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Lung Cancer in Never Smokers: A Call to Action

Charles M. Rudin, Erika Avila-Tang, and Jonathan M. Samet

Abstract

The causative association between tobacco use and lung cancer is a well-established fact. However, lung cancer also occurs, at surprisingly high rates, in lifelong never smokers. In fact, lung cancer in never smokers is among the leading causes of cancer-related mortality. This CCR Focus summarizes recent data, identifies knowledge deficits, and suggests future research directions with regard to this critically important subset of lung cancer patients. (Clin Cancer Res 2009;15(18):5622–5)

Lung cancer caused by tobacco smoking is a well-documented public health tragedy. This highly fatal and largely avoidable cancer now causes more than 1 million deaths worldwide each year and more than 160,000 deaths annually in the United States (1). Lung cancer is responsible for more American deaths than colon cancer, breast cancer, and prostate cancer combined. An estimated 90% of cases are linked to cigarette smoking, based on the American Cancer Society's Cancer Prevention Study II (CPS; ref. 2). The exceptionally high risk for lung cancer in smokers has obscured the problem of lung cancer in never smokers. Not all cases of lung cancer can be attributed to current or former smoking, and several environmental risk factors for lung cancer other than smoking have been identified. Worldwide, clear estimates of the number of lung cancer cases in never smokers are not consistently available, but several populations have been described with particularly high rates that are not readily explained. In the United States, lung cancer in never smokers is almost as common a cause of death as atherosclerosis, and is among the most common causes of cancer mortality (see Fig. 1; refs. 3, 4).

The articles in this CCR Focus series were developed to summarize what is known about lung cancer in never smokers, covering multiple aspects of the problem: epidemiologic characteristics, risk factors, molecular and biological underpinnings, natural history, response to therapy, and outcome (5, 6). These articles are the products of a multidisciplinary workshop held at Johns Hopkins and supported by the Flight Attendant Medical Research Institute, with an international faculty representing public health, epidemiology, molecular biology, pathology, and oncology. They reflect the available literature across these disciplines along with recommendations developed from this workshop. The workshop was held in 2007; where appropriate, select key studies in the interim since the workshop have been incorporated into the articles and overview. Briefer and focused reviews of some of the individual topics covered here have been also published in recent years (7–9): a goal of this workshop, and of this issue of CCR Focus, is to provide a broad, current, and comprehensive summary of knowledge about this disease.

The workshop and the resulting articles were intentionally focused exclusively on evidence pertaining to lung cancer among never smokers. Studies pertaining to nonsmokers, which included former smokers, were therefore excluded from these analyses. For several of the studies that were included, the exposure status of nonsmoker was not clearly defined. Many of these studies were conducted among women living in countries with a very low prevalence of smoking among females, and we therefore considered their inclusion to be appropriate. Throughout the articles we specify whether the study subjects were never smokers (clearly defined) or nonsmokers (not clearly defined, or definitions vary).

General Conclusions

Several general conclusions from the literature, and recommendations about future research on the issue of lung cancer in never smokers were derived from this workshop:

- Lung cancer in never smokers is a worldwide public health concern, with incidence and mortality similar to many other major cancer types. In the United States, it is as common a cause of death as cancer of the liver or of the esophagus.
- Some causal risk factors for lung cancer in never smokers have been identified. These include second-hand exposure to tobacco smoke, radon and other ionizing radiation, asbestos, indoor air pollution, underlying chronic lung disease, and family history.
- Estimates for the United States indicate that about half of cases are attributable to indoor radon in homes or to exposure to second-hand smoke. However, the relative importance of the various risk factors in contributing to disease burden worldwide is not clearly defined and likely varies from country to country. In some places, indoor exposure to smoke from biomass fuel combustion is a major contributor.
Overall, comparing lung cancers in never smokers and ever smokers, there are clinically significant differences in tumor biology, prognosis, and response to therapy. Tumors arising in never smokers are more often adenocarcinomas and infrequently small cell or squamous cell carcinomas. Never smokers with lung cancer have a better natural history and prognosis with therapy than ever smokers with lung cancer. In comparison to lung cancers in smokers, cancers in never smokers are more likely to have EGFR mutations and to benefit from treatment with epidermal growth factor receptor (EGFR) small molecule inhibitors.

Research on lung cancer in never smokers has long been hindered by the difficulty in assembling large series, in part because of the need to separate never smokers from the far larger numbers of ever smokers with lung cancer. In most clinical trials, analysis of outcome by smoking status has not been reported.

Research on lung cancer in never smokers has been generally underfunded in relation to the burden of morbidity and mortality. Even relative to this baseline, targeted funding to study lung cancer in never smokers has been inadequate.

**Research Needs**

The following research needs were identified in the workshop:

- Reliable population estimates of incidence and prevalence of lung cancer in never smokers are needed among...
different ethnic groups, in different countries, and over time.
• Causation in a large fraction of lung cancers in never smokers remains undefined. Research to characterize unidentified and emerging risk factors should continue and should focus on populations likely to be particularly informative, such as cases with early age of onset. Factors of particular interest include exposures early in life, including in utero.
• Studies of genetic determinants of susceptibility in never smokers have been limited and primarily inconclusive. Further research is needed to address candidate genes, including but not limited to those implicated in tobacco carcinogenesis. Detailed exposure assessments in future studies of lung cancer in never smokers may provide insight into gene-environment interactions.
• Although exposure questionnaires can be further refined, complementary biomarkers of longer term exposure to lung carcinogens, particularly tobacco smoke, are needed. Better, easy-to-use monitors for long-term assessment of ambient tobacco smoke would be an important complement to such biomarkers.
• Lung cancers in never smokers with well-characterized exposures should be a focus of future studies of the cancer genome. Recent genome-wide association studies and large scale molecular profiling screens have included predominantly current or former smokers, with limited analysis to date of the included never smokers (10–18). A genome-wide association study focused on lung cancer in never smokers should be considered. These approaches will contribute to identifying new molecular targets of particular relevance for treatment in never smokers.
• Optimal treatment approaches for never smokers have not been established. Therapeutic clinical trials should address never smokers, through trial designs oversampling never smokers, through stratified designs based on ever-versus-never smoker status, or in some cases through studies limited to never smokers, and should when possible include classification of EGFR and KRAS status. Therapeutic trials focused on lung cancer generally should include prospective data collection about never, former, and current smoking status of study participants.

**Recommended Research Approaches**

- All studies on lung cancer, regardless of purpose, should include information sufficient to classify study participants by active smoking status (never, current, former) and by exposure to second-hand smoke status.
- To facilitate comparison across studies, a consistent definition of never smoking is needed. On the basis of an emerging consensus of recent and ongoing studies, we support a definition of fewer than 100 lifetime cigarettes smoked. At a minimum, publications on never, non, or oligo smokers should provide clear definitions of the classifications used.
- An approach to surveillance of lung cancer rates by smoking status (never, current, and former) in the general population in the United States and elsewhere should be established. Coverage should be sufficient to characterize rates by gender and by racial and/or ethnic group. In the United States, this tracking could be accomplished through the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program as a special study and would constitute a framework for etiologic research.
- Research on lung cancer in never smokers is hindered by the small numbers of cases available to individual researchers or centers. Mechanisms should be established for facilitating collaborative research on lung cancer in never smokers, including
  a. Establishing mechanisms for recruiting never smokers with lung cancer, including consideration of web-based approaches, advocacy groups, and subspecialty providers.
  b. Using existing epidemiologic and clinical consortia to investigate lung cancer in never smokers.
  c. Establishing a shared biorepository of lung cancer specimens from never smokers in the United States and worldwide, along with information on exposures. Cases should be actively sought from groups with high exposures to causative agents, e.g., second-hand smoke and radon. The biorepository would be a shared and limited resource with governance to evaluate research proposals. Such a repository has been initiated by a member of the workshop, Dr. Pao, and his colleagues in the interim since the workshop.1
- Recent work has begun to define differences in lung cancer biology associated with smoking status and tobacco exposure. These areas should constitute a continued focus of research, with implications for both lung cancer prevention and lung cancer treatment.

The past decade has been notable for an emerging focus of interest in lung cancer in the never smoker across multiple disciplines including advocacy, epidemiology, clinical medicine, and bench sciences, reflected in increasing numbers of focused research publications addressing this patient population. This trend has been in part driven by a simple clinical observation: never smokers with lung cancer, especially those with EGFR mutations, show preferential benefit from a new class of anti-cancer drugs, the EGFR tyrosine kinase inhibitors. Continued interrogation of the biology of lung cancer in never smokers is likely to reveal additional therapeutic targets of relevance to smokers and never smokers alike.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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1 http://www.mskcc.org/neversmokerswithlungcancer
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