Prior Lung Disease, Gender, and Lung Cancer Risk
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Lung cancer in never-smokers is now the 5th leading cause of cancer death globally, and disproportionately affects women who have a more than two-fold higher risk than never-smoking men.[1,2] Part of this gender disparity is due to the fact that never-smoking women face a remarkably elevated lung cancer risk when prior respiratory disease is present. For example, it has been known for more than forty years that never-smoking women with prior tuberculosis have an 8-fold increased risk of lung cancer, while no such association existed among female smokers.[3] Wu et al. reported that never-smoking women with previous lung disease have a 56% increased lung cancer risk, driven primarily by tuberculosis prevalence. Among never-smokers, COPD prevalence is nearly twice as high in women (~3%) compared to men (~1.5%).[5] In addition, emphysema and pneumonia were found to remain independently associated with lung cancer in women after multivariable adjustment, but not in men.[6] The link between asthma and lung cancer risk also exhibits gender specificity. Meta-analyses reveal that females with asthma have a 23% increased lung cancer risk, suggesting that chronic airway inflammation may interact differently with female biology to promote carcinogenesis.[7]

The molecular and genetic basis for this gender disparity is only just beginning to be understood. There is increasing evidence that prior lung disease and female predominance in never-smoker lung cancer are mechanistically interconnected. Imaging studies reveal that women with COPD exhibit more small airways disease and airway wall thickening, while men show greater emphysema burden.[8] This observation is recapitulated in murine models, as female mice develop more small airways disease and males more emphysema for identical cigarette smoke exposure. Interestingly, these effects are ablated in female mice following ovariectomy or tamoxifen treatment, implicating estrogen as protective against emphysematous destruction, but potentially stimulating pathological inflammatory and fibrotic processes that predispose to lung cancer development.[9]

At the molecular level, estrogen receptor α (ERα) and β (ERβ) are expressed in the lung tissue of both sexes and regulate lung development, physiology, and pathology. In lung adenocarcinoma, the predominant type of cancer in never-smokers, estrogen promotes cancer cell proliferation through genomic (E2/ER complex inducing c-myc, cyclin D) and non-genomic pathways (PI3K/MAPK/AKT/ERK activation). Estrogen also modulates the tumor microenvironment by recruiting regulatory T cells (Tregs) that express TGF-β1 and create an immunosuppressive niche, thereby fostering tumor growth.[10] Consistently, estrogen has been found to act in a profibrotic manner in females. For example, in bleomycin-induced lung fibrosis, increased Treg and TGF-β1 expression was observed in menstruating females compared to males or ovariectomized females. Interestingly, ovariectomized mice with estrogen replacement and gut dysbiosis showed the highest collagen deposition, suggesting a synergistic interaction between gonadal hormones and microbiome-driven inflammation in fibrogenesis.[11]

The estrogen-fibrosis relationship may explain the tuberculosis-lung cancer linkage specifically in never-smoking women. TB establishes chronic inflammation with granulomatous fibrosis, extensive ECM remodeling, and persistent immune activation,[12] conditions that promote the development of cancer.[13] In never-smoking pre-menopausal women suffering from TB, prolonged estrogen

exposure during the inflammatory insult may amplify fibrotic ECM remodeling, creating a pro-tumorigenic environment.[14]

Similar to TB, chronic inflammatory lung diseases such as IPF, chronic bronchitis and asthma are also associated with aberrant ECM remodeling that supports the development of lung cancer, and which is characterized by collagen deposition, altered matrix architecture, increased stiffness, and release of matricryptins with pro-tumorigenic properties.[15] Women develop more airway-centric inflammation (chronic bronchitis pattern), while men develop more emphysema (parenchymal destruction).[16] This airway-predominant inflammatory phenotype may generate more extensive ECM remodeling per unit of injury, amplifying cancer risk.

Never-smoker lung adenocarcinoma is molecularly distinct, with EGFR mutations present in 45% of never-smokers compared to 7% of ever-smokers.[17,18] Among never-smoking Asian women, the prevalence of the EGFR mutation reaches 50%.[19] EGFR signaling is activated by chronic inflammation and air pollution, which are linked to prior lung disease.[20,21] Estrogen exposure has been associated with EGFR pathway activation,[22] and ER expression correlates with EGFR mutation status in some cohorts.[23,24] It is therefore plausible that gender disparity in lung cancer risk is caused by multiple related factors, including the predominance in women of small airways disease and chronic inflammation associated with TB, chronic bronchitis, or air pollution, together with prolonged EGFR pathway activation in an estrogen-rich milieu with extensive ECM remodeling, conditions that select for EGFR-mutant clones.[25]

The mechanistic linkage between prior lung disease and female predominance in never-smoker lung cancer has clinical and research implications. Never-smoking women with history of TB, chronic bronchitis, asthma or COPD represent a high-risk population that is inadequately captured by current screening guidelines based solely on smoking history. Longitudinal screening of women with inflammatory lung disease could enable detection at earlier, more treatable stages. In terms of intervention, understanding whether antifibrotic therapies such as pirfenidone and nintedanib in IPF patients reduce subsequent lung cancer risk, and whether hormonal status modulates this risk, could open up new strategies for mitigating lung cancer risk. Furthermore, the observation that gut dysbiosis synergizes with estrogen to worsen lung fibrosis might suggest that microbiome modulation may mitigate lung cancer risk in women with prior lung disease. Finally, public health messaging about lung cancer risk factors must extend beyond smoking to emphasize occupational exposures, air pollution, and chronic lung disease, particularly for women. The paradigm that lung cancer is a smoker's disease actively harms never-smoking women who delay seeking care for respiratory symptoms.

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