Editorial Commentary

Sex disparities in lung cancer incidence: validation of a long-observed trend

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Lung cancer remains one of the most common causes of cancer and cancer deaths worldwide (1). Over the past decade, intensive smoking cessation programs have led to reductions in tobacco use and, consequently, significant declines in incidence rates and deaths attributable to lung cancer in the United States (2). However, lung cancer incidence rates have not decreased as much as expected, and increasing evidence shows variations in rates of decline by sex and race/ethnicity. Data from over 20 years ago, for example, first reported sex-based lung cancer incidence disparities with higher cancer incidence in females, despite lower rates of tobacco use among females as compared with males (3). In several recent studies, including our own work, sex-based incidence disparities persist (4). While the drivers behind higher female lung cancer rates remain elusive, many have attributed smoking as the reason for the disparate increases in incidence in recent years. However, others have refuted smoking as the sole reason for the higher incidence rates among females (5), and suggest that non-smoking related risk factors may be contributing to the disparate rates of lung cancer incidence among females as compared with males.

In a recent study, "Higher Lung Cancer Incidence in Young Women Than Young Men in the United States", Jemal and colleagues show continued sex-based incidence disparities and present compelling evidence that these discrepancies may not be attributed to smoking behaviors in the United States (6). The investigators ascertained incidence trends from 1995 to 2014 using the North American Association of Central Cancer Registries and smoking prevalence trends from 1970 to 2016 by race/ethnicity, age, and sex, using the National Health Interview Study. Similar to prior studies (7), the authors found an overall decrease in the rate of new lung cancer diagnoses; however, that trend was driven primarily by a decrease in incidence among non-Hispanic white and Hispanic males (4). The authors noted increased lung cancer incidence rate ratios (IRR) among females as compared with males from the mid-1990s to 2010–2014 [IRR among persons 40–44 increased from 0.82 (95% CI, 0.79–0.85) to 1.13 (95% CI, 1.08–1.18)]. The authors also noted that the rates of increase were disproportionate by race and ethnicity. Specifically, while females from black and Asian or Pacific Islander populations experienced narrowing IRRs over time from mid-1990s to 2010–2014 as compared with males, non-Hispanic white and Hispanic females experienced relatively higher increases in IRR over time, respectively [age group 40–44: non-Hispanic white: 0.88 (95% CI, 0.84–0.92) to 1.17 (95% CI, 1.11–1.23), Hispanic: 0.79 (95% CI, 0.67–0.92) to 1.22 (95% CI, 1.04–1.44)]. The increased incidence was primarily among the adenocarcinoma histologic subtypes, similar to data shown by our group and others (4). The authors reveal that males born prior to 1960s had a higher smoking prevalence than females and prevalence was only minimally higher among women born in 1965.

Furthermore, among non-Hispanic and Hispanic women born after the 1970s, smoking prevalence did not exceed that of men.

Other, more recent studies have corroborated the findings by Jemal *et al.*, although they lack the associated smoking prevalence data. For example, Lu *et al.* (7) used the Surveillance, Epidemiology, and End results (SEER) database from 1973 to 2015 and demonstrated a peak lung cancer incidence overall from 1973 until 1992, with subsequent declines until 2015. Similar to Jemal *et al.*, Lu and colleagues noted that declines in lung cancer incidence were driven by males (97.9/100,000 in 1984 to 55.3/100,000 in 2015) while incidence rose among females (20.2/100,000 in 1973 to 44.2/100,000 in 2015). Although incidence declined across all racial/ethnic groups, disparities in the rates of decline were seen among black populations, who persistently experience higher lung cancer incidence rates as compared with other racial/ethnic groups. In our work, we similarly found increased incidence among females as compared with males and noted lesser declines in incidence rates over time among populations residing in neighborhoods with low socioeconomic status (4).

What are other factors that could be contributing to these sex-based lung cancer incidence disparities? Several theories exist in the literature to explain these observations. First, is the idea that females are biologically more susceptible to the effects of carcinogens compared to males. This is supported by epidemiological data showing that female smokers have a higher likelihood of developing lung cancer compared with male smokers; in one study, females with an estimated 40 pack-year smoking history had a three-fold higher odds ratio (27.9 *vs.* 9.3) of developing lung cancer compared with males with the same smoking patterns (8). To better understand the biology behind these observations, one gene expression study found sex-based differences in the levels of cytochrome P4450 (CYP) enzyme CYP1A1, the enzyme responsible for polycyclic aromatic hydrocarbon activation in human lung and thus plays a role in lung carcinogenesis, These findings support the theory that females may be more susceptible to the carcinogenic effects of tobacco (9). Another theory is that the lung cancer incidence disparities are the result of an unequal reduction in different histologic subtypes following smoking cessation. For example, data has shown that after quitting smoking, the risk of developing small cell carcinoma decreases by about 17% per year, while the decrease in adenocarcinoma is only 8% per year (10,11), potentially revealing why there may be increased incidence rates of adenocarcinoma among female populations. Finally, environmental and workplace carcinogenic exposures have declined over the last decades, and this may have resulted in declines in lung cancer incidence among males, who historically have been in professions with exposure to these toxins (6). However, females are often underrepresented in occupational exposure studies, which makes an accurate comparison of these exposures between males and females difficult (12).

These theories, while potentially explanatory for sex-based disparities among smokers, do not explain the increase in female, never-smoking lung cancer, calling into question whether lung cancers experienced by females may be a different phenotype, with different risk factors for their occurrence, than the lung cancers experienced by males. Supporting this theory is data showing superior lung-cancer specific survival among females than males, indicating the possibility of a subtype of more indolent cancers among females compared with males (13). In addition, driver mutations such as *EGFR*, *ALK*, and *ROS1*, which have become increasingly relevant for many non-smoking related lung cancers, appear to occur more frequently among females than males (14,15). These driver mutation cancers occur mostly in the adenocarcinoma subtypes, which Jemal *et al.*, and others (4) have shown to be more common and increasing in incidence among females.

While administrative data, such as the ones used in the study by Jemal and colleagues along with our own work, can help to identify population-based trends overtime, they lack information on these increasingly important driver mutations along with other potential environmental and behavioral contributors. To bridge these gaps in knowledge, recent studies have begun to comprehensively evaluate potential demographic and environmental factors that may confer increased lung cancer incidence among non-smoking female populations. Several, including our own ongoing study (16), are investigating factors that may contribute to non-smoking related lung cancers, especially those with driver mutations. From 2007 to 2012, for example, an analysis of 2,035 Spanish women with non-small cell lung cancer (NSCLC) showed that of the 39.5% who were classified as never smokers, *EGFR* mutations appeared to have driven the increased incidence, and noted that over one-third of participants were exposed to passive smoking, mainly at home (17).

While there is much work to be done to understand the etiologies for the increased incidence among females as compared with males, the data is clear—sex-based disparities in lung cancer incidence persist and may be

worsening for particular racial/ethnic populations. A better understanding of the etiologies for increased incidence may help to determine actionable ways to prevent lung cancer in these high-risk populations. Future studies should investigate the potential demographic, environmental, and behavioral factors that may be driving these findings and inform interventions to reduce lung cancer incidence disparities among females and racial and ethnic minorities.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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