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Research Article

Associated Links Among Smoking, Chronic Obstructive Pulmonary Disease, and Small Cell Lung Cancer: A Pooled Analysis in the International Lung Cancer Consortium

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Abbreviations: COPD, chronic obstructive pulmonary disease; CPG, cigarettes per day; ILCCO, International Lung Cancer Consortium; MeSH, medical subject headings; NSCLC, non-small cell lung cancer; OR, odds ratio; SCLC, small cell lung cancer.

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ABSTRACT

Background: The high relapse and mortality rate of small-cell lung cancer (SCLC) fuels the need for epidemiologic study to aid in its prevention.
Methods: We included 24 studies from the ILCCO collaboration. Random-effects panel logistic regression and cubic spline regression were used to estimate the effects of smoking behaviors on SCLC risk and explore their non-linearity. Further, we explored whether the risk of smoking on SCLC was mediated through COPD.
Findings: Significant dose–response relationships of SCLC risk were observed for all quantitative smoking variables. Smoking pack-years were associated with a sharper increase of SCLC risk for pack-years ranged 0 to approximately 50. The former smokers with longer cessation showed a $43\%_{quit\_for\_5–9\ years}$ to $89\%_{quit\_for\_\geq 20\ years}$ declined SCLC risk vs. subjects who had quit smoking <5 years. Compared with non-COPD subjects, smoking behaviors showed a significantly higher effect on SCLC risk among COPD subjects, and further, COPD patients showed a 1.86-fold higher risk of SCLC. Furthermore, smoking behaviors on SCLC risk were significantly mediated through COPD which accounted for 0.70% to 7.55% of total effects.
Interpretation: This is the largest pooling study that provides improved understanding of smoking on SCLC, and further demonstrates a causal pathway through COPD that warrants further experimental study.

1. Introduction

Small cell lung cancer (SCLC) comprises approximately 15–18% of all lung cancers worldwide (Fruh et al., 2013). SCLC is the most aggressive subtype of lung cancer and is characterized by rapid doubling time, high growth fraction, and early widespread metastasis (Kalemkerian et al., 2013). Despite high response rates to initial treatment, SCLC usually relapses and becomes refractory to treatment within one year. The median survival is 14–20 months for limited SCLC and 9–11 months for extensive SCLC (Kalemkerian et al., 2013). These statistics highlight the need for new tools to aid in diagnosis and prevention.

Smoking is the major risk factor for SCLC (Pesch et al., 2012; Engeland et al., 1996; Freedman et al., 2008). However, previous studies were limited in sample size and statistical power to estimate more precise effect size of smoking on SCLC risk as well as the non-linear exposure–response relationships, which have been thoroughly explored in the previous non-small cell lung cancer (NSCLC) studies (Zhai et al., 2014a, b). Furthermore, smoking is also an independent risk factor for chronic obstructive pulmonary disease (COPD), which shares similar genetic and biological characteristics to lung cancer (Houghton, 2013; Roca et al., 2012; Schwartz and Ruckdeschel, 2006; Young and Hopkins, 2011), while concomitant COPD has not been fully examined with regard to SCLC risk (Purdue et al., 2007; Fan et al., 2011). Precise understanding of the association between smoking, COPD, and SCLC using a large sample size will shed light on its pathogenesis.

To address these knowledge gaps, we conducted a pooling analysis of 24 case–control studies in the International Lung Cancer Consortium (ILCCO) that in total included 4346 SCLC cases and 37,942 cancer-free controls. We examined: 1) exposure–response relationships between SCLC risk and cigarette smoking indicators, including cumulative smoking, age of initiation, and time since quitting smoking; 2) the association between physician diagnosis of COPD and SCLC risk; and 3) the interaction and mediation effects of COPD and cigarette smoking on SCLC risk.

2. Methods

2.1. Ethics

Individual studies were approved by their respective ethics committees.

2.2. Study Population

This pooled analysis comprised data from the ILCCO collaboration (http://ilcco.iarc.fr), which was established in 2004 to share data among ongoing lung cancer studies (Hung et al., 2008). We included 24 ILCCO studies that met the following criteria: 1) had histologically confirmed SCLC cases; 2) used a structured questionnaire to evaluate lifestyle; and 3) provided an intact study protocol. Among the 24 studies, two (Schottker et al., 2013; Goodman et al., 1998) were cohort studies. The remaining 22 had a case–control design, ten (Miller et al., 2002; Muscat et al., 1995; Loriot et al., 2001; Lopez-Cima et al., 2012; Kim and Hong, 2013; Ito et al., 2012; Lee et al., 2009; Ruano-Ravina et al., 2014; Zhang et al., 2010; Park et al., 2005) were hospital-based, ten studies (Kreienbrock et al., 2001; Landi et al., 2008; Luce and Stucker, 2011; Schwartz et al., 2009; Field et al., 2005; Heck et al., 2009; Sevilya et al., 2014; Cote et al., 2012; Hashibe et al., 2006; Wang et al., 2014) were population-based, and the other two (Yang et al., 2005; Brenner et al., 2010) were mixed case–control studies. The included studies were performed in North America (Goodman et al., 1998; Miller et al., 2002; Muscat et al., 1995; Park et al., 2005; Schwartz et al., 2009; Heck et al., 2009; Hashibe et al., 2006; Wang et al., 2014; Yang et al., 2005; Brenner et al., 2010), Europe (Schottker et al., 2013; Loriot et al., 2001; Lopez-Cima et al., 2012; Lee et al., 2009; Kreienbrock et al., 2001; Landi et al., 2008; Luce and Stucker, 2011; Field et al., 2005; Cote et al., 2012; Ruano-Ravina et al., 2004), and Asia and Oceania (Lopez-Cima et al., 2012; Kim and Hong, 2013; Ruano-Ravina et al., 2014; Heck et al., 2009). Each included study was approved by the institutional review boards of the respective institutions, and each participant provided informed consent.

2.3. Case Ascertainment

Incident lung cancer cases were diagnosed pathologically and verified through review of medical records (Schottker et al., 2013; Goodman et al., 1998; Miller et al., 2002; Muscat et al., 1995; Loriot et al., 2001; Kim and Hong, 2013; Ito et al., 2012; Lee et al., 2009; Ruano-Ravina et al., 2014; Park et al., 2005; Kreienbrock et al., 2001; Landi et al., 2008; Schwartz et al., 2009; Field et al., 2005; Wang et al., 2014; Yang et al., 2005; Brenner et al., 2010; Etzel et al., 2006), linkage to cancer registries (Lopez-Cima et al., 2012; Ito et al., 2012; Luce and Stucker, 2011; Schwartz et al.,