testing. Perhaps targeted neoadjuvant or adjuvant strategies will help. Large-scale studies are underway or planned, including the Lung Cancer Mutation Consortium 4 PROMISE study.³ The comparatively poor outcome found in stage II never-smokers in the current study should provide the impetus for enrollment into that study and would seem to answer an important question. Non-small cell lung cancer in never-smokers is a very different disease.

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Commentary: Smoke or fire? Resected lung cancer in never-smokers

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Apparently, there is a growing proportion of never-smokers, those self-identified as someone with fewer than 100 cigarettes smoked in their lifetime, afflicted with non-small cell lung cancer (NSCLC) despite its known strong causal association to cigarette smoking.¹ However, the clinical distinction between these patient groups of never-smokers compared with ever-smokers, especially in terms of risk factors, has been difficult to precisely define.

In this issue of the *Journal*, Tang and colleagues² perform a retrospective analysis comparing never-smokers with ever-smokers using advanced, more accurate statistical methods that include group matching based on a balancing score and employment of machine learning to individually characterize the impact of specific cancer characteristics (ie, tumor size, etc). Patients in this single institution report all underwent surgical resection as part of treatment. Interestingly, when survival is assessed by tumor-node–

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CENTRAL MESSAGE

Among never-smokers, NSCLC is an important problem, yet the clinical profile of this patient population and their specific outcomes remain to be fully elucidated.

References

1. Tang A, Ahmad U, Toth AJ, Bourdakos N, Raja S, Raymond DP, et al. Non-small cell lung cancer in never and ever-smokers: is it the same disease? *J Thorac Cardiovasc Surg*. 2021;161:1903-17.e9.
2. Stiles BM, Rahouma M, Hussein MK, Nasar A, Nguyen AB, Harrison S, et al. Never smokers with resected lung cancer: different demographics, similar survival. *Eur J Cardiothorac Surg*. 2018;53:842-8.
3. Blumenthal GM, Bunn PA, Chaft JE, McCoach CE, Perez EA, Scagliotti GV, et al. Current status and future perspectives on neoadjuvant therapy in lung cancer. *J Thorac Oncol*. 2018;13:1818-31.

metastasis stage, there appears to be paradoxical worse survival of never-smokers assigned to more advanced pathologic stage, whereas the same category of patients enjoyed better survival in early pathologic stage. This phenomenon was observed in a subset of 90 matched pairs of patients who were stage I and in a subset of 44 matched pairs of patients who were stage II. The authors infer, overall, that smoking status should be incorporated into future NSCLC staging systems to improve prognostic performance as cigarette smoking seems to impart unique impacts.

In contradistinction to the findings here, the previous study by Stiles and colleagues³ concluded that in stage and propensity-matched cohorts of never-smokers and smokers the overall survival was similar, not distinct. They reported statistical nonsignificance in cancer-specific survival rates among never-smoker versus smokers (N = 498 patient in each matched group). Looking at

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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.

References

1. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers—a different disease. *Nat Rev Cancer*. 2007;7:778-90.
2. Tang A, Ahmad U, Toth AJ, Bourdakos N, Raja S, Raymond DP, et al. Non-small cell lung cancer in never and ever-smokers: is it the same disease? *J Thorac Cardiovasc Surg*. 2021;161:1903-17.e9.
3. Stiles BM, Rahouma M, Hussein MK, Nasar A, Nguyen AB, Harrison S, et al. Never smokers with resected lung cancer: different demographics, similar survival. *Eur J Cardiothorac Surg*. 2018;53:842-8.
4. Subramanian J, Govindan R. Molecular genetics of lung cancer in people who have never smoked. *Lancet Oncol*. 2008;9:676-82.

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Commentary: Where there is no smoke, but fire

Walker M. Blanding, MD, and Barry C. Gibney, DO

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