cancer-specific survival by stages in their unmatched cohorts, the paradoxical worse survival of never-smokers was seen in patients with stage II (77 never-smokers and 410 smokers). For the rest of their study cohort in stages I (392 never-smokers vs 1479 smokers) and stages III/IV (112 never-smokers vs 409 smokers), there were no significant survival differences. Subsequently, in the context of NSCLC, the importance of this apparent paradox to outcome associated with never-smokers remains obscure. The limited numbers (44 matched pairs of stage II) from Tang and colleagues may not be enough to support any definitive conclusions, nor did they examine the other higher lung cancer stages for any persistence of this paradoxical effect.

As the title implies, cigarette smoking likely exerts specific biologic effects that serve to produce distinct clinical populations afflicted with NSCLC. This notion, pointed out by the authors, is supported by a large body of histopathologic and quantitative molecular-based information describing differences in pathology, oncogenic driver

genes, and tumor mutational burden among these patient groups.⁴ However, based on the older time frame of data collection, the authors were not able to incorporate into this analysis the tumor genetic data that is now a routine part of molecular diagnosis. Thus, what specifically comprises those “unique tumor behaviors” impacting outcome among never-smokers versus ever-smokers continues to be studied. Tang and colleagues present interesting data to help frame our ongoing discussion on this important topic of thoracic surgery.

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Commentary: Where there is no smoke, but fire

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Non-small cell lung cancer (NSCLC) remains a major public health problem, accounting for 25% of all cancer-related deaths.¹ Our knowledge of the epidemiology and biology of NSCLC is constantly expanding; however, since Dr Luther L. Terry, MD, released the first report of the Surgeon General's Advisory Committee on Smoking and Health,² the role of tobacco abuse as a primary driver

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CENTRAL MESSAGE

Smoking status may portend a different tumor biology in NSCLC.

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of the disease process remains unchanged. Despite this, never smokers also develop NSCLC—which represents a similar but distinct entity that deserves its own characterization and, perhaps, treatment.³

In this issue of the *Journal*, Tang and colleagues⁴ present their experiences treating never-smokers at a high-volume

academic center, comparing outcomes postresection for 172 never-smokers and 1376 ever-smokers. The epidemiologic data of their cohort showed what we have known to be true from previous observational studies⁵: never-smokers were more likely to be women, to have lower lobe–predominant disease, and to have adenocarcinoma as the histopathologic subtype of their cancer when compared with ever-smoker counterparts.

Perhaps the most interesting finding lies in the comparison of matched pairs for the 2 groups, where 5-year survival of never-smokers with stage 1 disease was substantially better (96%) than in ever-smokers (78%). However, never-smokers with stage 2 disease fared significantly worse than matched ever-smokers, with 5-year survival of 54% versus 78% in ever-smokers. These results differ from previous reports that demonstrated similar survival at all stages between never- and ever-smokers.⁵ These data may suggest that as tumors in never-smokers grow from smaller to larger, they become disproportionately more aggressive than their counterparts in ever-smokers, possibly resulting from different underlying molecular mechanisms. Although this manuscript does not account for the potential mechanism of this finding, we do know that never-smokers show a different subset of mutations and therapeutic targets than do their smoking counterparts.^{6,7} Although it is unclear at this time whether these findings will change clinical practice, it is reasonable to look ahead to the possibility that separate staging may be required for the 2 groups, given their different behavior, or

that clinicians should be more aggressive at treating larger tumors in never smokers.

Tang and colleagues provide an epidemiologic baseline on which to further explore the differences in tumor biology between never- and ever-smokers. This suggests that we may one day be using smoking status to identify those that may be at risk for rapid progression of disease, and provide further personalization in the treatment of NSCLC.

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