

INTRODUCTION (refs 1-4)

- Current evidence confirms cancer and its treatments accelerating biological aging.
- Emerging preclinical models suggest aging can protect against cancer development or progression.
- This paradox is mirrored in humans where cancer incidence peaks at age 70 year then plateau or decline.
- We systematically characterized phenotypes manifesting resistance to both smoking-related (**SMK**) lung cancer (**LC**) and aging.

METHODS

- In a 20-year prospectively followed patient cohort, we identified 4627 people in five subgroups (**G1** - **G5**, see **Table**):
G1, SMK-LC cases diagnosed after age of 85 years and had >20 pack-year cigarette smoke history; n=411.
G2, normal age cases diagnosed 66-75 years old (norm-age) but survived ≥15 years; n=172.
G3, norm-age SMK-LC cases died <5 years, n=3634.
G4, SMK-No-LC *controls* died of competing causes before 75 years of age; n=248;
G5, Never-smoker (**NS**)-LC cases diagnosed after age 85, a comparator of late-onset LC, n=162.
- Comprehensive EHR data collected and analyzed, by sex, smoking, and comorbidity before LC diagnosis; Bonferroni-adjusted P-value threshold used for multiple testing.

RESULTS

G1 was highest in:

- being men,
- former smokers,
- had other cancer & lung diseases.

G1 similar to **G4**:

- pack-year history,
- diabetes

G1 similar to **G5**:

- heart diseases,
- hypertension,
- stroke,
- obesity.

G2 was unique in:

- favorable tumor features,
- lower comorbidity
- higher BMI.

CONCLUSIONS

- We observed more men than women among heavy smokers experienced successful aging and developed LC two decades later in life than the majority.
- We identified three unique LC-Aging Co-Resistant (LACOR) phenotypes:
G1, **SMK-late-onset (LACOR-I)**;
G2, **SMK-norm-age-onset and long-term surviving (LACOR-II)**;
G5, **NS-late-onset (LACOR-III)**.
- Our preliminary results set groundwork to investigate the mechanisms that provide resistance to the late onset of lethal malignancies and physiological decline of aging.

Heat-Map Table.
Selected features
Differentiating
Study Groups:
% or Mean of
Column N^{a,b}

Total of 20816 Lung Cancer (LC) Cases and 4361 No-LC Controls					
1340 Heavy-Smoking (SMK) Controls	12902 Heavy Smoker LC (SMK >20 pack-year history) 77.3% of 16687 all smoker				2861 LC Cases, Never-Smokers (NS)
G4 Norm-age (66-75) Controls; n=248, 18.5%	G3 Norm-age (66-75) Cases; n=3634, 28.2%	G2 Norm-age cases, ≥15-year Survivors; n=172, 1.3%	G1 Late-onset (≥85 years) Cases; n=411, 3.2%	G5 Late-onset (≥85 year) Cases; n=162, 5.7%	
Male sex ^c	65.3	61.4	45.9	71.3	28.4
Former smoker ^c	49.6	53.8	76.7	83.2	NA
Pack-years (mean) ^c	55.8	60.4	50.3	54.9	NA
Small Cell LC ^c	NA	18.3	3.5	14.6	3.1
Stage I/II NSCLC ^c	NA	26.9	88.9	46.1	36.9
Self-prior LC history ^c	NA	3.4	8.1	4.4	1.9
Other disease history ^e					
Cancer (not lung) ^c	37.1	22.5	31.4	44.0	40.1
COPD ^c	49.2	54.1	45.9	46.7	10.5
Other lung diseases ^c	46.8	37.7	41.9	48.2	30.2
Heart diseases ^c	35.1	25.8	19.8	47.9	48.8
Hypertension ^c	38.3	34.2	40.1	51.6	60.5
Stroke ^c	6.5	5.8	4.7	10.0	11.1
Type-II diabetes	16.1	13.5	8.7	15.3	8.6
Obesity ^c	31.0	16.2	22.1	7.1	6.8

Abbreviations: LC, lung cancer; NSCLC, non-small cell lung cancer; COPD, chronic obstructive pulmonary disease;

NA, not applicable or not available. Color background: Highest; Higher; Reference; lower.

^a 6.0% cases missing smoking data; 1.6% missing stage data; ^b 18.4% missing comorbidity data in G3 only|

^c P<0.006; ^d Exploratory with ~10% sample; ^e ≥1 Recorded in medical records prior to LC diagnosis.

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