HHS Public Access

Author manuscript

J Thorac Oncol. Author manuscript; available in PMC 2021 April 30.

Published in final edited form as:

J Thorac Oncol. 2018 September ; 13(9): e172–e173. doi:10.1016/j.jtho.2018.04.018.

Caution Needed for Analyzing the Risks of Second Cancers

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To the Editor:

Recently, Thakur et al. calculated standardized incidence ratios (SIRs) and evaluated cumulative risks of second primary lung cancer (SPLC).[1] We would like to address several issues related to the interpretation of SIRs and the statistical methods for analyzing cumulative risks of SPLC.

Thakur et al.[1] reported that younger patients (age 20–49 years) had a high SIR (12.74) compared with that of older patient groups (4.47 for ages 60–69 years and 2.6 for age ≥70 years, respectively). They concluded that this could be because young patients with lung cancer may be more likely to survive their initial primary lung cancer (IPLC) and go on to experience development of SPLC (i.e., have a high risk of SPLC). By definition, however, SIR compares the incidence of SPLC with the incidence of IPLC within a subgroup; hence, comparing SIRs across different subgroups requires caution because the denominators of SIRs (i.e., incidence of IPLC) can differ substantially by subgroup. The SIR of 12.74 for ages 20 to 49 indicates that the incidence of SPLC among patients age 20 to 49 is 12.74-fold higher than the incidence of IPLC among those at the same age; it does not necessarily mean that a younger IPLC cohort is at a higher risk for SPLC than older IPLC cohorts are. A high SIR in young patients is expected given the low incidence of IPLC in this cohort, as has already been reported in other cancer sites.[2] In fact, the Surveillance, Epidemiology, and End Results data used by Thakur et al.[1] shows that a young age at IPLC diagnosis is associated with a *lower* risk of SPLC (see Table 1 in Thakur et al.[1]); in their table, a smaller proportion of young patients (5.5%) is observed among individuals with development of SPLC than among subjects without SPLC (8.5%) ($p < 0.0001$). This finding is consistent

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with our results, which are also based on Surveillance, Epidemiology, and End Results data[3]; we found that young age (<45 years) at IPLC diagnosis was associated with a reduced risk of SPLC (hazard ratio = 0.54, $p < 0.001$) when the age group 70 to 75 years is used as a reference.

Thakur et al. used the Kaplan- Meier method for estimating the cumulative risk of SPLC.[1] However, such standard survival methods can produce a bias (e.g., overestimate the risk) when study subjects are under competing risks of death from other causes.[4] Although direct comparison of the two studies is not feasible owing to different definitions used for SPLC to define the study cohorts, the median 10-year cumulative risk of SPLC in our study[3] (which is based on a competing risk regression method[5]) was 8.36%, which was estimated among patients with lung cancer who survived at least 5 years after diagnosis of their IPLC. This is lower than the risks reported by Thakur et al.[1] (an 11%–12% risk at 10 years and a 16%–20% risk at 15 years since diagnosis of the IPLC) on the basis of the standard survival method, possibly owing to bias from not incorporating competing risks into statistical analyses.

Despite the differences in approaches and findings between the two studies, both studies evaluate SPLC risk by using large population-level cohort data and demonstrate that the risk stratification approach in SPLC can be potentially useful for identifying high-risk patients for screening.

Acknowledgments

Dr. Plevritis received grants from National Cancer Institute for the submitted work.

Disclosure:

Dr. Plevritis has served as scientific consultant to GRAIL, Inc. Dr. Wakelee reports other from Peregrine; grants from Novartis and honoraria from Novartis for serving as a consultant; grants from Bristol-Myers Squibb, XCovery, AstraZeneca/MedImmune Lilly, Celegene, Gilead, Pharmacyclics, Roche/Genentech, and Exelisis; honoraria from ACEA for serving as a consultant; grants and other from Pfizer; and other from Helsinn outside the submitted work. The remaining author declares no conflict of interest.

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