Is Previous Respiratory Disease a Risk Factor for Lung Cancer?

Background/Rationale

Cigarette smoking increases the risk for both lung cancer and other respiratory diseases. While a history of respiratory disease has been reported to increase the risk of lung cancer, inflammatory respiratory diseases frequently co-occur, making assessment of their influence on lung cancer risk challenging to assess.

Objective

Determine the relationship between multiple respiratory diseases and lung cancer.

Methods

Design: Meta-analysis of multiple case-control studies as part of the SYNERGY consortium(2).

Setting: Thirteen international sites

Participants: The study population included data collected from a total of 12,739 case subjects with lung cancer and 14,945 control subjects without lung cancer enrolled from between 1988-2006 as part of hospital and population-based case-control studies.

Data Sources/Measurements: Data were collected through face-to-face and telephone interviews. Data included: age, sex, smoking history, occupation, level of education, and previous respiratory disease were collected. Previous respiratory disease (PRD) was self-reported and included chronic bronchitis, emphysema, asthma, pneumonia, tuberculosis.

Outcomes: Lung cancer risk associated with PRDs; Influence of cigarette smoking status (never, current, former) on lung cancer risk associated with PRDs; Association of PRDs and lung cancer subtype; Association between latency of PRD diagnosis and lung cancer risk;

Main Results

The authors examined the relationship between several respiratory diseases and lung cancer. They identified frequent co-occurrence of the PRDs assessed. Chronic bronchitis and emphysema were associated with a higher risk of lung cancer, regardless of the latency period between PRD and lung cancer diagnosis. Pneumonia was associated with a higher risk for lung cancer, a relationship which was stronger when pneumonia was diagnosed less than 2 years prior to lung cancer. Co-occurrence of chronic bronchitis and/or emphysema and pneumonia increased the positive association with lung cancer risk beyond that of chronic bronchitis or emphysema alone. Asthma was inversely associated with risk for lung cancer, which was stronger when asthma was diagnosed more than 5 years prior to lung cancer.

Conclusion

The authors identified frequent co-occurrence of common respiratory diseases including chronic bronchitis, emphysema, asthma, pneumonia, and tuberculosis. Positive associations between

lung cancer and chronic bronchitis, emphysema, and pneumonia were observed. A negative association between lung cancer and asthma was observed. One strength of the study is the analysis of a large study population drawn from multiple international case-control studies. Limitations of the study include the use of self-report for diagnosis of previous respiratory disease, and a low proportion of never smokers which limits generalization to this population.

Commentary

Chronic obstructive pulmonary disease (COPD) has long been recognized as an independent risk factor for lung cancer. An early description of the relationship between these two diseases showed that COPD was not only a risk factor for lung cancer, but also more strongly contributed to this risk than age or cumulative smoke exposure. The 1994 Lung Health Study showed that lung cancer was the most common cause of death after 5-years of follow up in participants with mild to moderate airflow obstruction(3). The severity of airflow obstruction and the severity of emphysema have also been described to independently increase the risk of lung cancer(4, 5). As suggested by prior studies(6, 7), the authors report a positive association between chronic bronchitis and emphysema, and lung cancer risk. There are several hypotheses about the mechanisms by which COPD increases the risk of lung cancer. First, chronic inflammation has been proposed to play a role in both diseases. COPD is a disease of heightened inflammation within the lung as compared to individuals without airflow obstruction, and there may also be a component of systemic inflammation(8). This chronic inflammation may lead to increased oxidative stress and ultimately DNA damage predisposing to lung carcinogenesis(8–10). Oxidative stress associated with chronic inflammation and cigarette smoking may further increase the inflammatory response contributing to worsened COPD and risk for lung cancer(8, 11, 12). Impaired clearance of carcinogens and toxins in cigarette smoke in individuals with COPD may also pre-dispose to lung carcinogenesis(8, 13). Environmental factors such as cigarette smoking may also interact with genetic variants to influence the development of these diseases(8). Genetic variants that influence the metabolisms of nicotine and other components of cigarette smoke may also play a role.

In this study, the authors also report that pneumonia also increases the risk of lung cancer, though the time between pneumonia and lung cancer diagnosis may influence this relationship. While this relationship may be related to inflammation, it is also possible that this relationship is due to more intensive clinical evaluation of patients with pneumonia, resulting in lung cancer diagnosis; or lung cancer-associated processes including intrinsic or extrinsic airway compression which may increase the risk of pneumonia.

The inverse relationship between asthma diagnosis and the risk for lung cancer is intriguing. There are several potential explanations for this relationship. First, while the analysis accounted for smoking status and pack-years, the presence of asthma may lead patients to avoid other exposures potentially associated with lung cancer risk, such as second hand smoke exposure and occupational exposures. Another possibility is that the inflammatory pathways and cytokines associated with asthma may be less carcinogenic. Alternatively, the chronicity of inflammation associated with asthma may be lower than that associated with COPD. Finally, it is possible that treatments for asthma, such as inhaled corticosteroids, may influence inflammatory pathways and other cancer signaling pathways that may be associated with the development of lung cancer(14).

The associations between respiratory diseases and lung cancer risk could potentially be used to help develop improved risk-prediction models for lung cancer. Existing clinical risk models, such as the Bach(15), Spitz(16), and Liverpool Lung Project(17) models, which incorporate age,

smoking history, and exposure to asbestos. However, these models were shown to have low negative predictive value in an independent dataset(18). The addition of variables related to specific respiratory diseases such as COPD, emphysema, asbestos, and pneumonia to clinical risk models may improve our ability to identify individuals with early and potentially curable stages of lung cancer. Furthermore, accounting for the association of these respiratory diseases with lung cancer risk may help further inform the selection of patients for lung cancer screening with low-dose helical computerized tomography. For example, the updated Prostate Lung Colon and Ovarian Cancer study model for lung cancer ($PLCO_{m2012}$), which includes additional variables such as body mass index and COPD, demonstrated improved sensitivity for lung cancer as compared to the inclusion criteria for the National Lung Cancer Screening Trial. These approaches may ultimately prove useful for decreasing the high-false positive rate of LDCT by improving patient selection, and improving cost-effectiveness of lung cancer screening by my accurately risk-stratifying individuals prior to screening.

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