COVID-19 AND LUNG CANCER

BACKGROUND

- **COVID-19:** (severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2)
  - COVID-19 is an infectious disease caused by a newly discovered coronavirus.
 - Most people infected with the COVID-19 virus will experience **mild to moderate respiratory illness.**
  - It seems that many people have lasting adverse health effects and/or permanent lung damage following a case of COVID-19.

- **LUNG CANCER:**
  - Lung cancer is out of control cell growth that originated in the lungs of the body.
  - Lung cancer is the second most common cancer in both men and women.
  - It accounts for an estimated 25% of all cancer diagnoses.
  - Lung cancer is the **leading cause of death** among all cancers globally (approximately 1 in 4 per year).
  - Death often occurs in only a few short years after diagnosis.
- **CONNECTION:**
  - COVID-19 and lung cancer share some common symptoms (cough, breathlessness, fatigue, chest tightness, etc.), diagnostic criteria, and management.
  - **Both COVID-19 and lung cancer primarily impact the same organ system with the human body.**
  - Recent research shows that there may be a higher risk of COVID-19 in lung cancer patients and for the symptoms to be more severe.
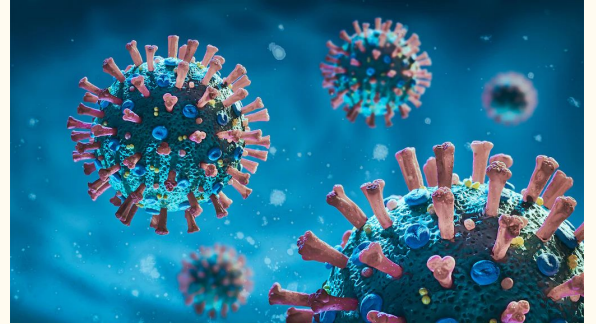
COVID-19

HOW DOES IT AFFECT YOU?

Designed by Avesta Rastan
- www.azuravesta.com
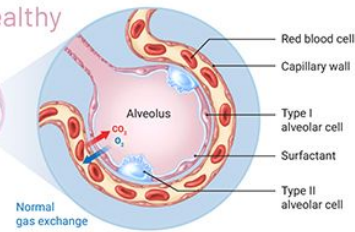- @azuravesta
- @azuraviz

Coronavirus Disease 2019 (COVID-19) is a pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2, also called SARS-CoV-2. Despite the widespread awareness regarding COVID-19, many are still unaware about how it affects the human body.

- Left Lung
- Trachea
- Bronchus
- Alveoli (sg. alveolus)
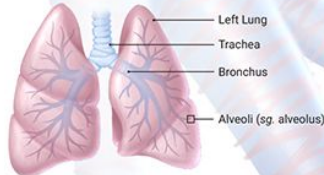
SARS-CoV-2 starts its journey in the nose, mouth, or eyes and travels down to the alveoli in the lungs. Alveoli are tiny sacs of air where gas exchange occurs.

Healthy

- Red blood cell
- Capillary wall
- Alveolus
- Type I alveolar cell
- Surfactant
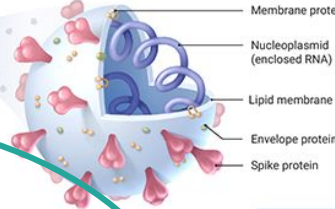- Type II alveolar cell

Normal gas exchange

Gas Exchange

Each sac of air, or alveolus, is wrapped with capillaries where red blood cells release **carbon dioxide** (CO_2) and pick up **oxygen** (O_2). Two alveolar cells facilitate gas exchange; **Type I** cells are thin enough that the oxygen passes right through, and **Type II** cells secrete **surfactant** – a substance that lines the alveolus and prevents it from collapsing.
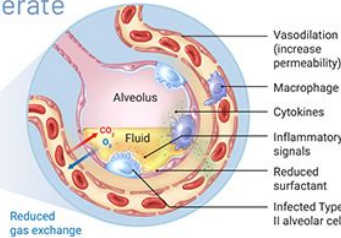
Infected

SARS-CoV-2 Structure

- Membrane protein
- Nucleoplasmid (enclosed RNA)
- Lipid membrane
- Envelope protein
- Spike protein

Viral Infection

The spike proteins covering the coronavirus bind ACE2 receptors primarily on type II alveolar cells, allowing the virus to inject its RNA. The RNA "hijacks" the cell, telling it to assemble many more copies of the virus and release them into the alveolus. The host cell is destroyed in this process and the new coronaviruses infect neighbouring cells.

Moderate

- Vasodilation (increase permeability)
- Macrophage
- Cytokines
- Alveolus
- Fluid
- Inflammatory signals
- Reduced surfactant
- Infected Type II alveolar cell

Reduced gas exchange

Severe

- Fluid-filled interstitium
- Loss of surfactant
- Protein-rich fluid
- Neutrophil
- Protein and cellular debris
- Formation of scar tissue

Greatly hindered gas exchange

Impaired Gas Exchange

When the immune system attacks the area of infection it also kills healthy alveolar cells. This results in three things that hinder gas exchange:

1) Alveolar collapse due to loss of surfactant from Type II cells
2) Less oxygen enters the bloodstream due to lack of Type I cells
3) More fluid enters the alveolus

Stay Home
- Symptoms may start to show (e.g. dry cough, fever, etc.)
- Pneumonia develops
- Shortness of breath

Hospitalization
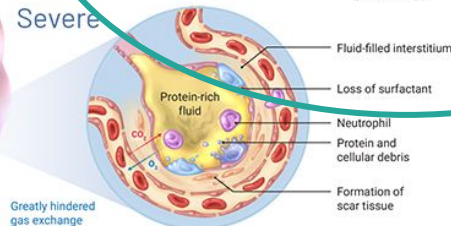- Dangerous for high-risk individuals; secondary infections may occur

Intensive Care (ICU)
- Patients may require ventilators and life-support
- Complications unrelated to COVID-19 may occur

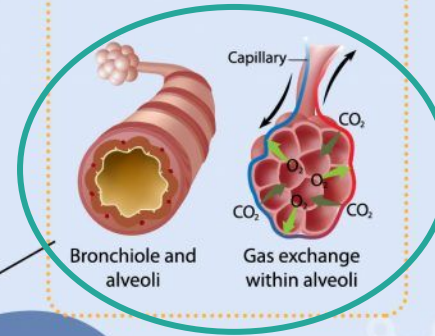With proper care, patients may recover at any point during this process

Immune Response

1. After infection, Type II cells release **inflammatory signals** that recruit **macrophages** (immune cells).

2. Macrophages release **cytokines** that cause vasodilation, which allows more immune cells to come to the site of injury and exit the capillary.

3. Fluid accumulates inside the alveolus.

4. The fluid dilutes the surfactant which triggers the onset of alveolar collapse, decreasing gas exchange and increasing the work of breathing.

5. **Neutrophils** are recruited to the site of infection and release Reactive Oxygen Species (ROS) to destroy infected cells.

6. Type I and II cells are destroyed, leading to the collapse of the alveolus and causing **Acute Respiratory Distress Syndrome** (ARDS).

7. If inflammation becomes severe, the protein-rich fluid can enter the bloodstream and travel elsewhere in the body, causing **Systemic Inflammatory Response Syndrome** (SIRS).

8. SIRS may lead to **septic shock** and **multi-organ failure**, which can have fatal consequences.

Lung Cancer

Trachea

Bronchus

Bronchi
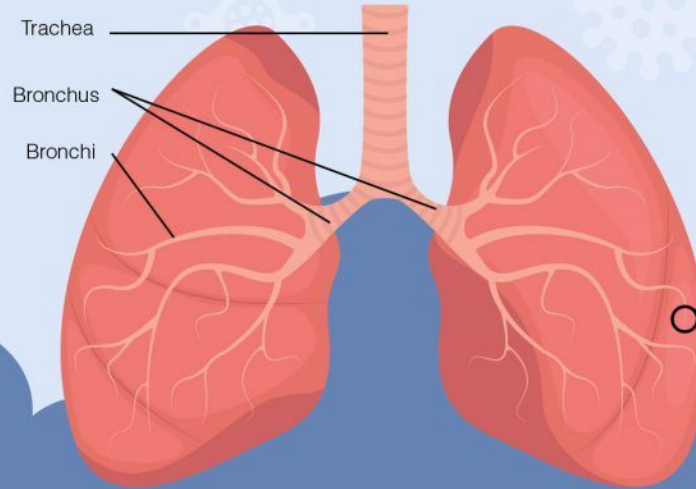
Main Function
Process of Gas Exchange called Respiration

Capillary

CO_2

O_2 O_2

CO_2 O_2 CO_2

Bronchiole and alveoli

Gas exchange within alveoli

- Lung Cancer is the uncontrolled growth of malignant cells that originate in the lungs.

- Lung cancer may spread to lymph nodes or other organs in the body, such as the brain.

INCIDENCE RATE & MORTALITY RATE

Explore Cancers Further: Lung Cancer
Cancer Incidence Rate, All Races, 2013-2017

66.2 per 100k	3,546
Cases Diagnosed per 100k people (Incidence Rate)	Cases Diagnosed per Year on Average

Differences by Geography

Cancer Rates
- Highest Rates (Top 25%)
- Above Average
- Below Average
- Lowest Rates (Bottom 25%)

Changes over Time: 1988-2017

Rate per 100,000

Statewide — United States

Differences by Age

Differences by Sex & Race

Rate per 100,000

Female   Male   Black   White

Explore Cancers Further: Lung Cancer
Cancer Mortality Rate, All Races, 2013-2017

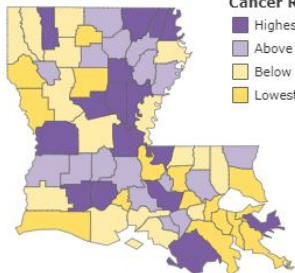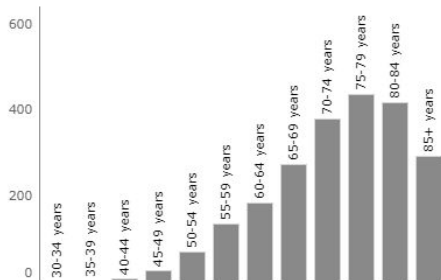| 49.7 per 100k	2,622
Deaths per 100k people (Mortality Rate)	Deaths per Year on Average

Differences by Geography

Cancer Rates
- Highest Rates (Top 25%)
- Above Average
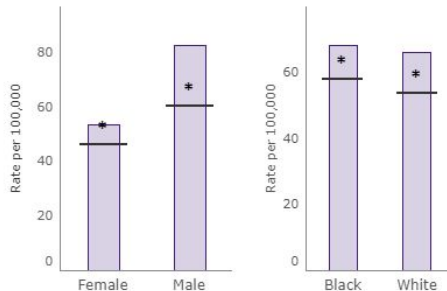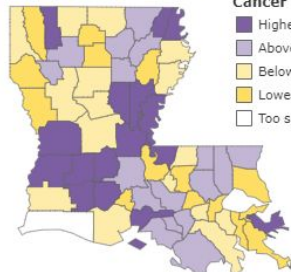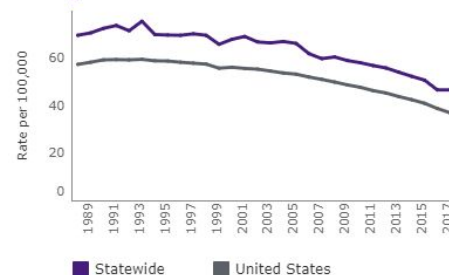- Below Average
- Lowest Rates (Bottom 25%)
- Too small to display
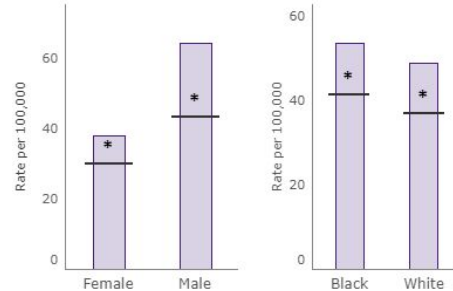
Changes over Time: 1988-2017

Rate per 100,000

Statewide — United States

Differences by Age

Age distribution is not available for mortality data.

Differences by Sex & Race

Rate per 100,000

Female   Male   Black   White

PUBLIC HEALTH CONCERN / IMPACT

- COVID-19 has been a major global pandemic with a significant public health impact.
  - According to the WHO there have been more than 140 million cases and 3 million deaths (as of April 2021).
  - It is a newly emerging and very timely topic for epidemiologic research.
- Lung cancer already has the **highest mortality** of all cancers globally.
- According to the Louisiana Tumor Registry (LTR) 3,546 lung cancer cases are diagnosed per year on average.
- COVID-19 is a new infectious disease and cancer takes many years to manifest.
- It is still too early to know, but what about the COVID-19 as the exposure?
- Is COVID-19 going to make these statistics even worse?
- Are people now more susceptible to lung cancer?

RATIONALE:

- **Is it possible that COVID-19, which primarily negatively impacts the respiratory system and (possibly permanently) damages the lungs, might cause early-onset, more severe, and/or increased incidence of lung cancer?**

TIMELINE

DATES	MILESTONE	TASKS
June 2021 to December 2021	Development & Funding	• Research and compile literature review • Draft study protocol (goals, hypotheses, aims, approach, data collection, etc.) • Obtain IRB approval(s)
August 2021 to December 2022	Approvals & Document Creation	• Obtain funding and submit grant applications • Draft informed consent and other documents • Survey design: draft, evaluate via cognitive testing, test flow/branching, and validate instrument • Develop database for data • Create publicity pieces and develop implementation plan
January 1, 2023 To Study End	Recruitment	• Implement publicity plan • Recruit participants from the LTR
January 1, 2023 To Study End	Data Collection & Case-Control Matching	• Collect survey and EHR data / obtain exposure and outcome measurements • Individually match cases (with replacement) and controls • Confirm survey and EHR information match • Compile demographic information and data for potential confounders • Continue to publicize the study, recruit participants, and collect data until minimum sample size of 525 is reached or until funding is exhausted
January 2033	End Recruitment & Data Collection	• Close the study (unless more funding or grants are available) • Compile and download data
February 2033	Coding	• Write code for statistical analyses
March 2033	Analysis	• Analyze findings (odds ratios, confidence intervals, multivariate analysis, etc.) • Explore effect measure modifiers and confounders
April 2033	Draft Findings	• Articulate conclusions • Evaluate study design and implementation (strengths, weaknesses, bias, error, etc.)
May 2033	Publish Findings	• Report finds • Submit for publication
June 2033	Follow-Up Studies	• Design follow up research studies (particularly prospective cohort)

RESEARCH QUESTION

Does COVID-19 increase the odds of lung cancer in never-smokers?

HYPOTHESIS:

- Individuals with clinically confirmed diagnosis (via molecular testing such as polymerase chain reaction) of COVID-19 will have increased odds of being diagnosed with primary lung cancer despite never smoking.

STUDY DESIGN:

- Case-Control

STUDY APPROACH

- **TARGET POPULATION:** Louisiana residents (never-smokers)
- **SAMPLING FRAME:** Louisiana Tumor Registry (LTR)
- **OUTCOME VARIABLE:** Lung Cancer
- **EXPOSURE VARIABLE:** Clinically confirmed COVID-19 diagnosis via PCR molecular testing
- **SAMPLE POPULATION FOR CASES: Primary lung cancer diagnosis** in the LTR (never-smokers)
  - **SIZE:** Approximately 350 never-smokers will be diagnosed with lung cancer in Louisiana each year. This study will enroll a minimum of 175 (10%) of those individuals.
- **SAMPLE POPULATION FOR CONTROLS: Any other cancer diagnosis** in the LTR (never-smokers)
  - **SIZE:** Minimum of 350 individuals matched on age, sex, and race/ethnicity
- **SAMPLE SIZE:** 525 minimum

STUDY APPROACH

- **INCENTIVES / BENEFITS:**
  - $20 for completing initial Computer assisted self-interviewing (CASI) survey from home (demographics, health history, COVID status, etc.) and consenting to Electronic Health Record (EHR) access
  - $20 once EHRs are received and survey data is validated
- **DATA COLLECTION WILL INCLUDE:**
  - General demographics (age, sex, race/ethnicity, marital status, education, etc.)
  - Health history (alcohol use, tobacco exposure, overweight/BMI status, physical activity, etc.)
  - COVID diagnosis and test type, COVID vaccination, monoclonal antibody treatments
  - Cancer diagnosis and other medical condition diagnosis, etc.
- **RISK:** Minimal and rare -- possible emotional distress (No risk of death)

RECRUITMENT: PUBLICITY

AT THE LTR:
- Flyers
- Brochures
- Posters
- Word-of-mouth via practitioners and staff
- Emails to listserv / direct email to individuals if consented to be contacted for research studies
- Info booths periodically (one day every other month)

NOTE: It will not be publicized that this study is looking at COVID and lung cancer in an effort to help to prevent measurement or researcher bias. Publicity documents will only ask if they are willing to participate in a cancer research study.

RECRUITMENT: INCLUSION CRITERIA

- **CASES: First diagnosis of anatomopathologically confirmed primary lung cancer**

- **CONTROLS:** Other non-metastatic cancer diagnosis (not lung cancer)

- Age ≥ 18 years
- Have never smoked
- Able and willing to complete survey and provide access to EHRs
- Provide written approval by physician or other qualified healthcare provider
- No planned major surgery during the study period

RECRUITMENT: EXCLUSION CRITERIA

- Has ever smoked
- COVID-19 diagnosis via rapid antibody/antigen testing and not molecular testing such as polymerase chain reaction
- Evidence of **metastatic cancer**
- Concurrently actively treated other cancer
- Currently enrolled in another research study or clinical trial
- Unable or unwilling to give informed consent
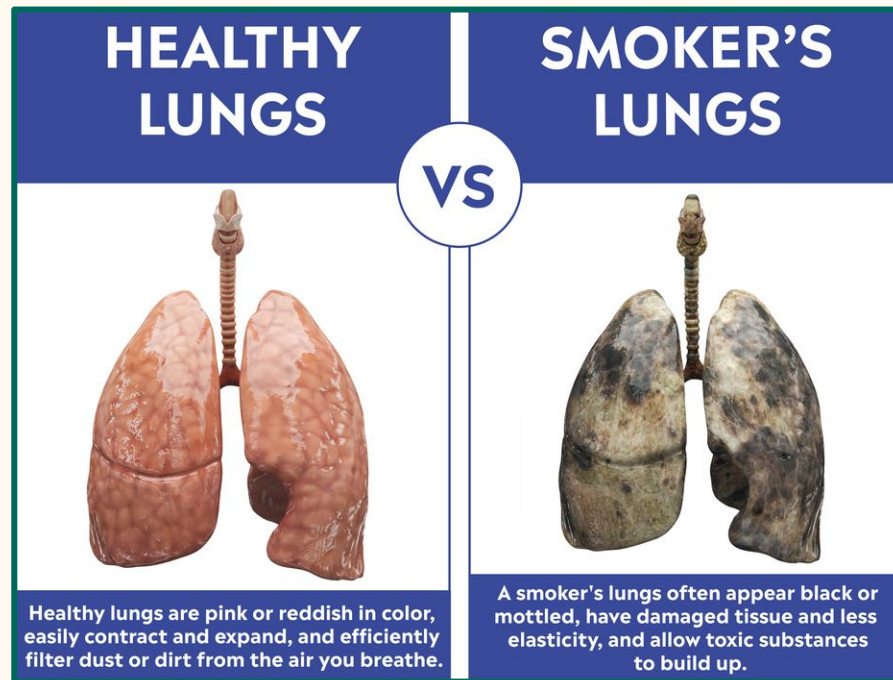- Any other condition that may impede testing of the study hypothesis

SMOKING

CIGARETTE SMOKING:
- The CDC explains that "**cigarette smoking is the number one risk factor for lung cancer**. In the United States, cigarette smoking is linked to about 80% to 90% of lung cancer deaths."
- Because there is already a known and very significant risk for developing lung cancer as a result of smoking, this population **(ever-smokers) will be excluded** entirely in order to rule smoking out as a confounder.

OTHER RELATED TOBACCO EXPOSURES THAT MAY BE CONFOUNDERS:
- Hookah
- E-cigarettes
- Cigar and pipe smoking
- Smokeless chewing tobacco
- Secondhand smoke exposure

HEALTHY LUNGS **VS** **SMOKER'S LUNGS**

Healthy lungs are pink or reddish in color, easily contract and expand, and efficiently filter dust or dirt from the air you breathe.

A smoker's lungs often appear black or mottled, have damaged tissue and less elasticity, and allow toxic substances to build up.

https://www.prevention.com/health/health-conditions/a25350185/lung-cancer-facts/

CONFOUNDING

- Education (lower)
- Socioeconomic status (lower)
- Cancer screening delays because of pandemic
- Alcohol consumption
- Lack of physical activity
- Overweight/obese BMI
- Radiation therapy to the chest / Chemotherapy
- Genetics / Family history of lung (or other) cancer

- **Diagnosis:**
  - Diabetes
  - Cardiovascular disease
  - Metabolic syndrome
  - Lung disease (asthma, cystic fibrosis, etc.)

- **Environmental Exposures:**
  - Air pollution
  - Arsenic
  - Asbestos
  - Chromium
  - Diesel exhaust
  - Geographic location ("Cancer Alley")
  - Inhaled chemicals or minerals
  - Marijuana
  - Nickel
  - Radioactive ores such as uranium
  - Radon
  - Tobacco (from sources other than smoking)

- **EFFECT MEASURE MODIFIER:**
  - Monoclonal Antibody (mAb) Treatment
  - COVID-19 vaccination

RESULTS

Data will be blinded for analysis to eliminate bias.

Look for effect measure modification:
- **Monoclonal Antibody (mAb) Treatment**
- **COVID-19 vaccination**

Calculations to perform:
- Chi-squared
- T-test
- Logistic Linear Regression Odds Ratios
- Multivariate regression analysis
  - To examine several potential confounders
- Stratified analyses according to age, sex, race, family history, etc.
  - To do subset analyses

STRENGTHS

https://pixabay.com/illustrations/chain-strong-protection-1027864/

- **Exposure and outcome measures are objective and laboratory confirmed**
  - Not susceptible to recall, interviewer, observation, or social-desirability biases
- **Cheaper, quicker, and easier** than many other study designs.
  - Good for an initial, exploratory study.
- Minimal loss to follow-up.
- Suitable for rare outcomes and those with long latency
- **Small sample size**
- No ethical concerns

LIMITATIONS

STUDY DESIGN:
- Assesses odds and not risk because cannot determine causality or incidence (retrospective and observational only).
  - Delays in lung cancer screenings due to the pandemic may impact lung cancer diagnosis.

SELECTION BIAS:
- Only 10-15% of lung cancer **cases** are never-smokers.
- Difficult to identify/enroll **control** group.
  - The best controls would be those from a generally healthy population rather than other cancer patients.
  - A second option might be from electronic health records from Louisiana hospitals and clinics.
  - The cost and time needed to recruit them would be high and would still likely result in a reduced sample size.
  - Recruiting from the LTR is faster and will result in a larger sample.
    - Participants will self-select to complete the survey and provide consent for access to EHRs.

LIMITATIONS

INFORMATION / MEASUREMENT BIAS:
- Both are possible with any type of survey.
- EHRs will be used to verify clinical information such as cancer and COVID-19 diagnosis, monoclonal antibody treatments, and COVID-19 vaccination in addition to basic health information (height, weight, etc.).
- COVID-19 diagnosis will specifically be confirmed by PCR testing, which is the most reliable, and not antigen or antibody rapid tests.
- **This may reduce the sample size further.**

RECALL / INTERVIEWER / SOCIAL-DESIRABILITY BIAS:
- Information collected regarding potential confounders could contain errors.
- Confirming survey information via EHRs will help to reduce these issues.

VALIDITY:
- Small sample size and selection of controls may result in **external validity concerns.**
- Cases are matched to eliminate some confounders, but this reduces generalizability of the findings.

FUTURE RESEARCH

The next logical research study on this topic would be to answer the question below with a **prospective cohort design.**

- **Does COVID-19 increase the risk of lung cancer in never-smokers?**
- Because COVID-19 is a new infectious disease and cancer takes many years to manifest, right now is a prime opportunity to establish a cohort and initiate such a research study.

NATIONAL CANCER INSTITUTE: THE COVID-19 AND CANCER LINKAGE STUDY

- In collaboration with state health departments, Division of Cancer Epidemiology and Genetics (DCEG) investigators are leading an effort to link data from several state cancer registries and COVID-19 surveillance systems.
- The COVID-19 and Cancer Linkage (COVCan) Study will:
  - Allow investigators to assess the risk of COVID-19 hospitalization and death among cancer patients and survivors
  - Identify patient characteristics and cancer sites exhibiting the strongest associations with severe COVID-19.

ADDITIONAL RESEARCH QUESTIONS TO CONSIDER

1. Does COVID-19 increase the odds of lung cancer in never-smokers **throughout the United States**?
2. Does COVID-19 increase the risk of lung cancer in **never-smokers versus ever-smokers**?
3. Do never-smokers who received a monoclonal antibody treatment following a severe acute respiratory syndrome coronavirus 2 (COVID-19) diagnosis have **reduced odds** for the development of lung cancer?
4. Does COVID-19 increase the odds of lung cancer in never-smokers compared to the odds of developing **other types of cancers?**
5. Has COVID-19 increased the odds of diagnosis of lung cancer in **earlier stages**?
6. Are there any **predictive or preventive biomarkers** associated with lung cancer following COVID-19 diagnosis?
7. Are the odds of lung cancer diagnosis equal in **symptomatic versus asymptomatic** COVID-19 cases?
8. Are the odds of post-COVID-19 lung cancer diagnosis **equal in smokers versus those that quit smoking**?
9. Are the rates of lung cancer **incidence and mortality equal** in never-smokers diagnosed with COVID-19?
10. Are those with multiple diagnoses **(recurrence) of COVID-19** at greater risk for lung cancer?
11. Does COVID-19 impact the **two major types of lung cancer equally** in never-smokers?
    - Small Cell Lung Cancer (SCLC) vs. Non-Small Cell Lung Cancer (NSCLC)

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    https://dceg.cancer.gov/research/what-we-study/covid#:~:text=The%20COVID%2D19%20and%20Cancer%
    20Linkage%20(COVCan)%20Study%20will,associations%20with%20severe%20COVID%2D19.

Louisiana Cancer Data Visualization, based on November 2018 submission data (2013-2017): Louisiana Tumor
    Registry; https://sph.lsuhsc.edu/louisiana-tumor-registry/data-usestatistics/louisiana-cancer-data-
    visualization-dashboard, January 2020.

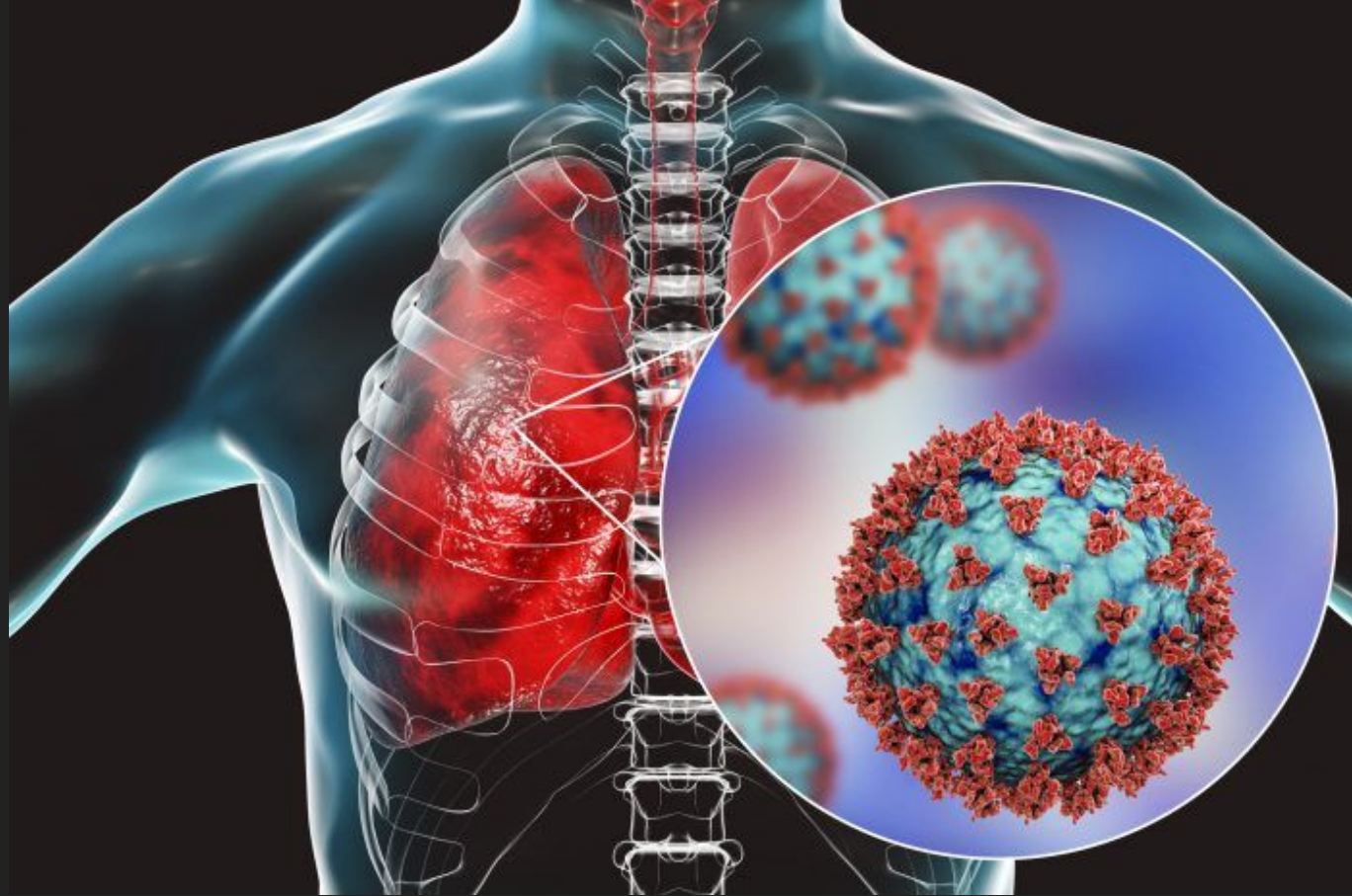*What are the risk factors for lung cancer?* (2020, September 22).
    https://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm.

WHO coronavirus (COVID-19) Dashboard. (n.d.). https://covid19.who.int/.

Wu, Mingxin MDa,b; Mou, Ruiyu MDa; Liu, Xiaodi MMa; Guo, Shanqi MDa; Kong, Fanmingb; Li, Xiaojiang MDa,b; Jia,
    Yingjie MDa,b,∗ *Is COVID-19 a high risk factor for lung cancer?*, Medicine: January 08, 2021 - Volume 100 -
    Issue 1 - p e23877 doi: 10.1097/MD.0000000000023877
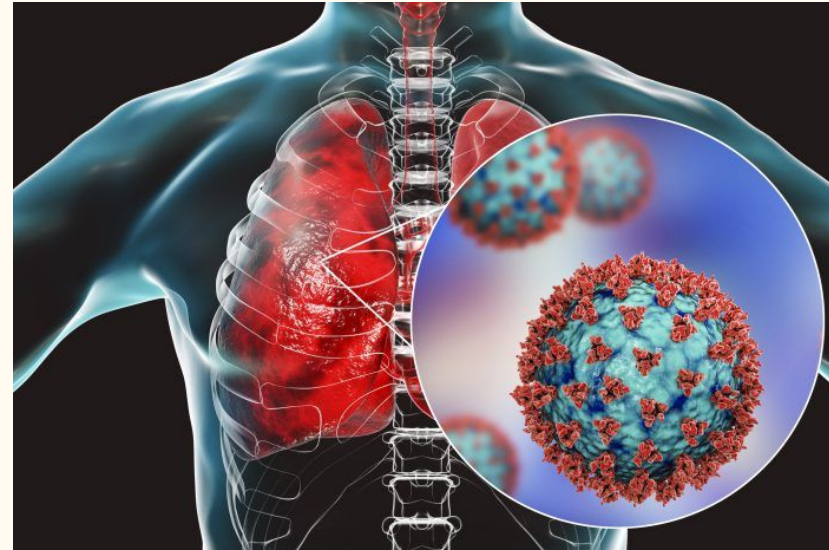
QUESTIONS?

COVID-19 AND LUNG CANCER

EPID 6223:Chronic Disease Epidemiology
Spring 2021
Sarah Grunblatt, MS, MS, MEd, MEd, MA

https://www.clinicalomics.com/topics/patient-care/coronavirus/lung-cerebral-organoids-reveal-responses-to-sars-cov-2-infection/

DOES COVID-19 INCREASE THE ODDS OF LUNG CANCER IN NEVER-SMOKERS?

- **CONFOUNDING:** The CDC explains that "cigarette smoking is the number one risk factor for lung cancer. In the United States, cigarette smoking is linked to about 80% to 90% of lung cancer deaths."
  - Because there is already a known and very significant risk for developing lung cancer as a result of smoking, this population (ever-smokers) will be excluded entirely in order to rule smoking out as a confounder.
- **STUDY DESIGN:** Case-Control
- **EXPOSURE VARIABLE: COVID-19** (severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2)
  - COVID-19 is an infectious disease caused by a newly discovered coronavirus.
  - Most people infected with the COVID-19 virus will experience mild to moderate respiratory illness.
  - It seems that many people have lasting adverse health effects and/or permanent lung damage following a case of COVID-19.
- **OUTCOME VARIABLE: Lung Cancer**
  - Lung cancer is out of control cell growth that originated in the lungs of the body.
  - Lung cancer is the leading cause of death among all cancers globally.
- **CONNECTION:**
  - COVID-19 and lung cancer share common symptoms, diagnostic criteria, and management.
  - **Both COVID-19 and lung cancer primarily impact the same organ system with the human body.**
  - Recent research shows that there may be a higher risk of COVID-19 in lung cancer patients and for the symptoms to be more severe.
- **PUBLIC HEALTH CONCERN/IMPACT:**
  - COVID-19 has been one of the worst global pandemics. According to the WHO there have been more than 140 million cases and 3 million deaths (as of April 2021).
  - Lung cancer already has the highest mortality of all cancers globally.
  - It is still too early to know, but what about the COVID-19 as the exposure?
  - Is COVID-19 going to make these statistics even worse?
  - Are people now more susceptible to lung cancer?
  - **Is it possible that COVID-19, which primarily negatively impacts the respiratory system and (possibly permanently) damages the lungs, might cause early-onset, more severe, and/or increased incidence of lung cancer?**

https://www.clinicalomics.com/topics/patient-care/coronavirus/lung-cerebral-organoids-reveal-responses-to-sars-cov-2-infection/