Inflammatory Biomarkers and Risk of Lung Cancer

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About a century ago, the visionary cell biologist Theodor Heinrich Boveri postulated that tumorigenesis is promoted by chronic inflammation and that “parasites” can promote tumorigenesis by inducing inflammation (1). Several infectious agents have now been documented to cause cancer in humans. Whereas specific molecular processes are implicated as key players in cancer pathogenesis from hepatitis B virus and certain types of human papillomavirus infections, chronic inflammation is likely to play a key role in the development of hepatocellular carcinoma from hepatitis C virus infection (2,3). Moreover, several investigations including prospective cohort studies on the association of C-reactive protein (CRP), a nonspecific systematic marker of chronic inflammation, with cancer occurrence indicated that individuals with elevated levels of serum CRP are at increased risk for a spectrum of cancer types that do not have a predominant infectious etiology, including lung cancer (4–6). It appears that chronic inflammation, whether induced by biological agents or other exposures such as smoking (7), has reentered a center stage as a pathogenic process in cancer causation. A recent review article (8) summarized that inflammation may be involved in several stages of carcinogenesis, from tumor initiation to tumor promotion and even metastatic progression, through mechanisms involving genomic instability, epigenetic modifications, localized immunosuppression, and angiogenesis.

With respect to lung cancer, clinical studies have suggested that high serum levels of interleukin 6 (IL-6) and interleukin 8 (IL-8) are associated with increased risk of the disease (9,10).

In this issue of the Journal, Pine et al. (11) evaluated the associations of IL-6 and IL-8 with lung cancer risk among the National Cancer Institute-Maryland (NCI-MD) study participants using a case–control design (270 case patients and 296 control subjects) and participants from the screening arm of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial using an incidence density nested case–control design (532 case patients and 595 control subjects). In the NCI-MD case–control study, IL-6
and IL-8 were measured after the diagnosis of lung cancer among case patients and both hospital-based and population-based control subjects were recruited. In the PLCO nested case–control study, which has the attributes and advantages of an underlying cohort investigation, measurements of IL-6, IL-8, and CRP were conducted in blood samples collected at baseline, before the diagnosis of lung cancer. Lung cancer case patients and control subjects were finely matched for pack-years of smoking to minimize confounding by smoking, because smoking is positively associated with both lung cancer risk and levels of IL-6 and IL-8 (12,13). Moreover, in the component PLCO nested case–control study, the associations of IL-6 and IL-8 with lung cancer risk were evaluated separately for cancer cases that were diagnosed within and after 2 years of biomarker measurement. This approach is regularly used in prospective cohort epidemiological studies (or nested case–control studies) to distinguish reverse causation from forward causation; in the component PLCO study, it was used to determine whether preclinical lung cancer caused the increase of the studied biomarkers or whether inflammation, reflected in the increased levels of these biomarkers, contributed to the occurrence of lung cancer. In both the NCI-MD and PLCO components of this study by Pine et al. (11), higher levels of serum IL-6 and IL-8 were associated with lung cancer, but the PLCO study also provided compelling evidence that high levels of IL-8, though not IL-6, can precede the diagnosis of the disease by more than 2 years.

An important strength of the study (11) is that it merges the converging results of the two largest studies conducted thus far on the associations of IL-6 and IL-8 with lung cancer risk. Nevertheless, even though the results of the two component studies qualitatively reinforce each other, they are quantitatively different. We refer, for simplicity, to the dichotomized contrasts (above vs below median concentrations in the serum) of the evaluated biomarkers in relation to lung cancer. For IL-6, the NCI-MD case–control study indicates an increase in lung cancer risk by 182% (adjusted odds ratio [OR] = 2.82), whereas the PLCO nested case–control study indicates an increased risk by 26% (adjusted OR = 1.26). For IL-8, the NCI-MD case–control study indicates an increase in lung cancer risk by 86% (adjusted OR = 1.86), whereas the PLCO nested case–control study indicates an increase in lung cancer risk by 47% (adjusted OR = 1.47). The results of the PLCO nested case–control study deserve more confidence, not only because the study design is methodologically superior but also because the residual confounding by tobacco smoking is probably less substantial because of more fine control for this important potential confounder, compared with the NCI-MD component study. Of note, the apparent difference in the results of the two component studies is more evident for IL-6 than for IL-8, possibly because, at least in part, tobacco smoking is more strongly associated with IL-6 than with IL-8, as shown in Supplementary Table 5 (available online) (11).

The positive association of both IL-6 and IL-8 with lung cancer risk in both NCI-MD and PLCO component studies establishes the involvement of inflammatory processes in the pathogenesis of lung cancer. There was no evidence that the strength of the associations depends on histology or disease stage. However, in the component PLCO study, which allowed the authors (11) to study lung cancer cases diagnosed within 2 years from the measurement of inflammatory biomarkers separately from those diagnosed 2 years or longer after these measurements, there was evidence that it is only the increase of serum IL-8 that precedes the development of clinically evident lung cancer. The increase of serum IL-6 appears to be a consequence of lung cancer development.

The finding in the PLCO study that increases in both IL-8 and CRP can lead to improved prediction of lung cancer occurrence (11), prompted the authors to speculate that these and perhaps other proinflammatory cytokines could be jointly used as a screening tool. We do not share this optimism. The sensitivity of such a tool for the preclinical diagnosis of lung cancer may or may not be high, but the specificity is probably too low to allow its effective use, even in high-risk groups on account of their heavy smoking habits. Instead, we believe that the important findings of this study could lead to a better understanding of the processes that underlie the prolonged effects of smoking on lung cancer risk, even after smoking cessation. It has been shown that circulating concentrations of CRP in tobacco smokers remain unchanged following documented smoking cessation for at least 1 year (14). In this study, Pine et al. (11) found that concentrations of IL-8, an apparent predictor of lung cancer risk (10,11,15), are higher among ever-smokers than among never-smokers and fail to decline after cessation of tobacco smoking even after the passage of many years, as shown in Supplementary Table 5 (available online) (11). This indicates that inflammatory processes, which are associated with tobacco smoking and appear to contribute to lung cancer etiology, persist even after cessation of tobacco smoking. Of note, although cessation of smoking leads to a gradual reduction of the excess lung cancer risk, the former smokers never quite reach the low lung cancer risk levels of the never-smokers (16).

The study by Pine et al. (11) has generated important results that may or may not be of immediate use. However, it does provide a valuable insight into the etiology of lung cancer and how the most common cause of cancer–related deaths worldwide (17) is associated with tobacco smoking and chronic inflammation.

References


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