**Background**: Residential segregation is a known driver of lung cancer mortality in African Americans (AAs), but its role in lung cancer etiology remains unclear. Our objective was to examine the relationship between residential segregation and lung cancer incidence in AAs and to identify modifiable factors mediating this relationship.

**Methods:** Data from the Southern Community Cohort Study (SCCS) were analyzed, encompassing AA and non-Hispanic white (NHW) participants without prior cancer diagnoses. Analysis was performed from April 2022 to January 2024.The SCCS, spanning 12 southeastern states, enrolled over 85,000 participants from community health centers or random sampling.The cohort comprises 71,634 participants (50,898 AA, 20,736 NHW) enrolled between 2002-2009.Residential segregation, measured by the isolation index using 2010 census block group data, was linked to baseline census tracts within the SCCS.

**Main Outcome(s)/ Measure(s):** Incident lung cancer cases were identified through linkages with state cancer registries and the National Death Index as of Dec 31, 2016, to Dec 31, 2019, depending on the state. Parametric g-computation estimated cumulative lung cancer risk under various hypothetical interventions reducing residential segregation. Mediation analyses were performed using inverse propensity weighting and marginal structural models to estimate the direct and indirect effects of mediators.

**Results**: AAs resided in more segregated areas (median isolation index: 0.81) than NHWs (median: 0.15), p-value (<0.001). Among AAs, all hypothetical scenarios of lowering the isolation index led to lower 17-year culminative incidence of lung cancer. For example, decrease in isolation index from above 0.26 (first quartile) to exactly 0.26 led to a 12.35% (95% CI: 1.18%, 23.83%) reduction in lung cancer incidence in AAs (Figure). No such reduction occurred among NHWs. Approximately 27.69% of the isolation index-lung cancer incidence effect in AAs was mediated by personal smoking, 12.39% by PM2.5, 4.85% by second-hand smoke, and 4.41% by education.

**Conclusion:** Lower residential segregation significantly decreased lung cancer risk in AAs but not NHWs. Structural racism, driving segregation, likely impacts lung cancer risk through smoking and air pollution exposure. These findings suggest the need for policy and research interventions addressing structural racism to reduce lung cancer risk and promote equity in population health.

**Figure: Cumulative Incidence Ratio of Lung Cancer and 95% CI Comparing Different Strategies to Lower Isolation Index to Natural Course among AAs**

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