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| **Exploring the lung cancer microbiome using metagenomics in an Australian cohort**  |
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| **Introduction/Aim:** Lung cancer (LC)remains the leading cause of global cancer deaths. Given frequent late-stage disease presentation and significant morbidity, earlier diagnosis and novel treatments are needed. Recent international studies have begun unveiling microbial dysbiosis in LC. However, similar studies have yet to be conducted in Australian cohorts. We aimed to identify the LC microbiome in Australians with early-stage LC.**Methods:**In this prospective single-centre cohort study, we obtained 87 specimens from 28 Australians with early stage (I/IIa) disease (25 non-small cell LC, 3 small cell LC). Shotgun metagenomics was undertaken on 16 oral washes taken pre-bronchoscopy to define the oral microbiome, 27 LC site and 27 contralateral (non-tumour side) lung washes taken pre-biopsy to compare extratumoural vs. normal lung microbiota, 18 LC biopsies, and 8 reagent-only controls to define background contamination. **Results:** Comparison of LC site and contralateral wash microbiota identified seven commensal oropharyngeal microbes that were significantly less abundant within the LC site (*p<*0.05), whereas two microbes (*Capnocytophaga* sp. oral taxon 878 and *Klebsiella aerogenes*) were significantly more abundant within the LC site (*p<*0.05). No significantly enriched or depleted microbes were identified in transbronchial lung biopsy specimens. Finally, the previously LC-linked bacteria, *Acidovorax temporans* and *Bradyrhizobium japonicum*, were not identified in this cohort, indicating potential geographic differences in LC microbial signatures.**Conclusion:**Our study provides the first reported insights into the LC microbiome in early-stage LC in an Australian setting. Our findings suggest that reduced prevalence of certain commensal oropharyngeal microbes in the extra-tumoural environment may be a hallmark of early-stage LC. Larger studies examining microbiome alterations in both the intra- and extra-tumoural environments across LC subtypes are needed to provide a more in-depth assessment of subtype-specific microbiome signatures. Our findings consolidate international studies showing that microbial differences in early-stage LC may yield new biomarkers for earlier diagnosis and provide novel treatment targets.**Grant Support:** Sunshine Coast Health Institute (SCHI) Collaborative Seed Grant – $35,000; Advance Queensland Fellowships (EPP [$300,000] and OSO [$90,000]).**Key Words:**Lung cancer; microbiome; non-small cell lung cancer; small-cell lung cancer*\*Authors contributed equally* |