**Literature Review Summaries & Relevant Notes to Study**

*Effects of COVID-19 on Cancer Patients and Vice Versa*

Passaro A. Testing for COVID-19 in lung cancer patients. Annals of Oncology; published online April 9, 2020. <https://doi.org/10.1016/j.annonc.2020.04.002>

* Fatality rate is significantly higher for those with underlying diseases like C disease, diabetes, cancer, and old age. CFR in China was 2.3%, but 7.2% in Italy, suggesting that it’s more serious in Caucasian populations. Specifically higher for older patients. However, this is unreliable because Italy restricted testing to those who had symptoms, this **paper advocates to test lung cancer patients with a priority**
* Smokers are 1.4 times more likely to develop severe symptoms than non-smokers
* “Structural and immunologic-induced modifications are the two main tobacco-related damages accounting for susceptibility to infections. Peribronchiolar inflammation and fibrosis facilitate pathogen adherence and potentially amplify pulmonary inflammation.7 In addition, changes in humoral, macrophage and cell-mediated immune response may aggravate the immunosuppressive effect.8,9 It has been postulated that prior tobacco-related lung damage, including chronic obstructive pulmonary disease (COPD) and lung cancer, additionally predispose to more severe COVID-19 complications”
* “While all types of malignancies seem to be associated with high COVID-19 prevalence, morbidity and mortality, lung cancer represents a specific scenario of cumulative risk factors for COVID-19 complications, including older age, significant cardiovascular and respiratory co-morbidities, smoking-related lung damage, as well as the unavoidable addition of treatment-related immune impairment or suppression.”
* Lung surgery, defective pulmonary organs/ airways,
* “Changes in the anatomy of airway and pulmonary tissue lead to intratumoral and peritumoral microenvironment alteration, which may secondarily affect immune cell infiltration characterized by an increase in macrophages and inflammation. The presence of macrophage infiltration in lung tissue poses a higher risk for cytokine release. During SARS-CoV-2 infection, massive cytokine release has been postulated to be the major step in leading to the development of ARDS (Acute respiratory distress syndrome)”
* Lung cancer patients also use corticosteroids for treatment, which reduces inflammation and immune cellular activity – this can be very dangerous when a patient is battling with corona.

Lee L, Cazier JB, et al. COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study. *Lancet*; published online May 28, 2020. <https://doi.org/10.1016/S0140-6736(20)31173-9>

* On March 18, 2020, created the UK Coronavirus Cancer Monitoring Project (can be found online), which is the largest database of patients with cancer who had symptomatic COVID-19 at the time of publishing.
* Purpose was to look at how having cancer as well as chemotherapy and other anticancer treatments affect COVID-19 patients as these attack cells.
* Cancer patients defined to be those with metastatic cancer or on anticancer treatment in any setting or treated within last 12 months with surgery cytotoxic chemotherapy/ radiotherapy.
  + 11% were lung cancer
* Only 21% had only cancer, the rest had other comorbidities like hypertension, diabetes and CV disease
* Those who died had higher rates of being male, elderly, and having comorbidities
* 22% of the patients had their anticancer treatments interrupted by COVID-19
* COVID-19 patients with cancer who had received chemotherapy within the 4 weeks of testing positive did NOT have a higher death rate than those who hadn’t had chemo. This was also true after accounting for adjustments in age, gender, and comorbidities (the ones receiving chemo were younger). Also true for cancer patients not on versus cancer patients on immunotherapy, hormonal therapy, radiotherapy, and targeted therapy.
* Disruption from COVID-19: increasing concern from patients about their perceived vulnerability, cancelled cancer operations, drive toward telemedicine. Also a lot of oncologists have to do COVID-19 related activities.

The Lancet Oncology. COVID-19: global consequences for oncology. *Lancet Oncol* 2020; **21**: 467

* Cancer patients are vulnerable to infection because they already have an illness and are immunosuppressed. Therefore, they’re more likely to have potentially deadly complications.
* COVID-19 may be prioritized, delating cancer treatments. In addition, cancer patients may not be able to ravel to appointments/ get medicine due to quarantines.
* Operations and some types of cancer treatment/ appointments are being cancelled/ postponed to prioritize hospital beds for those with COVID-19.
* Many research institutions/ meetings are being transferred to an online setting

Yang K, Sheng Y, Huang C, Xiong N, Jieng K, Lu H. Clinical Characteristics, outcomes, and risk factors for mortality in patients with cancer and COVID-19 in Hubei, China: a multicentre, retrospective, cohort study. *Lancet Oncol*; Published online May 29, 2020.

* 205 patients with laboratory-confirmed COVID-19 and a malignant tumor in 9 hospitals in Hubei, China from 1/3 to 3/18 all of whom either recovered or died.
  + Those with benign tumors were excluded
* [Cancer patients] “are often immunosuppressed because of their underlying illness, poor nutrition, and treatment-related side-effects. Therefore, they are at increased risk of opportunistic infections, developing severe complications, requiring admission to an intensive care unit (ICU), or even death”
* Those who didn’t survive had higher respiratory rates and lower levels of blood oxygen saturation. Shortness of breath and dsypnea were significantly more common in non-surivovrs. No significant differences in age and other comorbidities.
  + This means **that having hypertension as a cancer patient didn’t increase the cancer patens’ death rates according to this study?**
* Those who didn’t survive had higher NLR, creatinine, blood, urea, nitrogen, C-reactive protein, platelet counts, etc.
* Found that **people who had received chemotherapy within 4 weeks before symptom onset had a higher rate of passing away (p = 0.026).**
* This study seems quite small and maybe not the most reliable?

Kuderer NM, Choueiri TK, Shah DP, Shyr Y. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*; published online May 28, 2020. <https://doi.org/10.1016/S0140-6736(20)31187-9>

* Used SEER registries of 18 states for the diagnosis years of 2000-2011
  + 612 counties
  + 28% of US population
  + Split into two time periods for random effect regression models as opposed to looking at each year which would assume a linear relationship over time
* County-level data not individual data was used for most of the environmental factors such as smoking, socioeconomic status, etc.
  + **TCR data has interesting individual level data**
* Incidence rates age-adjusted by the census 2000 US population
* **Temporal analysis**: time trend plots and maps of age-adjusted rates for area, gender, and histologic type. Significance was tested through a joinpoint regression analysis (finds the number of areas where trends change) using a monte carlo permutation method
  + <https://surveillance.cancer.gov/joinpoint/>
* Random effects generalized linear mixed model fit with 11 variables (race, % of physicians, % of smokers, etc.), two-way interactions, and spatial random effects for county-level variables. Assessed by AIC and pseudo R­2.
  + Lung cancer incidence rates weighted in the model by county population in order to account for the differences for large and small counties.
  + Separate models by gender and histologic type
  + Two-way interactions were selected through the **elastic net approach, a weighted-average of the least absolute shrinkage and selection operator (LASSO), and Ridge regression variable selection methods.**
* Temporal trends/ racial pattersn similar to what has been observed in previous studies
* Countiies with higher current smoking and family poverty were strongly associated with higher risk of lung cancer for all genders and types. Counties with more diagnostic radiologists were associated with higher TLC rates (p <0.03), and counties with greater primary care physician access were associated with lower TLC rates.
* “TLC incidence rates were higher in eastern and southern states than western areas. Male rates were higher than female rates along the West Coast. Males and females had similar small cell rate patterns, with higher rates in the Midwest and southeast. Squamous cell carcinoma and adenocarcinoma rate patterns were similar to TLC patterns, except for relatively higher female adenocarcinoma rates in the northeast and northwest.”
* Major strength is the new, larger, updated, and high quality data

*Spatiotemporal Relationships Regarding COVID-19*

*Spatiotemporal Relationships Regarding Lung Cancer*

Christian WJ, et al. Spatiotemporal Analysis of Lung Cancer Histological Types in Kentucky, 1995-2014. *Cancer Control*, Vol 26: 1-8. March 21, 2019. DOI: 10.1177/1073274819845873

* US: lung cancer has the second highest incidence rate and highest mortality of all cancers
* Wanted to investigate spatiotemporal relationships between high obesity, high smoking, high poverty, and lung cancer in the state of Kentucky.
* Collected data on the prevalence of smoking and obesity in various counties in Kentucky.
* Analysis involved a **spatial span statistic** which identifies clusters of a certain disease/ condition/ behavior. They “compare the rate of an event within a large number of candidate clusters which are determined by drawing concentric circles around a specified set of event locations or regular grid points to the corresponding rate outside each candidate cluster.”
  + **Clustering analysis will be useful because corona tends to spread via clusters, communities tend to be hit hardest b/c it’s so contagious**, whereas cancer isn’t necessarily as contagious but also tends to be studied in clusters according to this study.
* Used a multinomial model to see if there were regional differences in the proportions of the 4 types of lung cancer (by histology which is cell appearance) relative to each other.
  + Identified one region with significantly different proportions. Higher adenocarcinoma (not from smoking) cancer.
* 4 poisson-based spatiotemporal scan statistics were then used to analyze each type of lung cancer
* **Look into whether Texas had data regarding the 4 types of lung cancer as this may give important information regarding the “whys” for rates in certain regions**

Hosgood HD 3rd, Farah C, Black CC, Schwenn M, Hock JM. Spatial and temporal distributions of lung cancer histopathology in the state of Maine. Lung Cancer. 2013; 82(1):55‐62. doi:10.1016/j.lungcan.2013.06.018

* Several environmental factors have been changing such as increasing risk of the danger of tobacco and protections against radon.
* “Used a **spatial span statistic assuming a discrete Poisson distribution** adjusted for age and population density”
* Certain types of cancer were the same throughout Maine, but adenocarcinoma among women and squamous cell among men were high
  + Higher rates of large cell lung cancer in one of the poorest counties in the US

Lewis DR, Pickle LW, Zhu L. Recent Spatiotemporal Patterns of US Lung Cancer by Histologic Type. Front Public Health. 2017; 5:82. Published 2017 May 19. doi:10.3389/fpubh.2017.00082

*Investigating Demographic (i.e. race & gender) patterns*

Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020. MMWR Morb Mortal Wkly Rep. ePub: 15 June 2020. DOI: <http://dx.doi.org/10.15585/mmwr.mm6924e2>

Lewis DR, Check DP, Caporaso NE, Travis WD, Devesa SS. US lung cancer trends by histologic type. Cancer. 2014;120(18):2883-2892. doi:10.1002/cncr.28749

* 95% and 90% of the risk for lung cancer for, respectively, men and women, result from smoking. Rest is attributable to chemicals, radon, asbestos, hormonal factors, secondhand smoke, arsenic, infections and inflammatory processes
* Histologic types investigated include
  + Squamous cell carcinoma
  + Small cell carcinoma
  + Adenocarcinoma
  + Large cell carcinoma
  + Other specific carcinoma
  + Unspecified types
* Methods: omitted cases that were noncarcinomas or metastatic type. Calculated incidence counts, rates per 100,000; incidence rate ratios (IRRs) and 95% CI’s.
* For all racial groups, rates have been declining for males and famles have been plateauing, so they’re approaching each other. Squamous and small cell have been decreasing for both genders.
* Adenocarcinoma are increasing among females while declining among men
* Trends in smoking rates are very similar to those of age-adjusted lung cancer rates
* The introduction of filters changed the way that cigarette smoke was inhaled which changed the histologic lung cancer type that formed.

Houston KA, Mitchell KA, King J, White A, Ryan BM. Histologic Lung Cancer Incidence Rates and Trends Vary by Race/Ethnicity and Residential County. J Thorac Oncol. 2018; 13(4):497-509. doi:10.1016/j.jtho.2017.12.010

* Main types of lung cancer are
  + SCLC
    - 10-15%
    - More strongly associated with cigarette smoking
  + NSCLC (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma)
    - 85%
    - Squamous cell carcinoma more strongly associated with cigarette smoking
* NH blacks have higher rates of lung cancer than NH whites despite having lower smoking rtes and later ages of smoking initiation and lower numbers of cigarettes smoked per day
  + Perhaps a result of other environmental exposures like radon, pollution, exposure to asbestos, ambient air quality, pesticides, diesel, additional pollutants, etc.
* Highest rates in the south, highest adenocarcinoma rates in the Northeast
* Higher altitudes associated with reduced lung cancer incidence
* Used **rural urban continuum codes (RUCC)** in order to quantify the rurality/ urbanization of various counties as well as their proximity to other metropolitan/ urban counties
* All except SCLC (higher for whites) were higher among blacks for both genders younger than 55 years.
* **Squamous cell**: higher in adjacent metropolitan and nonadjacent counties than for those living in metropolitan counties. Difference between rates among black and white men increased as they got closer to metropolitan areas. Declining rates overall especially those in metropolitan counties.
* **SCLC**: Declining rates overall especially those in metropolitan counties. Lower incidence in NH blacks and Hispanic adults than in NH whites
* **Adenocarcinoma**: significantly higher among NH black than NH white men in metropolitan counties and counties not adjacent to metropolitan counties with the difference increasing with rurality.
* **Large cell lung cancer**: significantly higher in nonmetropolitan counties than in metropolitan counties
* Overall, the higher incidence of lung cancer in black men than white men is observed in metropolitan and nonadjacent counties, with the difference increasing the further the county is from metropolitan areas
* Limited studies on smoking. “smoking is a very complex exposure to capture. In addition to status (i.e., current smoker, former smoker, and never-smoker), dose (cigarettes per day), duration, age at initiation, time to first cigarette, and daily versus nondaily use are key aspects of smoking relevant to its relationship with cancer. Moreover, depth of inhalation, smoking efficiency, type of tobacco (filtered, menthol, smokeless, etc.), are all factors that likely contribute to the complex relationship between smoking, lung cancer, and racial disparities.”
* **Use page 4 table to determine how to mathematically account for demographic difference between counties at the national level – can do comparison of counties to Texas numbers as well as at the country wide level**

*Modeling structures & Statistical Analyses to be Utilized*

Moraga, Paula. *Geospatial Health Data: Modeling and Visualization with R-INLA and Shiny*

All notes are hand-written/ hi-lighted within the book

Melin, P, Monica JC, Sanchez D, Castillo, O. Analysis of Spatial Spread Relationships of Coronavirus (COVID-19) Pandemic in the World Using Self Organizing Maps. *Elsevier*; May 18 2020. <https://doi.org/10.1016/j.chaos.2020.109917>

* Used **unsupervised neural network called self-organizing map** to create country **clusters** defined by the number of COVID-19 cases they had for confirmed cases, recovered cases, and deaths.
  + Used when identifying groups in a dataset without having to use traditional statistical techniques. Used to find patterns in high-dimensional datasets.
* Repeated for the states in Mexico as well as for hypertension and diabetes rates in the states of Mexico. Comparing the way things were clustered, there was a relationship between the states with
  + higher numbers of deaths and states with higher numbers of hypertension
  + higher numbers of deaths and states with higher numbers of diabetes cases

Li, J., Guo, W., Ran, J. et al. Five-year lung cancer mortality risk analysis and topography in Xuan Wei: a spatiotemporal correlation analysis. BMC Public Health 19, 173 (2019). <https://doi.org/10.1186/s12889-019-6490-1>

* Very thorough and deep analysis of one particular county in China
* Hot spot analysis conducted by calculating a getis-ord gi\* statistic on the ARCgis software which is a software for working with maps and geographical information
  + Lung cancer mortality hotspots were areas where there with lots of coal mining/ large population densities
* Conducted a regression analysis where y was the lung cancer mortality rate and the independent variables were indexes such as coal mine productivity/ parameters that are specific to certain locations
* Created “categories” in the region based on the population-level health risk