of emphysema dates back more than 200 years, and studies conducted 30 years ago reveal a familial aggregation of lung cancer associated with COPD that is not explained by α1-antitrypsin genotype or smoking history (24,25). Familial aggregation is well documented for multiple cancers, although it has been difficult to separate the contributions of genetic differences and environmental exposures in the development of lung cancer. Nevertheless, recent work (26,27) has confirmed a high incidence of familial lung cancer, showing that individuals with a family history of lung cancer are at approximately two- to threefold higher risk of developing this disease than the general population even after adjusting for cigarette smoking. A number of linkage studies (28) have investigated genes involved in both lung function and COPD and candidate susceptibility genes involved in COPD and lung cancer. These studies have led to the identification of markers on chromosome 6q for lung cancer and abnormal lung function and on chromosome 12 for lung cancer, COPD, and lung function, as well as numerous other candidate susceptibility genes involved in detoxification, immune regulation, matrix remodeling, DNA repair, cellular proliferation, and tumor suppression (28). Among the genetic connections between COPD and lung cancer, it is particularly interesting to note that both the Z and the S alleles of the α1-antitrypsin gene are more common in patients with lung cancer compared with the general population, as is a polymorphism in the neutrophil elastase gene (29,30), suggesting that an imbalance between neutrophil elastase and α1-antitrypsin may contribute to the development of both COPD and lung cancer (31). These data stress the importance of expanding studies of familial risk of lung disease, performing more linkage and association studies, and standardized collection of family history in lung cancer and COPD patients. As an example of the potential impact of this kind of investigation, a recent analysis of gene expression profiling of nontumor–involved lung tissue from COPD patients who underwent lung tissue resection for lung cancer showed selective regulation of specific signaling pathways and highlighted new potential therapeutic targets (32).

The role of epigenetic modifications in the common pathogenesis of COPD and lung cancer also deserves attention. Although there is growing evidence implicating DNA methylation, histone deacetylation, and protein phosphorylation in lung cancer pathogenesis (33–35), this knowledge is only now being applied to COPD, alone or when associated with lung cancer (36,37). It is plausible that several candidate risk genes and pathways identified by lung cancer studies may be shared by these two diseases and could constitute potential targets for the newly developed drugs (eg, demethylating agents and histone deacetylase–inhibiting agents) that modify epigenetic alterations.

Pathological Considerations

Diagnosis of COPD is generally confirmed by physiological testing (spirometry) that assesses the presence of an airflow limitation that is not fully reversible with the use of a bronchodilator. The airflow limitation in COPD is often associated with a variable mixture of emphysema (destruction and enlargement of mature airspaces distal to terminal bronchioles) and small airway disease (obstructive bronchiolitis), as detected by radiographic and/or histological methods (38). Loss of elastic recoil and airway inflammation are also characteristic features of the disease, but it is the small airway thickening in all three of its components (epithelium, lamina propria, and adventitia) that is most strongly associated with airflow obstruction (39–41).

Lung cancer, by contrast, occurs in several different histological types, possibly reflecting the highly complex structure of the organ from which it originates. These types can be broadly divided into small cell lung carcinoma (SCLC), which occurs in approximately 20% of lung cancer patients, and non–small cell lung carcinoma (NSCLC), which includes squamous cell carcinoma, adenocarcinoma, and large cell carcinoma, and occurs in the remaining 80%. Although squamous cell carcinomas and SCLC are often centrally located (in the airways), adenocarcinomas and large cell carcinomas are typically of peripheral origin. The incidence of adenocarcinomas now surpasses that of squamous cell carcinomas in both sexes, possibly due to changes in cigarette smoke composition and/or inhalation (42). This rather simplified classification into two basic types becomes much more complex when molecular biology studies are applied to further distinguish the lesions by their phenotype (43,44). Knowledge of the early molecular events that lead to squamous cell carcinomas is growing (45), but little is known about the early molecular events that lead to the development of other types of lung carcinoma.

As a practical consequence of the epidemiological associations between COPD and lung cancer, an important question is whether the relationship between lung cancer and COPD is subtype specific. A small case–control study (46) showed that airflow obstruction is primarily a risk factor for squamous cell lung cancer (odds ratio = 3.49, 95% CI = 1.63 to 18.5; P = .006), whereas symptoms of chronic bronchitis without COPD is a risk factor (risk greater than fourfold) for adenocarcinoma of the lung. A subset analysis, having concurrent bronchitic symptoms and COPD was associated with a more than threefold increased risk for squamous cell carcinoma. Another study (47) showed that increased risk of lung cancer was more strongly associated with the presence of...
computed tomography–diagnosed emphysema than with spirometric–diagnosed airway obstruction, a finding that was confirmed in a US cohort (48). Cytological atypia is associated with substantial risk of lung cancer, but there is no association between the severity of atypia and the degree of airflow obstruction (49) despite the high incidence of sputum dysplasia in subjects with airflow obstruction (50).

**Mechanisms of Disease: Field Effect, the Epithelial–Mesenchymal Transition, and Inflammation**

Our understanding of the pathogenetic mechanisms that lead to lung cancer has been greatly enhanced by the discovery of the presence, in high frequency, of multiple foci of histological and/or molecular alterations in topologically disparate tissues within the aerodigestive epithelium, a phenomenon that gave rise to the field effect concept (51,52). A molecular analysis of preneoplastic lesions in the central or peripheral airways has contributed to the delineation of different carcinogenetic pathways (45). For example, a generalized hyperactivation of the translational machinery appears to be required for maintenance of the malignant phenotype in lung cancer and triggers the epithelial-to-mesenchymal transition (EMT), a process in which cells undergo a switch from an epithelial phenotype to a mesenchymal phenotype (53–55). EMT is important not only in lung cancer but also in COPD development and progression. Recent studies (56,57) underscore how activation of transforming growth factor β pathways, receptor tyrosine kinase/Ras signaling, autocrine factors, prostaglandins, Wnt-, Notch-, Hedgehog-, and nuclear factor kB–dependent pathways, and repression of E-cadherin by transcriptional regulators, such as Snail or Twist, all contribute to EMT in both diseases. Recent studies indicating that inflammation directly promotes EMT by inducing the expression of E-cadherin transcriptional repressors belonging to the zinc-finger family (58,59) provide evidence of additional connections between these diseases.

These findings can explain how abnormal inflammation is related to both COPD and lung cancer (60,61). Recent histopathological and clinical analyses show that COPD is associated with abnormal inflammatory features both in the lungs and systemically (40,62). Similarly, the connection between inflammation and cancer development is an old concept that has its roots in the comparison of the tumor with a wound that does not repair. Virchow’s hypothesis that cancer occurs at sites of chronic inflammation is now well established (63–65). A mechanistic understanding of these associations is now emerging as studies have shown that manipulation of prostaglandin production can affect both lung carcinogenesis and growth factor–driven pathways. These findings have led to several experimental trials of chemoprevention (66–68). Conversely, inflammatory elastolytic activity, which is essential in driving emphysema progression, is also capable of suppressing the growth of lung metastases (69,70). These findings highlight the balance between proteinases and inflammatory cells in mediating lung destruction, cancer development, and tumor progression. The close connection between COPD, inflammation, and lung cancer is even more apparent in light of recent findings that point to a possible relationship between inhaled corticosteroids and reduced lung cancer risk in COPD patients (71,72).

**Lung Cancer and COPD: Two Sides of the Same Coin?**

Recognition of the common epidemiological evidence and mechanistic pathways of COPD and lung cancer is not sufficient; we also need to understand why one of these diseases often becomes clinically prominent over the other in any given individual and to predict which individuals are at greatest risk for each disease. In this regard, some or the differences between these diseases may be informative. Cancer is an antiapoptotic process, and cancer cells are prone to invade tissues and are characterized by unlimited cell proliferation and sustained angiogenesis, whereas COPD is characterized by increased apoptosis, extracellular matrix degradation, ineffective tissue repair, and limited angiogenesis.

Gene expression analysis studies may shed some light on these differences. Studies show that the transcriptome of the normal bronchial epithelium is distinct from that of the lung parenchyma, that the SCLC transcriptome profile differs from that of NSCLC, and that there is in each individual an association between cumulative tobacco exposure and gene transcription (73,74). Not all genes are reversible to their pre-smoke exposure transcriptional status upon cessation of smoke exposure. Those reversible tend to be genes encoding detoxification/oxydoreductase enzymes, whereas those not reversible appear to be immune-modifying cancer-related genes (75). The gene expression profile of the individual’s lung cells may reveal which disease pathway predominates and why disease risk persists in ex-smokers (32,76).

An intriguing possibility is that risk of developing lung cancer, COPD, or both may ultimately be based on the susceptibility to somatic cell mutations. In addition to their role in lung cancer development, somatic mutations have been recently hypothesized to be fundamental contributors to the molecular pathogenesis of COPD, but this proposed role needs further exploration (77). Somatic mutations may affect both lung cancer and COPD and explain the initial convergence of the multiple pathways that are implicated in the pathogenesis of both diseases and the ultimate phenotypic divergence of the two diseases (45,77–79).

**Recommendations for Future Research**

To systematically address the many issues raised during the meeting, the participants of the working group identified four primary research objectives that should be actively pursued in the next 5 years. These objectives can be achieved by means of four research approaches. Finally, to facilitate this research, the lung cancer and COPD communities should engage in scientific and organizational interactions. This recommended strategy for advancing research at the interface of lung cancer and COPD is discussed in detail below.

**Research Objectives**

The working group members identified a need for collecting more and better epidemiological data regarding individuals with COPD and/or lung cancer. Clinical characteristics and molecular
phenotypes should be determined. Common genetic and epigenetic risk factors and their interactions need to be identified and clarified. Intermediate outcomes should be identified to facilitate studies of disease progression and response to therapies. The search for mechanisms involved in the pathogenesis of COPD and lung cancer should be broad and encompass multiple pathways. The following specific objectives are recommended:

1. Clarify the common epidemiological characteristics of lung cancer and COPD—including clinical characteristics and molecular phenotypes with attention to early molecular events; timing; subsequent course of each discrete subphenotypes of each disease; and relationships between disease risk and ethnicity, race, sex, and well-established and emerging environmental risk factors.
3. Identify and validate biomarkers; molecular signatures; and imaging-based measurements of risk, detection, severity, and progression of COPD and lung cancer and of responses to therapy.
4. Determine common and disparate mechanisms involved in the pathogenesis of COPD and lung cancer. Consider the roles of innate and adaptive immunity, redox balance, proteinases, DNA repair, stem cell proliferation, epigenetics, somatic mutations, microenvironment, and EMT in these diseases.

Research Approaches

There is a great need for comparing and sharing data coming from existing and future studies of COPD and lung cancer. Cohort studies of each disease should be designed to collect data relevant to both diseases. The development of animal models to address the two diseases was determined to be a high priority because these models are currently lacking. Both animal models and early-phase clinical trials could offer insights on common mechanisms of disease. COPD patients represent an ideal target population for chemoprevention studies because they have a mechanisms of disease. COPD patients represent an ideal target population for chemoprevention studies because they have a high risk of developing lung cancer. Such trials should test available agents that target inflammation, oxidative stress, or both, and the many new products that modify epigenetic alterations. Any drugs used must have an acceptable risk–benefit profile.

The efficacy and validity of known or new intermediate outcomes (ie, cytological changes in sputum, alterations in DNA methylation, apoptotic or proliferative effects) common to both lung cancer and COPD should be assessed because the definitive endpoint of lung cancer development requires clinical trials that are lengthy and costly. Recommended research approaches are the following:

1. Identify, publicize, and enable the evaluation and analyses of existing datasets and repositories of biospecimens. Consider expanding ongoing studies to provide data that would address mechanisms of both diseases.
2. Obtain phenotypic and outcome data and biospecimens from large, well-designed studies of subjects with and/or at risk for COPD and lung cancer.
3. Develop and use animal and other preclinical models to investigate pathogenetic links between COPD and lung cancer.
4. Conduct early-phase clinical trials of potential chemopreventive agents that are expected to modify pathways involved in both disease processes, with a comprehensive characterization of biological effects.

Research Interactions

Working group participants from both the COPD and the lung cancer communities saw an opportunity and a necessity to expand the collaborative efforts between National Cancer Institute (NCI) and National Heart, Lung, and Blood Institute (NHLBI) to effectively address the interface of chronic pulmonary disease and lung cancer. In addition to expanding data collection in clinical trials to include measurements that are important for both diseases, it was suggested with great enthusiasm that additional meetings should be held and mechanisms for fostering cooperation between the two research communities should be implemented via collaborative efforts between the two institutes.

1. In future longitudinal studies of lung cancer or COPD, incorporate baseline phenotyping and outcome measures for both diseases.
2. Expand collaborative efforts between NCI and NHLBI to address the interface of pulmonary disease and lung cancer. Consider additional meetings and mechanisms for fostering cooperation between the research communities.

References


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78. Kessler TW, Wakabayashi N, Biswal S. Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. Annu Rev Pharmacol Toxicol. 2007;47:89–116.


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