Review Article

Narrative review: respiratory tract microbiome and never smoking lung cancer

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Background and Objective: The lung microbiome was previously thought to be a sterile environment where only gaseous exchange takes place, but recent studies have shown the presence of microbiota in the lung. This review investigates the current literature on the effects of an environmental driven dysbiosis on the healthy oral and respiratory microbiome and its relationship to lung cancer risk in never-smokers.

Methods: An online electronic search was performed on PubMed of all English-language literature using combinations of the following keywords: "lung cancer", "dysbiosis", "non-smokers", "oral microbiome", and "respiratory microbiome". All population-based studies reporting results on oral and/or respiratory microbiome in adults were considered for our narrative review.

Key Content and Findings: Metagenomic analyses have been performed on isolated samples from healthy participants and compared to samples from those with lung cancer. Research shows that a decrease in alpha diversity of microbes in the oral microbiome is associated with increased risk of lung cancer, along with differences in beta diversity in the sputum of lung cancer cases and healthy controls. Further, several studies have observed that significant changes in the abundance of genera such as increased abundance of *Lactobacillales*, *Bacilli*, and *Firmicutes* associated with an increased lung cancer risk among participants with exposure to certain household solid fuels.

Conclusions: These findings suggest potential carcinogenic processes such as increased inflammation associated with changes in flora. Additionally, studies showed that increase in certain taxa such as *Bacteroides* and *Spirochetes* might have a protective effect on lung cancer risk. The review also provides insight into how understanding the microbial changes can be beneficial for lung cancer treatment and disease-free survival. Larger studies in different populations need to be performed to strengthen the current associations between microbial diversity and lung cancer risk.

Keywords: Respiratory microbiome; lung cancer; dysbiosis; never-smokers

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Introduction

A study in 2018 about worldwide cancer risk showed that in 14 regions, lung cancer was the number one reason for cancer related death (1). Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer cases and has two subtypes: squamous cell carcinoma and adenocarcinoma (2). Squamous cell carcinoma and small cell lung cancer are mostly driven by smoking, though small cell lung cancer is less common and more difficult to treat.

Table 1 The search strategy summary

Items	Specification
Date of search	01/15/2022
Databases and other sources searched	PubMed (NLM)
Search terms used	Lung cancer, dysbiosis, non-smokers, oral microbiome, respiratory microbiome
Timeframe	2002–2021
Inclusion and exclusion criteria	Inclusion: population-based studies; reported results on oral and/or respiratory microbiome in adults
	Exclusion: laboratory or animal-based studies; studies among children (aged <21 years old); results among adults with positive smoking history
Selection process	Selection process conducted by all authors

NLM, National Library of Medicine.

Adenocarcinoma, though also associated with smoking, is the most common lung cancer type found in non-smokers and this incidence is increasing globally (3), and potentially in the United States (4). Some of the possible agents of dysbiosis in the upper and lower respiratory microbiome include tobacco, inflammatory lung states such as asthma, lung diseases such as chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis and long-term antibiotic exposure (5-7). Questions remain as to what environmental factors besides tobacco smoking are increasing the risk of lung adenocarcinoma.

The lung microbiome was previously thought to be a sterile environment where only gaseous exchange takes place, but recent studies have shown the presence of microbiota in the lung. The goal of this review is to bring together the literature on how dysbiosis in a healthy oral and respiratory microbiome may be associated with lung cancer. Studying the microbiome of the lower respiratory tract in isolation of the oral microbiome is typically not feasible because of cross contamination when collecting sputum samples, which are often used for this research, so this review will cover changes in the entire respiratory tract in relation to lung cancer risk. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-885/rc).

Methods

An online electronic search was performed (*Table 1*) on PubMed of all English-language literature using combinations of the following keywords: "lung cancer", "dysbiosis", "non-smokers", "oral microbiome", and "respiratory microbiome". Bibliographies of identified papers were reviewed for additional articles of interest. Observational cohort, retrospective studies, randomized controlled trials (RCTs), meta-analyses, and review articles were examined. All population-based studies reporting results on oral and/or respiratory microbiome in adults were considered for our narrative review. Laboratory or animal-based studies, studies among children (aged <21 years old), and results among adults with positive smoking history were excluded.

The normal oral and lung microbiome

Understanding the microbial composition of normal, healthy lungs is a good way to understand what changes to the upper respiratory and lung microbiome may have a significant effect on lung cancer risk. Unlike the oral and upper respiratory tract, the lung microbiome was previously thought to be a sterile environment. Now it is understood that both the upper and lower respiratory tract contain phylogenetically diverse microbes with unique alpha diversity, or diversity within the microbial community, and beta diversities, meaning diversity between different microbial communities. The diversity of these environments is studied using 16S sequencing traditionally, and more recently metagenomic shotgun sequencing, to determine what types of bacteria phyla are present and how many of each type make up the microbial communities.

More extensive information about a typical healthy oral microbiome exists, most likely due to saliva sample collection being non-invasive and easy to obtain from participants. *Table 2* summarizes the peer-reviewed literature cited in this review that characterize the healthy oral and lung microbiome. Studies have shown that in participants without diagnosed lung cancer or other non-malignant respiratory diseases such as asthma or COPD,

Table 2 A summary of the collection method and key findings of oral, upper and lower respiratory microbiome for the healthy and non-healthy participants

Authors, year (reference)	Source; population	Participants	Body site; sample type	Key findings
Caselli *et al.*, 2020 (8)	Europe; male and female	20 participants who were healthy young adults	Oral; saliva	Alpha-diversity evidenced significant differences among the different sampled sites but not among the enrolled subjects, strengthening the notion of a recognizable HOM
Aas *et al.*, 2005 (9)	Europe; male and female	5 participants with no clinical signs of oral mucosa disease	Oral; saliva	There is a distinctive predominant bacterial flora of the healthy oral cavity that is highly diverse and site and subject specific
Hosgood *et al.*, 2014 (10)	China; female	16 participants. Controls: never smoking females with no lung cancer. Cases: never smoking females with incident lung cancer	Oral; saliva. Lung; sputum	Never smoking lung cancer cases have differing sputum microbiota than controls. Bacteria found in sputum may be influenced by environmental exposures associated with the type of coal burned in the home
Hosgood *et al.*, 2021 (11)	China; male and female	114 participants who were lifetime never smokers who had no lung cancer at baseline	Oral; saliva	Subjects with lower microbiota alpha diversity had an increased risk of lung cancer compared with those with higher microbial alpha diversity
Yang *et al.*, 2018 (12)	China; female	247 participants. Controls: non-smoking females with no lung cancer. Cases: non-smoking females with incident lung cancer	Oral; saliva	Non-smoking female lung cancer patients exhibited oral microbial dysbiosis. There was significantly lower microbial diversity and richness in lung cancer patients when compared to the control group
Gomes *et al.*, 2019 (13)	Portugal; male and female	103 participants undergoing evaluative for lung disease at the hospital	Lung; BAF	Lung cancer microbiota is enriched in *Proteobacteria* and more diverse in SCC than ADC, particularly in males and heavier smokers
Bingula *et al.*, 2020 (14)	France; male and female	18 patients diagnosed with primary NSCLC eligible for surgery with or without neoadjuvant therapy	Oral; saliva. Lung; BAF. Lung tissue biopsy	BAL fluid has unique lung microbiota and emphasize the importance of the sample choice for lung microbiota analysis. All samples showed increased abundance of phylum *Firmicutes* in the lower lung, with decrease in *Proteobacteria*
Hosgood *et al.*, 2019 (15)	China; female	90 participants. Controls: never smoking females with no lung cancer. Cases: never smoking females with incident lung cancer	Oral; buccal. Lung; sputum	Decreased microbial alpha diversity is associated with risk of lung cancer
Peters *et al.*, 2019 (16)	USA; male and female	19 patients identified on pre-op workup as having a pulmonary nodule suspicious for lung cancer	Lung; lung tissue	Tumor tissue had lower richness and diversity than paired normal tissue, though overall microbiome composition did not differ between the paired samples
Tsay *et al.*, 2021 (17)	USA; male and female	148 participants with lung nodules who underwent clinical bronchoscopy for diagnostic purposes	Lung; BAF	Lower airway dysbiosis was more prevalent in the stage IIIB–IV tumor-node-metastasis lung cancer group and is associated with poor prognosis
Greathouse *et al.*, 2020 (18)	USA; male and female	143 lung cancer cases who provided tumor and non-tumor adjacent tissue	Lung; lung tissue	Normal lung has a lower alpha diversity compared to non-tumor adjacent or tumor tissue. *Acidovorax* is enriched in smokers

HOM, healthy oral microbiome; BAF, bronchiolar lavage fluid; SCC, squamous cell carcinoma; ADC, adenocarcinoma; NSCLC, non-small cell lung cancer; BAL, bronchoalveolar lavage; pre-op, pre-operatively.

the relative taxon abundance of the oral microbiome should be high compared to unhealthy participants (8). A study of saliva samples from different locations in the oral cavity of healthy participants (n=20), sequenced by whole-genome sequencing and real-time quantitative polymerase chain reaction (PCR) microarray, found that each sample had its own unique microbial community made up of bacteria, fungi and viruses with over 200 microbial genera present (8). Interestingly, though there were intraindividual differences in alpha diversity among sample locations, interindividual alpha diversity lacked significant differences, suggesting the existence of a typical healthy oral microbiome. Consistent with another study that looked at the oral microbiome using saliva, the healthy microbiome was composed of microbes such as *Streptococcus*, *Granulicatella*, *Neisseria*, *Haemophilus*, *Corynebacterium*, *Rothia*, *Actinomyces*, *Prevolleta*, *Capnocytophaga*, *Porphyromonas*, and *Fusobacterium* (8,9).

The lung microbiome among healthy individuals is less characterized most likely due to the difficulty of collecting lower lung samples like sputum, bronchoscopy brushing, or bronchoalveolar lavage without oral contamination and because lung biopsy collection is unwarranted in healthy human participants. To date, only a few studies have overcome these limitations. A case-control study by Hosgood *et al.* in never smoking females in Xuanwei and Fuyuan China characterized the microbiota of sputum-buccal pairs, using 16S sequencing, and found that the pairs were not highly correlated in healthy participants, suggesting that the lung microbiome has unique microbial attributes compared to the oral microbiome (10). Additionally, research on the oral microbiome composition in never-smoking healthy participants suggests that the taxa most representative of the microbiome found in saliva samples include *Proteobacteria* (30.3%), *Firmicute* (26.6%), *Bacteroidetes* (21.7%), *Fusobacteria* (9.3%), and *Actinobacteria* (8.7%) (11). Other research has also shown that the dominant microbes at phyla level found in the saliva samples are *Proteobacteria*, *Firmicutes*, and *Bacteroidetes* presenting over 97% of the total phyla (12).

There is research that suggests that a low biomass in the lungs has a protective effect due to balanced immune modulation (19). The healthy lung microbiome was shown to consist of low bacterial biomass made up of commensal bacteria such as *Prevotella*, *Streptococcus*, and *Veillonella*. The samples were taken from micro aspiration of pharyngeal secretions in healthy subjects and represent the lung lower respiratory microbiome. These studies classified the lung microbiome into two distinct groups, one groups that was called the supraglottic predominant taxa (SPT) pneumotype which has a high bacterial load with *Prevotella* and *Veillonella* and a second group called background predominant taxa (BPT) pneumotype made up of a low bacterial load of *Acidocella* and *Pseudomonas* (19). Studies also show that the SPT pneumotypes enriched in commensal bacteria is balanced with the T helper immune response that is important for maintaining homeostasis and decreasing the inflammatory response in the lungs. It is proposed that immune dysregulation results from a decrease in the commensal bacteria but a high bacterial biomass with decreased community diversity and increased airway inflammation that leads to malignant transformation (19). Additional research supports that in healthy lungs the biomass is very low at about 5-8.25 log copies/mL because of the robust immune response of the pulmonary system including macrophages that help eliminate the non-commensal bacteria (20). More studies need to be completed to agree on the ideal composition of a healthy lung microbiome and which microbial compositions are commensal versus pathogenic.

The malignant lung microbiome

A study that characterizes the lung microbiome of patients with adenocarcinoma versus squamous cell carcinoma found that overall *Proteobacteria* was the most abundant phylum discovered in the bronchioalveolar fluid of both malignant and non-malignant tissues (13). It proposes the possibility that a significant increase in *Proteobacteria* can be a key feature of cancerous lungs, along with other groups such as increase in *Acinetobacter* in adenocarcinoma and *Enterobacter* in squamous cell carcinoma. Another study with 18 patients diagnosed with NSCLC where they analyzed the microbiome of the saliva, bronchoalveolar lavage fluid and tumor tissue from patients found that there was not only a distinct difference in diversity and abundance between oral and lung microbiome, but clear differences between bronchoalveolar lavage fluid and lung tissue microbiota (14). The oral microbiome of these patients was dominated by the phylum *Firmicutes* and the genus *Streptococcus*. They also found *Proteobacteria* and *Firmicutes* to be the most abundance phyla in normal and non-malignant lung tissue samples.

Oral and respiratory microbiome and lung cancer risk in non-smokers

There are many questions to why the incidence of lung

cancer is increasing in non-smokers but only a handful of studies have shed some light on this. Different types of outdoor pollutants such as ozone, particulate matter and nitrogen oxides, have been associated with incidence of lung cancer in never smokers (21). In addition, indoor pollutants such as cooking oil and smoke from solid fuel combustion have also been associated with lung cancer (22-26). In a case-control study in Xuanwei and Fuyuan China with 8 never smoking females with lung cancer and 8 without lung cancer, they found evidence that there was a strong association with the type of coal that was burned in homes and the bacterial composition of the sputum, suggesting that the certain taxa that are associated with lung cancer groups could be driven by the fuel-type exposure (10). Similar findings were also observed in a larger study observing the sputum of never smoking females with and without lung cancer (controls n=45, cases n=45) and found that decreased microbial diversity is associated with increased risk of lung cancer (15). The type of fuel used at home was also found to affect the alpha diversity, resulting in the smoky coal users having a significant increase in alpha diversity versus clean fuel users. More specifically, Laibin coal users without lung cancer had an increased alpha diversity compared to Laibin coal users with lung cancer. Taken together this suggests the possibility of a beneficial and potentially protective effect of a high lung diversity and lung cancer risk, among individuals who experience coal smoke exposures.

A nested case-control study within two prospective cohort studies investigated the association of the oral microbiota and lung cancer risk in never smokers (11). The study used the Shanghai Women's Health Study and the Shanghai Men's Health Study, collected oral rinse samples at baseline and assessed microbiome diversity and lung cancer risk. Their results showed that lower microbiota alpha diversity was associated with increased risk of lung cancer (11). Additionally, abundance of certain phyla was associated with a decreased risk of lung cancer including *Spirochaetia* and *Barcteroidetas* while greater abundance of *Bacilli* and *Lactobacillales* were associated with increased risk of lung cancer. This study replicated some of the key findings in the earlier retrospective case-control studies in never smoking women including that a greater abundance of *Lactobacillales* in the sputum is associated with lung cancer (10).

A case-control study that collected salivary samples from 75 non-smoking female lung cancer patients and 172 matched healthy participants reported that lung cancer patients had a higher richness in taxonomic composition in addition to oral microbial dysbiosis (12). The alpha diversity of the oral microbiome in lung cancer patients was lower and the structure of the microbiome was significantly different with an increase in genera such as *Blastomas* and *Sphimgomonas* while *Acinetobate* and *Streptococcus* was higher in non-lung cancer groups.

Oral and respiratory microbiome and lung cancer prognosis in non-smokers

The studies discussed thus far show that changes in abundance of certain microbial communities occur with exposure to different environmental hazards. It is not yet completely understood how the dysbiosis can lead to carcinogenic consequences. In a pilot study that sequenced 16S ribosomal RNA (rRNA) of tumor and normal tissues in 19 patients with NSCLC saw that the normal lung tissue had a higher richness and alpha and beta diversity than the tumor tissue (16). Tumor tissue microbiome had a lower richness but similar composition to normal tissues samples, suggesting that the abundance versus the type of bacteria may have a bigger impact on lung cancer. They also found that patients with higher richness and diversity in their normal lung tissue had reduced recurrence-free survival and reduced disease-free survival compared to patients with lower richness in the non-tumor lung tissue.

Research on associations between dysbiosis and inflammatory markers in never-smokers with NSCLC showed that compared to patients staged at I–IIIA, patients with stages IIIB–IV disease had a lower microbial diversity associated with upregulation of interleukin-17 (IL-17), phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinase (MAPK), and extracellular signal-regulated kinase (ERK) pathways driven by an increase in abundance of *Veillonella parvula* found in bronchioalveolar fluid (17). Further concerning the mechanism behind lung dysbiosis and cancer progression, a study by Cheng *et al.* using the mouse model showed how the lack in commensal bacteria post antibiotic treatment lowered the immune defense of the lungs, which is proposed to make the environment more vulnerable to tumorigenesis (27). This lack of host defense could be a result of a direct relationship between immune cytokines such as IL-17 and commensal bacteria that is yet to be elucidated. Additionally, a study has shown that protecting the gut microbiome with probiotics such as yogurt in the setting of antibiotic treatment reduced the hazard ratio for lung cancer incidence (28). More research needs to be completed to discover if these microbial shifts are directly leading to onset of lung cancer or worsening

disease progression. A study using 33 non-cancer controls and 143 tumor and non-tumor adjacent tissues from lung cancer samples from The Cancer Genome Atlas investigated the effect of different microbial disturbances on lung cancer progression (18). They found that shifts in microbial composition varied with disease state but observed an increase in *Proteobacteria* and decrease in *Firmicutes* in the samples associated with the lung cancer population versus the control population. *Prevotella* is a genus of anaerobic Gram-negative bacteria whose increase in abundance is associated with T-helper cells that aid in mucosal inflammation (29). It is possible that the increase in *Prevotella* abundance may promote progression of lung cancer because of its pro-inflammatory properties. Even though the oral microbiome is not a complete reflection of the microbiome in the lungs, it is still worth investigating to understand any possible association between certain gram-negative bacteria abundance, inflammation and lung cancer progression.

Conclusions

Taken together, studies have shown that an increase in lung cancer risk is associated with a lowered alpha diversity of the respiratory tract and different significant changes in abundance of microbes present in the diseased tissue such as increased abundance of *Lactobacillus*, *Granulicatella*, and *Streptococcus* (10,11). Current research suggests that there is a dysbiosis that occurs as a result of dangerous environmental exposures such as air pollution and that can increase risk of lung cancer development, but there is also a dysbiosis that occurs in lung cancer tissue versus healthy lung tissue. The lowered biomass is hypothesized to lead to an imbalance of homeostasis and lack of immune modulation resulting in an inflammatory state and malignant transformation (19,20). Some of these studies are limited by the lack of a healthy control group, for example the barriers to obtaining lung tissue biopsies from healthy patients, along with confounding variables such as age, diet, lifestyle, type of lung cancer treatment, or other respiratory disease states.

There is a gap in the literature that connects oral and lung dysbiosis to lung cancer survival, but there is evidence that more research in this area could help discover new approaches that are taken to diagnose and treat lung cancer. Studies that investigated the role of the lung microbiome in carcinogenesis found strong predictive potential of *Veillonella* in the diagnosis of squamous cell carcinoma and *Capnocytophag* in the diagnosis of adenocarcinoma (30). Additionally, studies demonstrated distinct gut microbiome compositions in NSCLC patients that were responders versus non-responders to immune checkpoint inhibition therapy (30). Further, previous studies on the gut microbiome and lung cancer treatment efficacy showed that antibiotic driven dysbiosis of the gut microbiome and shifts in diversity composition even transiently led to a reduced efficacy of anti-programmed death 1 (PD-1) treatment in patients with NSCLC (31).

In conclusion, studies have shown that environmental pollution increase risk of lung cancer among nonsmokers. However, it remains to be answered how the dysbiosis found in the oral and respiratory microbiome plays a role in this phenomenon (32,33). Additionally, how does understanding the changes in the microbiome and inflammation of malignant lungs inform or guide cancer treatment. Future research should focus on potential differences in the respiratory microbiome of non-smokers regarding how daily environmental exposures may affect microbial respiratory health, especially in cities with high levels of air pollution and household exposures. It is critical to elucidate geographical differences, as well as, intra-personal differences by body site. There is still much to be understood and investigated in order to provide more insight into the respiratory microbiome's connection to lung cancer among never smokers.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-885/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-885/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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