Title: Uncovering Hidden Risk: The Role of Family History in Lung Cancer Among Women and Low-Exposure Smokers.

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Encore Abstract.

The primary findings were presented as a poster at WCLC 2025 in Barcelona, Spain. This submission incorporates updated analyses of the somatic mutational landscape, with a particular focus on sex-specific effects. These data are novel and have not been previously disseminated in any prior presentation or publication.

Introduction:
While tobacco remains the primary cause of lung cancer, up to 25% of cases occur in never-smokers, indicating additional risk factors. A positive family history (FHx) increases risk 2–3 fold, suggesting heritable influences interacting with environmental exposures. Lung cancer incidence is rising in younger women and is more common in never-smoking females, highlighting the need to refine high-risk definitions. This study evaluates cancer FHx patterns in lung cancer to inform risk stratification.

Methods:
We retrospectively analyzed 2,038 lung cancer patients at the University of Chicago (2014–2024), including clinical, demographic, smoking, and self-reported race data. FHx patterns were assessed in relation to disease features.

FHx and all relevant clinical data in the UChicago cohort were manually curated for all patients. Personal and family cancer histories were extracted from both structured family history modules and unstructured clinical notes within the Epic EHR system across the entire UChicago Medicine health network. Additional data sharing was enabled through the Care. Everywhere interoperability platform, with patient consent to access relevant medical history across institutions. Each patient was manually reviewed and classified into one of three FHx categories, using a standardized framework adapted from the MSK classification schema. This manual curation strategy ensured a high degree of accuracy and was particularly valuable for capturing nuanced family history data in underrepresented subgroups, including younger individuals, never-smokers, and patients with limited or remote smoking exposure, who are often excluded from conventional screening criteria. Discrepancies between questionnaire responses and clinical documentation were adjudicated by trained abstractors through a consensus-based review process. In instances of conflicting data, priority was given to documentation from medical oncology, pulmonary, or thoracic surgery notes, as these are authored by core members of the multidisciplinary lung cancer care team and reflect their central role in diagnosis and longitudinal management.
Clinical sequencing was performed using the OncoPlus targeted panel, which covers 155–168 cancer genes, on tumor samples where somatic mutation data were available for a subset of 818 patients. Somatic genomic profiling was conducted on 818 diagnostic biopsy tissue samples utilizing various versions of the UChicago Medicine OncoPlus (UCM-OncoPlus) next-generation sequencing (NGS) panel, a hybrid-capture assay targeting 1005–1213 cancer-associated genes . Depending on the version, clinical reports included 147–171 genes for SNVs/indels, 136–146 genes for CNVs, and fusions involving ALK, RET, and ROS1. DNA was quantified using Qubit (Thermo Fisher), fragmented, and prepared with indexed adapters (Kapa HTP or IDT xGen kits), followed by hybrid capture with biotinylated probes (Roche Nimblegen or IDT). Libraries were sequenced on Illumina HiSeq 2500 or NovaSeq 6000 platforms (2 × 101 bp paired-end). Data analysis was performed using an in-house pipeline on a HIPAA-compliant high-performance computing system at UChicago's Center for Research Informatics.

Results

Among 2,038 lung cancer patients, 92.3% (n=1,881) had non–small cell lung cancer (NSCLC) and 7.7% (n=157) had small cell lung cancer (SCLC). The mean age at diagnosis was comparable between NSCLC (65.3 years) and SCLC (66.1 years), with 17.8% of patients identified as never smokers. Adenocarcinoma was the predominant NSCLC subtype (86.8%), and 40.8% were diagnosed at stage IV disease. Among SCLC patients, 68.8% presented with extensive-stage

disease. The NSCLC cohort was majority female (55.8%). Based on self-reported ancestry, 60.4% identified as White of European ancestry, 33.4% as Black or African American, and 3.9% as Asian.

In the subset with available family history data (n=1,988), 26.7% reported a lung cancer family history (FHx), 48.5% a non–lung cancer FHx, and 24.8% no FHx of cancer. Women with a FHx of cancer had significantly higher rates of multiple tumors than men in NSCLC (lung cancer FHx: 60.2% vs 39.8%, p = 1.3e-07; non–lung cancer FHx: 56.0% vs 43.1%, p = 6.7e-07), with a similar pattern observed in SCLC among women with a lung cancer FHx (63.2% vs 36.8%, p = 0.048). Lung cancer prevalence was markedly higher in women with a lung cancer FHx, particularly in never or light smokers (<1 PY: 79.2% vs 20.8%, p = 3.9e-8; 1–29 PY: 64.8% vs 35.2%, p = 1.1e-4), whereas sex differences attenuated among heavy smokers (≥30 PY). Enrichment of lung cancer FHx was most evident among White and African American patients, with smaller numbers observed in Asian and “Other” groups. Across NSCLC cases with a lung cancer FHx, prevalence was higher in females than males, with the highest rates among White, Asian, and “Other” females (31–33%), compared with 23% in African American females. In contrast, enrichment among males was greatest in the “Other” group (39%) and Whites (27%), with lower rates among African American (16%) and Asian (13%) men.

Family history was also associated with broader disease features. Overall, lung cancer FHx was linked to higher tumor multiplicity in both NSCLC (p < 0.0001) and SCLC (p = 0.001). This effect persisted across smoking strata (<1 PY: p = 1.7e-11; 1–29 PYs: p = 4.0e-05; ≥30 PYs: p = 8.9e-06), consistently stronger in women. Age at diagnosis was earlier in patients with a lung cancer FHx (mean 63.7 years) compared to those with no FHx or a non–lung cancer FHx (65.3 and 64.7 years; p = 0.00065 and 0.033, respectively). Ancestry-specific analyses revealed significant differences in lung cancer FHx, with enrichment in European ancestry patients, and sex-stratified models confirmed significant variation across ancestry groups (females: p = 2.3e-09; males: p = 2.1e-05).

In early-stage NSCLC (stage I–III), White and Black females were significantly more likely than males to report a lung cancer FHx (OR = 1.37 and 2.0; p = 0.0179 and 0.0197), whereas no significant differences were observed in stage IV, though similar trends persisted. At the molecular level, ATRX mutations were significantly more frequent in female former smokers (log2 OR = –1.97, FDR = 0.027), suggesting sex-specific genetic susceptibility. Exploratory analyses further identified nominally significant sex-specific trends in FHx-associated mutations, including RET, AXL, ATR, EPHA5, and APC in males.

Conclusions:
Family history of lung cancer is a significant marker of risk, particularly among women and never- to light-smokers, who demonstrated the highest prevalence and earlier onset of disease. These associations were consistently stronger in females, with enrichment observed in White and African American populations, while rates were lower in Asian patients. Our findings highlight the need to integrate family history and ancestry into lung cancer risk assessment and screening strategies, especially for populations traditionally underrepresented in current guidelines. This work underscores the importance of precision prevention frameworks that combine germline susceptibility with modifiable risk factors to improve early detection and reduce disparities in lung cancer outcomes.