GEOGRAPHIC VARIATION IN CHEST-CT SCAN LUNG CANCER DIAGNOSIS FROM ENVIRONMENTAL EXPOSURES

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Geographic variation in CT-scan lung cancer diagnosis from environmental exposures

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ABSTRACT

Chest CT scans allow radiologists to obtain a more detailed and thorough image compared to chest x-rays; therefore, chest CT scans frequently detect small suspicious non-urgent indeterminate pulmonary nodules. The goals of managing suspicious non-urgent indeterminate pulmonary nodules are early cancer detection, avoidance of unnecessary procedures for benign nodules, and efficient economic use of resources in distinguishing between benign and malignant nodules. The interpretation of these small suspicious non-urgent indeterminate nodules can vary. One reason that there may be variability in the interpretation of chest CT scan results is prior exposure to fungal lung infection causing spores such as histoplasmosis and coccidioidomycosis. This

dissertation first focuses on quantifying levels of exposure of histoplasmosis and coccidioidomycosis across the US more precisely. Second, we examine how histoplasmosis endemicity and exposure is associated with the detection and follow-up of suspicious non-urgent indeterminate pulmonary nodules on diagnostic chest-CT scans. Lastly, we quantify the costs of the imaging and follow-up of suspicious non-urgent indeterminate pulmonary nodules. The financial and health outcomes of this study may influence imaging procedure and policy prioritization for healthcare providers and health system decision makers.

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CHAPTER 1: INTRODUCTION

Radiographic chest imaging, including chest x-ray and chest computed tomography (CT) scans, is the most common outpatient diagnostic imaging study performed in the United States.[1,2] Chest CT scans are commonly used for a range of diagnostic purposes including for a variety of non-specific symptoms such as shortness of breath, chest pain, and suspected pulmonary embolism. A 2009 study found that additional imagining recommended after diagnostic chest CT scans was associated with a high diagnostic yield of clinically relevant findings; in fact, one in every thirteen diagnostic chest CT scans yielded a previously unknown malignancy.[1]

Chest CT scans allow radiologists to obtain a more detailed and thorough image compared to chest x-rays; therefore, chest CT scans frequently detect small suspicious non-urgent indeterminate pulmonary nodules. These nodules have the appearance of malignancies but remain unchanged. Small suspicious non-urgent indeterminate pulmonary nodules are usually defined as a single nodule (or an abnormality) that is less than 1 centimeter in diameter. Although most of these small suspicious non-urgent indeterminate pulmonary nodules never progress to lung cancer, clinical guidelines call for surveillance with repeat imaging for up to two years after detection to determine the stability of the nodule and likelihood of lung cancer.[3–6] Estimates of suspicious pulmonary nodule findings requiring surveillance or follow-up have ranged widely from 16% to 60% in cohorts of individuals undergoing diagnostic or screening chest CT imaging, and less than 10% of these individuals are subsequently diagnosed with lung cancer.[4,7,8] The goals of managing suspicious non-urgent indeterminate pulmonary nodules are early cancer detection, avoidance of unnecessary procedures for benign

nodules, and efficient economic use of resources in distinguishing between benign and malignant nodules.[5,9,10] Many individual-level factors contributing to the risk of malignancy for these suspicious non-urgent indeterminate nodules have to also be taken into consideration in managing these nodules, such as smoking history.[10–12] Gaps in follow-up of suspicious non-urgent indeterminate findings could lead to missed opportunities to treat early lung cancer while it has a higher likelihood of being curable.[6,13] However, the interpretation of these small suspicious non-urgent indeterminate nodules is variable, depending on a variety of factors including radiologist experience, quality of the diagnostic imaging, and condition of the patient's lungs. This variability in turn leads to false positives (a pulmonary nodule finding that is not later diagnosed as cancer).

One reason that there may be variability in the interpretation of chest CT scan results is because of differences in the underlying lung anatomy of various populations of patients. Prior exposure to fungal lung infection causing spores is one contributing factor to these potential differences. The two major fungal lung infections found in North America include histoplasmosis and coccidioidomycosis. Both of these infections are acquired through inhalation of spores in the environment and are associated with outdoor activities and geographic exposures.[14] With an estimated 50 million individuals in the US infected, histoplasmosis is the most prevalent of the two endemic fungal lung infections.[15] In endemic areas, up to eighty percent of the area population may be infected, with a majority of individuals being asymptomatic.[14,16] Because histoplasmosis causing spores are found in nitrogen rich soil, particularly soil that contains avian or bat feces, histoplasmosis is endemic across the Ohio, Mississippi, Missouri, Tennessee,

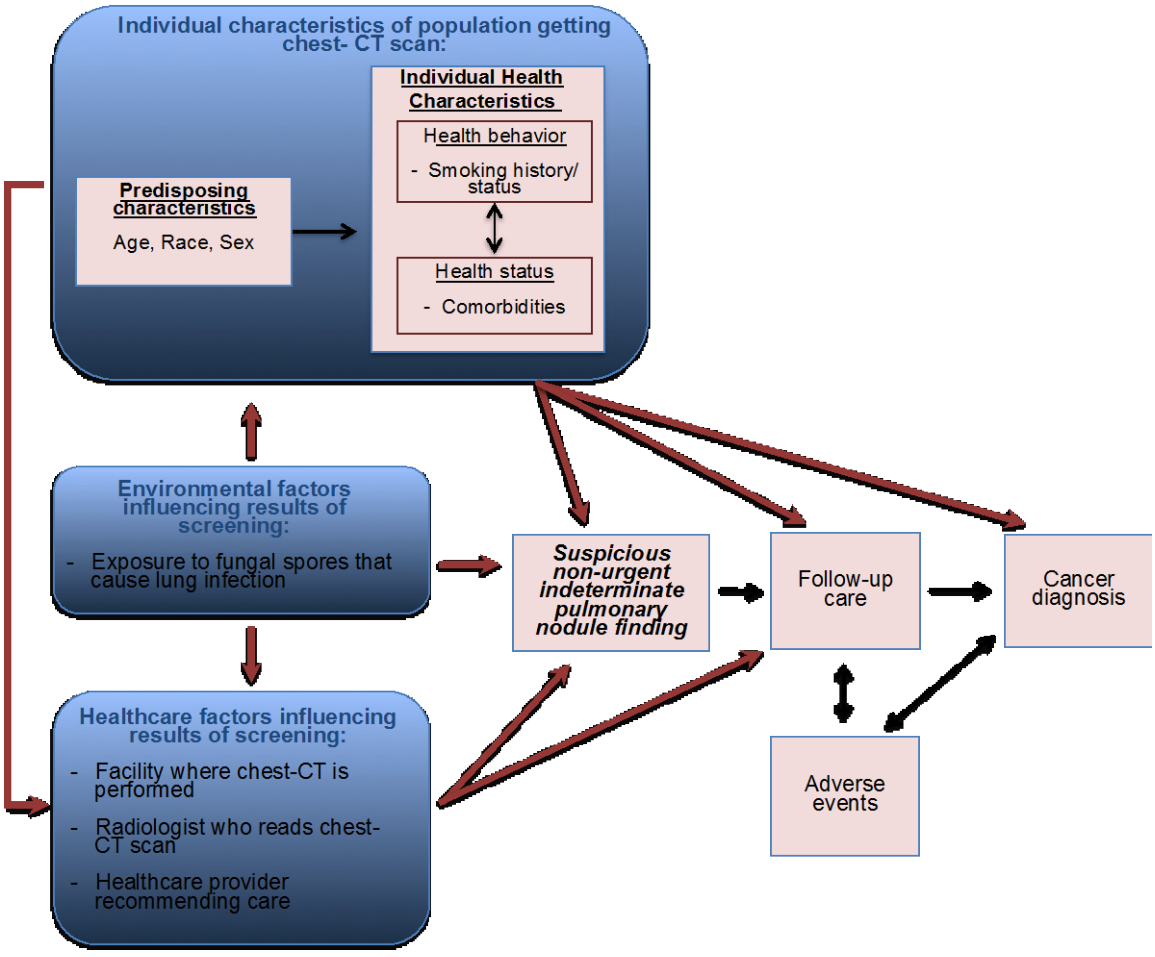
and St. Lawrence River valleys.[14,17,18] Coccidioidomycosis causing fungal spores thrive in areas characterized by hot summers and mild winters, annual rainfall of 10–50 cm, and in alkaline sandy soil; therefore, it is endemic to the southwestern region of the US.[19] There are an estimated 300,000 new infections in the US every year.[19] Coccidioidomycosis can be costly, with nearly 75% of patients missing work or school because of their illness, and more than 40% requiring hospitalization.[20]

A majority of individuals infected with either of these endemic fungal lung infections are either asymptomatic or experience such mild symptoms that they do not realize they are infected.[15,16,19,20] This makes it difficult to measure population infection and exposure rates. Moreover, granuloma inflammation, caused by histoplasmosis and coccidioidomycosis, can look identical to suspicious non-urgent indeterminate pulmonary nodules on a chest CT scan and retain all the hallmarks of a suspicious nodule finding including growth on repeated CT scans and lack of calcification.[21] A 2011 study found that in areas with a high prevalence of histoplasmosis, 61% of baseline screening chest CT scans were positive, but of those positive scans, only 9% were actually later diagnosed with lung cancer.[22,23] This is concerning given, there is risk that a patient could go through a cascade of follow-up procedures including surgery where they are at risk of harm from these procedures including a higher risk of mortality.

Prior studies that have included fungal lung infection rates in their analyses, have not used very precise measures, since detailed epidemiological information about geographic distribution and the prevalence of fungal lung infections are not routinely available.[22–24] This dissertation first focuses on quantifying levels of exposure of histoplasmosis and coccidioidomycosis across the US more precisely. Second, we

examine how histoplasmosis endemicity and exposure is associated with the detection and follow-up of suspicious non-urgent indeterminate pulmonary nodules on diagnostic chest-CT scans. Lastly, we quantify the costs of the imaging and follow-up of suspicious non-urgent indeterminate pulmonary nodules. The financial and health outcomes of this study may influence imaging procedure and policy prioritization for healthcare providers and health system decision makers.

Conceptual framework



To understand how environmental exposures influence imaging outcomes, I have provided a figure to explain the conceptual framework that is the basis of this

dissertation. This conceptual model is based on Andersen and Aday's *Behavioral Model of Health Services Use* and includes factors that contribute to the risk of suspicious non-urgent indeterminate pulmonary nodule findings and lung cancer diagnosis.[6,12,25,26] I formed the conceptual framework around Andersen's model because it takes into consideration how the external environment and the healthcare setting can influence a person's health and outcomes. As shown in the figure, pre-disposing characteristics influence an individual's health characteristics. These health characteristics, such as smoking, comorbidities, and other health problems, put the individual at a higher risk for lung cancer and increase the likelihood of a suspicious pulmonary nodule finding on a chest CT scan. We take these factors into account since patients at higher risk will cause healthcare providers to interpret imaging results with more caution and recommend more aggressive nodule management, even for a suspicious non-urgent indeterminate pulmonary nodule finding.[10–12] Environmental factors can also directly influence diagnostic chest CT scan findings since fungal lung infections can mimic lung cancer related abnormalities on CT imaging tests. Healthcare factors can also influence diagnostic chest CT scan results. Different health care providers who assume the responsibility for further evaluation and treatment of the suspicious non-urgent indeterminate pulmonary nodule finding may have different approaches to interpreting chest CT scans and follow-up care for the management of non-urgent nodules. Level of experience, judgment, and even the facility/practice could all influence their recommendations.[9,27] These healthcare provider factors are harder to measure and control in studies using claims-level data.

The factors that may influence the interpretation of a chest CT scan leads to variation in follow-up, detection of lung cancer, and possibly adverse events for patients with suspicious non-urgent indeterminate pulmonary nodule findings. Thus, individual characteristics, environmental exposures and variation in healthcare factors (e.g. radiologist interpreting scan results or hospital/practice trends for pulmonary follow-up) can all influence how frequently suspicious non-urgent indeterminate pulmonary findings are identified and managed.

Overview of research objectives

The goal of this dissertation is to explore the relationship between environmental exposure and diagnostic chest CT scan outcomes. The three aims are as follows:

1. To quantify levels of exposure of Histoplasmosis and coccidioidomycosis across the US at the VA planning sector level so that we can better estimate which individuals, based on geographic residence, are more likely to have been exposed to Histoplasmosis and coccidioidomycosis and are therefore at higher risk of adverse health outcomes that are influenced by these exposures.
2. To examine if greater histoplasmosis endemicity is associated with increased detection of suspicious non-urgent indeterminate pulmonary nodule findings on diagnostic chest-CT scans. Furthermore, to evaluate if histoplasmosis endemicity is associated with variation in lung cancer detection rates among those with suspicious non-urgent indeterminate pulmonary nodule findings.
3. To examine if greater histoplasmosis endemicity is associated with an increased number of follow-up procedures and total costs incurred over a 2-year

follow-up period for those with a suspicious non-urgent indeterminate pulmonary nodule following a diagnostic chest-CT scan.

References

1. Harvey HB, Gilman MD, Wu CC, et al. Diagnostic yield of recommendations for chest CT examination prompted by outpatient chest radiographic findings. *Radiology*. 2015;275(1):262-271. doi:10.1148/radiol.14140583.
2. Sistrom C, Dreyer K, Dang P. Recommendations for additional imaging in radiology reports: multifactorial analysis of 5.9 million examinations. *Radiology*. 2009;253(2):453-461.
3. Moyer V. Screening for lung cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(5):330-338. http://annals.org/article.aspx?articleID=1809422&csrt=1232520229353768527. Accessed November 3, 2014.
4. Black W. Computed tomography screening for lung cancer: review of screening principles and update on current status. *Cancer*. 2007;110(11):2370-2384. doi:10.1002/cncr.23059.
5. Wahidi M, MGovert J, Gouda R, McCrory D. American College of Chest Physicians Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132:94S - 107S.
6. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: When is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 SUPPL):e93S - e120S. doi:10.1378/chest.12-2351.
7. Silvestri G. Screening for lung cancer: it works, but does it really work? *Ann Intern Med*. 2011;155(8):537-540. http://annals.org/article.aspx?articleid=474996. Accessed November 3, 2014.
8. Wiener RS, Gould MK, Woloshin S, Schwartz LM, Clark JA. What do you mean, a spot?: A qualitative analysis of patients' reactions to discussions with their physicians about pulmonary nodules. *Chest*. 2013;143(3):672-677. doi:10.1378/chest.12-1095.
9. Cooper JD. Management of the solitary pulmonary nodule: Directed resection. *Semin Thorac Cardiovasc Surg*. 2002;14(3):286-291. doi:10.1053/stcs.2002.33430.
10. MacMahon H, John M Austin BH, Gamsu G, et al. Guidelines for Management of Small Pulmonary Nodules Detected on CT Scans: A Statement from the Fleischner Society. *Radiology*. 2005;237:395-400. doi:10.1148/radiol.2372041887.
11. Swensen S, Silverstein M, Lstrup D. The probability of malignancy in solitary pulmonary nodules. Application to small radiologically indeterminate nodules. *Arch Intern Med*. 1997;157(8):849-855.
12. Memorial Sloan Kettering Cancer Center. Lung Cancer Screening Decision Tool. http://www.mskcc.org/cancer-care/adult/lung/screening-decision-tool.
13. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. *Jama*. 2012;307(22):2418-2429. doi:10.1001/jama.2012.5521.
14. Lenhart S, Schafer M, Singal M, Hajjeh R. *Histoplasmosis: Protecting Workers at Risk*.; 2004.

15. Baddley J, Winthrop K. Geographic distribution of endemic fungal infections among older persons, United States. *Emerg Infect Dis*. 2011;17(9):7-12.
16. Gurney JW, Conces DJ. Pulmonary histoplasmosis. *Radiology*. 1996;199(212):297-306. doi:10.1136/thx.5.4.333.
17. Miller W. Thoracic Fungus Infections. In: *A Radiologic Approach to Disease of the Chest*.; 1997:481-501.
18. Smith JA KC. Pulmonary fungal infections. *Respirology*. 2012;(17):913-926.
19. Chu JH, Feudtner C, Heydon K, Walsh TJ, Zaoutis TE. Hospitalizations for endemic mycoses: a population-based national study. *Clin Infect Dis*. 2006;42(6):822-825. doi:10.1086/500405.
20. Centers for Disease Control and Prevention. *Increase in Reported Coccidioidomycosis--United States, 1998-2011.*; 2013. doi:10.1097/INF.0b013e31829e7a5c.
21. Sharma P, Mukherjee A, Karunanithi S, Bal C, Kumar R. Potential Role of 18F-FDG PET/CT in Patients With Fungal Infections. *Am J Roentgenol*. 2014;203(1):180-189. doi:10.2214/AJR.13.11712.
22. Starnes SL, Reed MF, Meyer C a, et al. Can lung cancer screening by computed tomography be effective in areas with endemic histoplasmosis? *J Thorac Cardiovasc Surg*. 2011;141(3):688-693. doi:10.1016/j.jtcvs.2010.08.045.
23. Aberle D, Adams A, Berg C. Reduced lung-cancer mortality with low-dose computed tomographic screening. *New Engl …*. 2011;365(5):395-409. http://europepmc.org/abstract/MED/21714641. Accessed December 28, 2014.
24. Singh S, Pinsky P, Fineberg N, Gierada D. Evaluation of reader variability in the interpretation of follow-up CT scans at lung cancer screening. *Radiology*. 2011;259(1):263-270. doi:10.1148/radiol.10101254/-/DC1.
25. Andersen RM. Revisting the Behavioral Model and Access to Medical Care: Does it Matter? *J Health Soc Behav*. 1995;36:1-10. http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Reproduced+with+permission+of+the+copyright+owner.+Further+reproduction+prohibited+without+permission.#1. Accessed January 11, 2013.
26. Cassidy A, Duffy SW, Myles JP, Liloglou T, Field JK. Lung cancer risk prediction: A tool for early detection. *Int J Cancer*. 2007;120(August):1-6. doi:10.1002/ijc.22331.
27. Pinsky PF, Gierada DS, Nath PH, Kazerooni E, Amorosa J. National lung screening trial: variability in nodule detection rates in chest CT studies. *Radiology*. 2013;268(3):865-873. doi:10.1148/radiol.13121530.

CHAPTER 2- Geographic variation in outpatient visit rates for histoplasmosis and coccidioidomycosis in the VA setting

Abstract

Background

Some geographic regions in the US are known to have high levels of exposure to fungal lung infections including histoplasmosis and coccidioidomycosis. Epidemiological data describing endemicity levels of these exposures have only been available at broader geographic areas such as states. The purpose of this paper is to quantify endemicity of histoplasmosis and coccidioidomycosis at more precise geographic levels by using detailed electronic medical record data from the largest integrated health care system in the US– the Veterans Health Administration (VHA).

Methods

Counts of unique VHA users with at least one outpatient histoplasmosis or coccidioidomycosis visit were identified for a 10-year period between fiscal years 2006-2015. The primary unit of geographic analysis was VHA planning sectors, which are geographic areas with uniform population densities based on US county borders. An average outpatient visit rate for each county-based sector was calculated using a person-year approach as the total number of histoplasmosis or coccidioidomycosis cases in the 10 year period in each sector divided by the total number of unique outpatient VHA users in 10 years in each sector. Annual rates are reported per 10,000 person-years.

Results

Between 2006 and 2015, the overall average national rate of outpatient visits for histoplasmosis was 7.99 per 10,000 person-years and 0.99 per 10,000 person-years for coccidioidomycosis. Ohio had the sector with the highest national histoplasmosis outpatient visit rate, 67.5 per 10,000 person-years, and a state rate range of 2.6 to 67.3 per 10,000 person-years. Arizona had the sector with the highest national coccidioidomycosis outpatient visit rate, 69.1 per 10,000 person-years, with a state range of 9.1 to 69.1 per 10,000 person-years.

Conclusions

Outpatient visit data provide a novel way to quantify endemicity of fungal lung infections. These data demonstrate there is considerable geographic variation in endemicity of fungal lung infections within county-based geographic areas in the U.S.. Rates should not be considered constant within a state, even in traditionally known endemic states.

Background

The two most common mycotic lung infections found in North America are histoplasmosis and coccidioidomycosis.[1] They are acquired through inhalation of mycotic spores in the environment and are associated with outdoor activities and geographic exposures.[1] Histoplasmosis is the more prevalent of the two endemic mycotic lung infections with an estimated 50 million individuals in the US infected. In endemic areas up to eighty percent of the area population may be infected.[1,2] Because histoplasmosis causing spores are found in nitrogen rich soil, particularly soil that contains avian or bat feces, histoplasmosis is endemic across the Ohio, Mississippi, Missouri, Tennessee, and St. Lawrence River valleys[1,3,4]. Coccidioidomycosis, also known as valley fever, is endemic in the southwestern region of the US. Coccidioidomycosis causing fungal spores thrive in areas characterized by hot summers and mild winters, annual rainfall of 10–50 cm, and in alkaline sandy soil.[5] In the southwestern US, an estimated 300,000 individuals are newly infected with Coccidioidomycosis every year.[5]

A majority of individuals infected with either of these endemic fungal lung infections are asymptomatic or experience such mild symptoms they do not realize that they are infected.[2,5–7] This makes it difficult to measure true infection and exposure rates for histoplasmosis and coccidioidomycosis. Therefore, detailed epidemiological information about geographic distribution, prevalence, or endemicity of histoplasmosis and coccidioidomycosis are not routinely available. A 2006 report describing nationally representative histoplasmosis and coccidioidomycosis hospitalization rates in children and adults used the Nationwide Inpatient Sample(NIS) database and US census

regions to describe geographic distribution.[5] Hospitalization is a rare outcome for these fungal lung infections; inpatient rates only capture the most severe infections and may miss more minor infections for which patients seek treatment but are not hospitalized.[4] A more recent 2011 paper, using Medicare inpatient admissions data, described state level geographic distribution of endemic mycoses in older adults, ≥65 years old.[7].The use of outpatient records from large health plans such as the Veterans Health Administration (VHA) provides the ability to examine smaller units, such as county level rates. Endemicity levels for smaller areas provides information to more closely approximate an individual patient's likely risk of lifetime exposure to fungal lung infection and can give health care providers more clarity in planning care, as well as provide insight into high levels of variation in rates of related conditions such as hemoptysis (coughing up blood) or incidentally detected pulmonary nodules.

The objective of this paper is to identify the smallest meaningful geographic level of endemicity for histoplasmosis and coccidioidomycosis across the US so that we can better estimate which individuals, based on geographic residence, are more likely to have been exposed to histoplasmosis and coccidioidomycosis and are therefore at higher risk of health outcomes that are influenced by these exposures. In order to do so, we report outpatient visit rates at the county level and describe variation in geographic distribution of histoplasmosis and coccidioidomycosis using VHA outpatient data for adults' ≥18 years old.

Methods

We examined outpatient encounters among VHA users with at least one outpatient visit occurring at any of VHA's national 168 medical centers or 1,047 outpatient facilities during ten fiscal years, 2006-2015.

Data source

We used two data repositories through the VHA Support Service Center (VSSC): 1) the Workload Cube, and 2) the Diagnosis Cube. The VSSC Cube database was developed to provide an approach to extracting detailed utilization data about VHA patients without requiring access to identifiable health information.

The Workload Cube database provides measures of all utilization and workload activities, such as visits, procedures, and prescription fills extracted from VHA's national electronic health record system. We identified all individuals who had at least one outpatient visit during fiscal years 2006-2015. This represented a count of 56,261,708 users, who may have used the VHA across multiple years. These counts represented the yearly denominators for the study.

The VSSC Diagnosis cube is used as a repository for diagnosis codes occurring during all patient encounters. Diagnosis codes from all outpatient and inpatient visits occurring with a VHA facility, and all visits provided by a contract or community facility that is paid for by the VHA (known as fee-source visits) are included in this database. For the yearly numerator counts, we identified unique patients within a fiscal year with at least one outpatient fungal lung infection visit using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9CM) codes. Histoplasmosis visits

were identified using codes 115.00 -115.99 and coccidioidomycosis visits were identified using codes 114.0-114.9.

Study population

Data were examined for Veteran users over age 18 receiving care at any VHA facility or a VHA contract/community facility; non-Veteran users were excluded from all counts. For this study, we defined Veteran users as those patients who had a cost greater than $0 for the fiscal year. Geographic residential information for each VHA user was based on self-reported residence for that year (the last self-reported recorded zip code for the year).

We only accessed de-identified patient data; therefore, we were not able to link individual patients across calendar periods or other databases. For this reason, inpatient data were not examined in order to not double count patients in a year period since most patients with an inpatient admission would have had at least one outpatient follow-up visit during the same year.

Geographic variation

Our goal was to identify stable rates for the smallest meaningful geographic units possible. We explored power assumptions in order to determine the minimum population that would allow for stable and meaningful infection rates. Using a two-sample proportions power calculation with alpha = 0.05 and with power = 0.80, the minimum population for a geographic area would need at least 7,844 unique patients to detect a non-zero infection rate greater than 0.1 per 10,000 person-year level. Our initial intention was to use U.S. counties; however, only 118 counties out of 3,141 counties had unique outpatient visit counts of over 7,844 unique patients.

In order to maintain robustness in our rate approximations in sparsely populated areas but overcome the issues that arise from small area estimates, for our primary analysis we combined small counties into larger county groups based on geographic planning sectors defined by VHA.[8] VHA planning sectors are groupings of US counties designed to combine smaller counties into larger planning units that reflect where groups of Veterans are likely to receive their care. VHA planning sector groupings are calculated annually by the VHA Enrollee Health Care Projection Model (EHCPM) to project geographic trends in VHA enrollment and utilization. Sector area definitions are influenced by state borders, geographic barriers (e.g., mountains), and distance and drive times to VHA healthcare sites.[17] Some sectors are defined as a single large county while other sectors include several smaller counties in one or more states. In 2015, there were a total of 507 sectors. Our study includes 504 sectors; we dropped 3 sectors in Alaska due to incomplete/missing outpatient data. VHA sector characteristics are presented in Table 1. The largest VHA sector includes 49 counties, while the average number of counties in a sector is 6 (standard deviation=7.03). The average population across sectors of unique VHA patients with at least one outpatient visit for fiscal year 2015 was 11,750. By using VHA sectors as our unit of analysis, we tried to eliminate small geographic areas and attempted to avoid misclassification of counties with low volumes of visits. We have included small area outpatient visits rates in the appendix, but they should be interpreted and used with caution.

Once the geographic areas were identified, we extracted the annual count of unique patients in each county and sector for the numerator (outpatient visit with an

ICD-9CM code for histoplasmosis or coccidioidomycosis) and the annual count of unique patients in each county or sector with any outpatient visit for the denominator.

Statistical analysis

An average overall outpatient visit rate for each fungal lung infection for each sector was calculated using the total number of users with a histoplasmosis or coccidioidomycosis-related visit in the 10 year period in each sector divided by the total number of outpatient VHA users in each year over the 10 year period. This reflects a person-year approach with the assumption that an individual treated in one year would be at risk of treatment in subsequent years. This person-year approach was utilized because we were not able link patients across fiscal years due to the de-identified nature of the VSSC Cube data, which only allows for extracting and reporting of annualized utilization. Therefore, each year represents a count of the prevalence of outpatient treatment for a fungal lung infection. Rates were calculated per 10,000 person-years.

The ten-year average rates for each planning sector are reported both at the sector level and the individual county level in Supplementary Material Appendix 1. Histoplasmosis and coccidioidomycosis outpatient visit sector rates are displayed on a map of the U.S. within their county borders (Figure 1) using decile distribution of sector rates as mapping cutoff points. Decile cutoff points were used to show the richness in variation of sector level rates. Sector level characteristics including the average number of counties in a sector were analyzed and reported in Table 1. Sector level outpatient rates were ranked and the ten highest rates were reported, along with county and state information to show how sector level rates varied within states.

All statistical analyses were performed using Stata statistical software, version 14.0 (StataCorp LP). R version 3.2.2 and *ggplot2* version 2.1.0 were used to create all the maps in this article.[9]

Results

We identified an average of 5,626,171 patients each year with at least one outpatient visit at any VHA facility between 2006 and 2015, for a total of 56,261,708 person-years at risk. The number of unique users with at least one outpatient visit increased over time with 5,132,090 in 2006 and 6,128,050 in 2015. On average, there were 27,465 patients each year with an outpatient visit for histoplasmosis, ranging from 24,412 in 2006 to 27,589 in 2015. The average national rate of histoplasmosis outpatient visits was 7.99 per 10,000 person-years during this time period.

There were, on average, 3,400 patients per year with an outpatient visit for coccidioidomycosis, ranging from 2,999 in 2006 to 3,486 in 2015. Overall, the national rate of coccidioidomycosis outpatient visits averaged 0.99 per 10,000 person-years during this 10 year time period.

Geographic variation

We observed substantial geographic variation in histoplasmosis and coccidioidomycosis outpatient visit rates across the US. Histoplasmosis outpatient visit rates across the 504 sectors are presented geographically in Figure 1. The geographic sector with the highest histoplasmosis outpatient visit rate (67.5 per 10,000 person-years) consisted of seven counties in Ohio State (Adams, Clinton, Fayette, Highland, Pike, Ross, and Scioto). There were only three geographic sectors with no reported cases of histoplasmosis outpatient visits over our 10-year time period. The median rate

for histoplasmosis outpatient visits across sectors was 4.84 per 10,000 person-years and the mean was 8.48 per 10,000 person-years (standard deviation=9.59).

Based on previous literature and after graphing the ranked distribution of histoplasmosis outpatient visit sector rates by US Census area (Figure 2), we considered VHA sectors to have a 'high histoplasmosis rate' if they had outpatient treatment rates higher than 15 per 10,000 person-years. Based on that definition, 11.7% (59 out of 504 VHA sectors) were considered to have high rates of histoplasmosis.

The ten VHA sectors with the highest rates of outpatient visits for histoplasmosis, along with information about the counties and states in which these VHA sectors are found, are presented in Table 2. Variation in histoplasmosis outpatient visit rates was found within states, as seen in the ranges of sector rates in Table 2.

Rates of outpatient visits for coccidioidomycosis across the 504 sectors are presented in Figure 3, along with ranges for the deciles used to highlight the geographic variability across the sectors. The highest coccidioidomycosis outpatient visit rate (69.1 per 10,000 person-years) existed in the geographic sector containing the county of Pima, Arizona. There were 57 (11.3%) geographic sectors with no reported cases of coccidioidomycosis outpatient visits over our 10-year time period. The median rate for coccidioidomycosis outpatient visits across sectors was 0.47 per 10,000 person-years and the mean was 0.96 per 10,000person-years (standard deviation=2.46).

Based on previous literature and after graphical examination of ranked coccidioidomycosis outpatient visit sector rates (Figure 4), we defined VHA sectors with 'high coccidioidomycosis rate' as those with an outpatient treatment rate higher than 2

per 10,000 person-years. Based on that definition, 10.9% (55 out 504 VHA sectors) were considered to have high rates of coccidioidomycosis.

The ten sectors with the highest coccidioidomycosis outpatient visit rates are presented in Table 4, along with information about county and state coccidioidomycosis outpatient visit rates in these sectors. As evidenced by the range of rates in Table 3, coccidioidomycosis outpatient visit rates vary both between and within states.

Discussion

This paper utilized electronic medical record data to calculate outpatient visit rates for histoplasmosis and coccidioidomycosis at the VHA sector level to identify geographic variation relative to endemicity of these fungal lung infections. The geographic sector with the highest histoplasmosis outpatient visit rate (67.5 per 10,000 person-years) consisted of the following seven counties in Ohio state: Adams, Clinton, Fayette, Highland, Pike, Ross, and Scioto. In our study, the geographic distribution of outpatient visit rates were consistent with previously described endemic areas; there were high outpatient visit rates for histoplasmosis in the mid-Western states along the Mississippi and Ohio River valleys.[1,2,4,5] Higher outpatient visit rates were also found in the eastern parts of Oklahoma and Nebraksa; these are areas not usually considered endemic. Higher rates were also found in sectors in Montana and other western states in the Columbia River valley. These higher outpatient visit rates provide evidence that histoplasmosis endemicity may be extending into these previously unidentified areas.[7,10]

Outpatient visit rates show that endemicity should not be considered constant within a state. Traditionally known non-endemic states that border endemic states showed pockets of endemicity (Oklahoma and Nebraska) and even in traditionally

known endemic states, there were wide ranges of endemicity. Ohio, the state with the highest histoplasmosis outpatient visit sector rate, had a state histoplasmosis outpatient visit range of 2.6 - 67.3 per 10,000 person-years.

The geographic distribution of coccidioidomycosis outpatient rates was consistent with previously described endemic areas: high rates in the Southwestern and Western VHA sectors. [1,2,4,5]The geographic sector with the highest coccidioidomycosis outpatient visit rate (69.1 per 10,000 person-years) contained Pima county in Arizona. Higher rates were also found the Pacific Northwest and Mountain west areas; these higher rates could indicate that coccidioidomycosis endemicity maybe extending into these areas. Outpatient visit sector rates also showed that coccidioidomycosis endemicity should not be considered constant within a state, especially in traditionally known non-endemic states that border endemic states. There were 57 (11.3%) geographic sectors with no reported cases of coccidioidomycosis outpatient visits over our 10-year time period.

Results from this study provide more precise geographic estimated endemicity rates compared to previous studies. This allows healthcare providers to better identify patients living in endemic histoplasmosis and coccidioidomycosis areas so that they can more thoroughly understand patients' possible exposure to infection causing spores.

The use of outpatient healthcare visit data is another strength of this paper. Because it is difficult to measure an individual's exposure, outpatient visit rates for fungal lung infections can be used as a proxy measurement to measure endemicity of a geographic area for its population, assuming individuals in geographic areas likely share the same risk.[11] Outpatient visit data provide a better proxy for endemicity estimates for

histoplasmosis and coccidioidomycosis than inpatient visit data because individuals with these infections are not as likely to be hospitalized. The results of this paper also highlight how electronic medical records can be used to measure and quantify endemicity in a population. This method can be used to estimate endemic pockets of environmental exposures of other difficult to measure exposures.

A few limitations to this paper are related to our inability to access and extract fully identifiable patient-level data. Our de-identified patient level data did not allow us to obtain or link other individual patient information to the calculated rates, therefore, we were not able to adjust for patient covariates and use small area estimation analysis methods. Small area estimation analyses are methods used to describe how rates of healthcare utilization vary across geographic areas.[12] Since variation in type and counts of medical care that individuals receive has been associated with where individuals live, there are methods to test the significance of this geographic variation, including calculating chi squared statistics and coefficients of variations. These tests, using covariates and other individual-level indicators, assess the reliability of the rates and the validity of the differences in regions.[12,13] We were not able to conduct these tests since we were not able to extract linked covariates with our patient-level data. This also meant that we were not able to use an empirical Bayes statistic as a way to obtain better-estimated rates of utilization through modeling the underlying statistic. Using a Bayes statistics would have helped us derive more optimal estimates and increase the precision in our outpatient visit rates.[8,14] We were able to maintain the robustness in our rate estimates in sparsely populated areas by using VHA planning sectors.

Therapy for histoplasmosis and coccidioidomycosis is continued for several months, with the possibility of relapse, and may require longer treatment in some individuals and chronic suppressive therapy in others.[15,16] Due to the de-identified data, we were not able to identify if unique VA endemic mycosis outpatient visits were new or repeat visits, so some individuals may be included in multiple periods in our counts. De-identified data also did allow us to take into consideration how long a patient had lived in their self-reported county. Estimates may also be imprecise in areas where there are more transient populations. Furthermore, Veteran populations may not reflect the civilian population of a region.

Another limitation to this paper is its probable underestimation of endemicity. Because a majority of individuals infected with histoplasmosis and coccidioidomycosis are asymptomatic, outpatient visit rates continue to under-estimate endemicity in the population. While 4.8 per 10,000 represents the average rate of outpatient utilization, this is not reflective of the rate of true exposure to histoplasmosis. Especially when we consider that an estimated 50 million individuals in the US are infected with histoplasmosis, and in endemic areas, up to eighty percent of the area population may be infected.

A further limitation to this study is our use of VA sectors. While the 504 geographic VA sectors we used are smaller units than states, they still are quite large units of analysis. An individual's level of risk within a sector may vary considerably due to individual characteristics including their proximity to geographic features such as the rivers, how long the individual has lived in the area, and typical activities the individual engages in including time spent outdoors or near/with soil. Due to this, there is risk of

ecological fallacy since we are transferring aggregated results (sector level rates) of endemicity to individuals.[15–17]

In summary, this is the first nationally representative study of mycotic lung infection endemicity at a level more precise than region or state using national electronic health records. Although this study only represents the burden of morbidity related to outpatient treatment for histoplasmosis and coccidioidomycosis infections, these findings can be used as a representation of the variation in endemicity within states including those traditionally considered endemic.

References

1. Lenhart S, Schafer M, Singal M, Hajjeh R. *Histoplasmosis: Protecting Workers at Risk*.; 2004.
2. Gurney JW, Conces DJ. Pulmonary histoplasmosis. *Radiology*. 1996;199(212):297-306. doi:10.1136/thx.5.4.333.
3. Miller W. Thoracic Fungus Infections. In: *A Radiologic Approach to Disease of the Chest*. ; 1997:481-501.
4. Smith JA KC. Pulmonary fungal infections. *Respirology*. 2012;(17):913-926.
5. Chu JH, Feudtner C, Heydon K, Walsh TJ, Zaoutis TE. Hospitalizations for endemic mycoses: a population-based national study. *Clin Infect Dis*. 2006;42(6):822-825. doi:10.1086/500405.
6. Centers for Disease Control and Prevention. *Increase in Reported Coccidioidomycosis--United States, 1998-2011.* Vol 62.; 2013. doi:10.1097/INF.0b013e31829e7a5c.
7. Baddley J, Winthrop K. Geographic distribution of endemic fungal infections among older persons, United States. *Emerg Infect Dis*. 2011;17(9):7-12.
8. Mercer L, Wakefield J, Chen C, Lumley T. A comparison of spatial smoothing methods for small area estimation with sampling weights. *Spat Stat*. 2014;8:69-85. doi:10.1016/j.spasta.2013.12.001.
9. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. New York, New York: Springer-Verlag; 2009.
10. Centers for Disease and Prevention MMWR. *Histoplasmosis in a State Where It Is Not Known to Be Endemic-Montana, 2012-2013*. Vol 62.; 2013.
11. Evans GW, Kantrowitz E. Socioeconomic status and health: the potential role of environmental risk exposure. *Annu Rev Public Heal*. 2002;23(Figure 1):303-331. doi:10.1146/annurev.publhealth.23.112001.112349.
12. Cain KC, Diehr P. Testing the null hypothesis in small area analysis. *Health Serv Res*. 1992;27(3):267-294.
13. Ibáñez B, Librero J, Bernal-Delgado E, et al. Is there much variation in variation? Revisiting statistics of small area variation in health services research. *BMC Health Serv Res*. 2009;9:60. doi:10.1186/1472-6963-9-60.
14. Song L, Mercer L, Wakefield J, Laurent A, Solet D. Using Small-Area Estimation to Calculate the Prevalence of Smoking by Subcounty Geographic Areas in King County, Washington, Behavioral Risk Factor Surveillance System, 2009–2013. *Prev Chronic Dis*. 2016;13(150536).
15. Wheat LJ, Freifeld AG, Kleiman MB et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 (update by the Infectious Diseases Society of America). *Clin Infect Dis an Off Publ Infect Dis Soc Am Infect Dis*. 2007;(45):807–825.
16. Subramanian S V., Jones K, Kaddour A, Krieger N. Revisiting Robinson: The perils of individualistic and ecologic fallacy. *Int J Epidemiol*. 2009;38(2):342-360. doi:10.1093/ije/dyn359.
17. Robinson WS. Ecological correlations and the behaviors of individuals. *Am Sociol Rev Relig Res*. 1950;15(January):351-357. doi:10.1093/ije/dyn357.

Tables and Figures

Table 1: Characteristics of VHA's 504 Geographic Planning Sectors

Total # of sectors included in the analysis	504
# of sectors consisting of only 1 US county	206 (40.9%)
# of sectors consisting of only 2 US counties	23 (4.7%)
Average # of US counties in a sector	6
Largest # of US counties in a sector	49
Largest sector population of unique VHA patients with at least 1 outpatient visit for fiscal year 2015	266,280
Smallest sector population of unique VHA patients with at least 1 outpatient visit for fiscal year 2015	368
Average population across sectors of unique VHA patients with at least 1 outpatient visit for fiscal year 2015	11,750

Table 2: Ten geographic sectors with the highest histoplasmosis outpatient visit rates

Rank	VHA sector outpatient visits rates [1]	Counties found in VHA sector	State	State outpatient visit rate [1] range	% of all histoplasmosis-related outpatient visits for FY 2015, (N = outpatient visits)
1	67.3	Adams, Clinton, Fayette, Highland, Pike, Ross, Scioto	OH	2.6 - 67.3	0.3% (76)
2	61.6	Athens, Fairfield, Hocking, Jackson, Meigs, Pickaway, Vinton, Washington	OH	2.6 - 67.3	0.2% (52)
3	53.6	Boyd, Carter, Elliott, Floyd, Greenup, Johnson, Knott, Lawrence, Lewis, Magoffin Martin, Pike	KY	16.3 - 53.6	0.1% (22)
4	49.3	Coshocton, Delaware, Knox, Licking, Madison, Marion, Morgan, Morrow, Muskingum, Perry, Union	OH	2.6 - 67.3	0.3% (70)
5	44.6	Allen, Auglaize, Champaign, Hardin, Logan, Mercer, Wyandot	OH	2.6 - 67.3	0.1% (29)
6	42.6	Bath, Bourbon, Clark, Estill, Fleming, Harrison, Madison, Mason, Menifee, Montgomery, Morgan, Nicholas, Powell, Robertson, Rowan	KY	16.3 - 52.6	0.1% (32)
7	41.8	Butler	OH	2.6 - 67.3	0.1% (31)
8	39.4	Breathitt, Casey, Clay, Jackson, Knox, Laurel, Lee , Leslie, McCreary, Owsley, Perry, Pulaski, Rockcastle, Russell, Taylor, Wolfe	KY	16.3 - 52.6	0.2% (47)
9	39.3	Dearborn, Franklin, Ohio, Ripley Boone, Bracken, Campbell, Gallatin, Grant, Kenton, Pendleton Brown, Clermont	IN KY OH	7.7-39.3 16.3 - 52.6 2.6 - 67.3	0.2% (57)
10	38.0	Anderson , Boyle, Fayette, Franklin, Garrard, Jessamine, Lincoln, Marion, Mercer, Washington, Woodford	KY	16.3 - 52.6	0.2% (63)

[1]rates are presented per 10,000 person-years

Table 3: Top 10 coccidioidomycosis outpatient visit sector rates

Rank	VHA sector outpatient visits rates [1]	Counties found in VHA sector	State	State outpatient visit rate [1] range	% of outpatient visits for FY 2015, (n of outpatient visits)
1	69.1	Pima	AZ	9.1-69.1	5.4% (187)
2	38.7	Kern	CA	0.5-38.7	1.0% (35)
3	31.1	Cochise, Graham, Greenlee, Pinal, Santa Cruz	AZ	9.1-69.1	1.6% (56)
4	30.1	Maricopa	AZ	9.1-69.1	5.2% (181)
5	27.0	Kings, Tulare	CA	0.5-38.7	0.7% (26)
6	22.4	San Luis Obispo	CA	0.5-38.7	0.2%(7)
7	21.3	Inyo	CA	0.5-38.7	0.03% (1)
8	16.8	Apache, Gila, Navajo	AZ	9.1-69.1	0.3% (10)
9	13.8	Fresno	CA	0.5-38.7	0.7% (23)
10	13.6	Santa Barbara	CA	0.5-38.7	0.3% (11)

[1]rates are presented per 10,000 person-years

Figure 1: Average annual Histoplasmosis outpatient visit rates by VHA planning sector at county level per 10,000 person-years for fiscal years 2006-2015

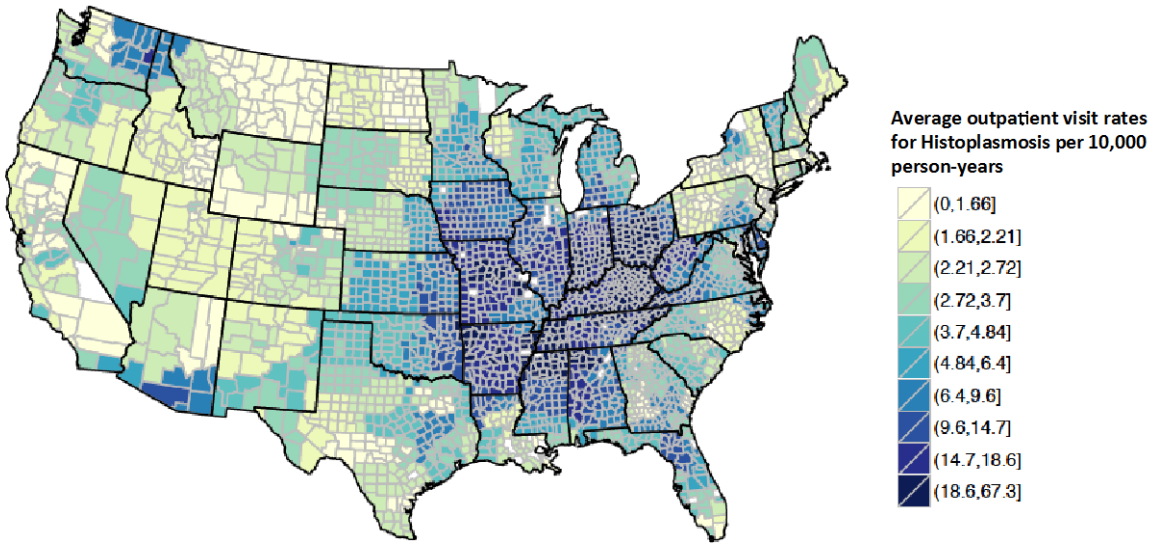


Figure 2: Average annual Histoplasmosis outpatient visit rates by VHA sector per 10,000 person- years for fiscal years 2006-2015, grouped by US Census regions

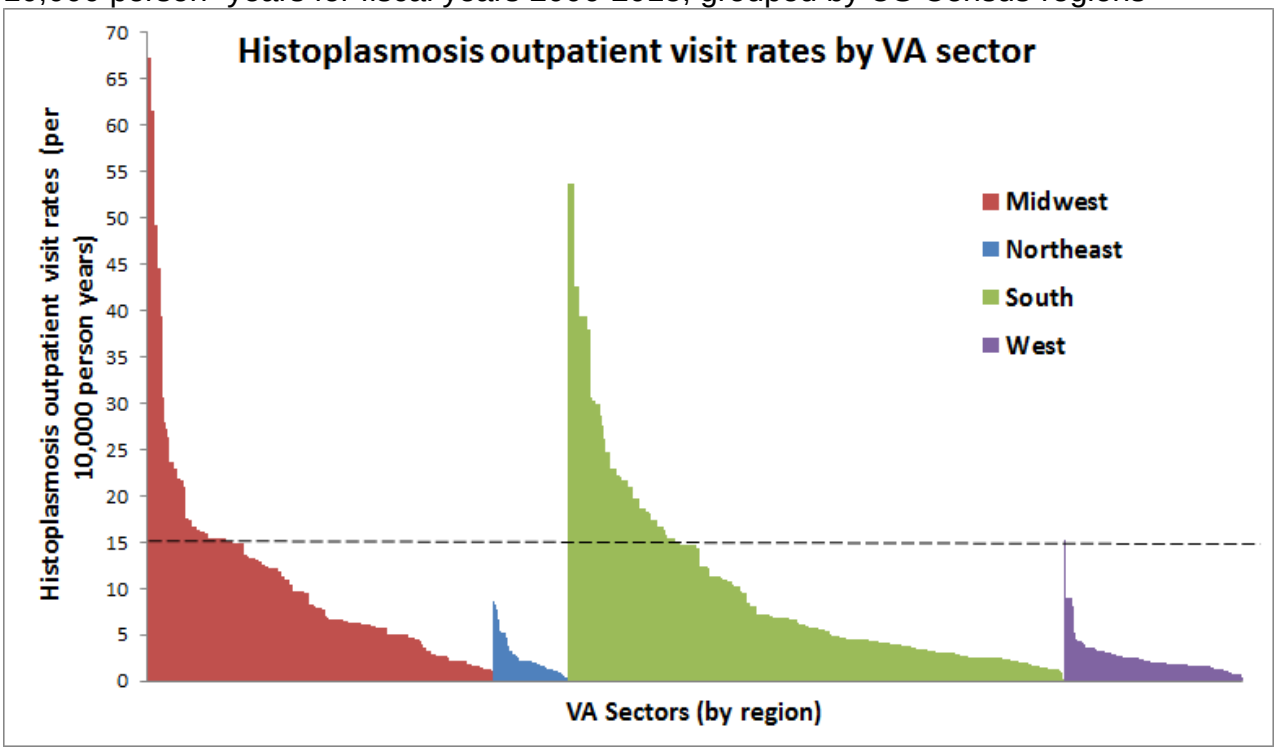


Figure 3: Average annual Coccidioidomycosis outpatient visit rates by VHA sector at county level per 10,000 person- years for fiscal years 2006-2015

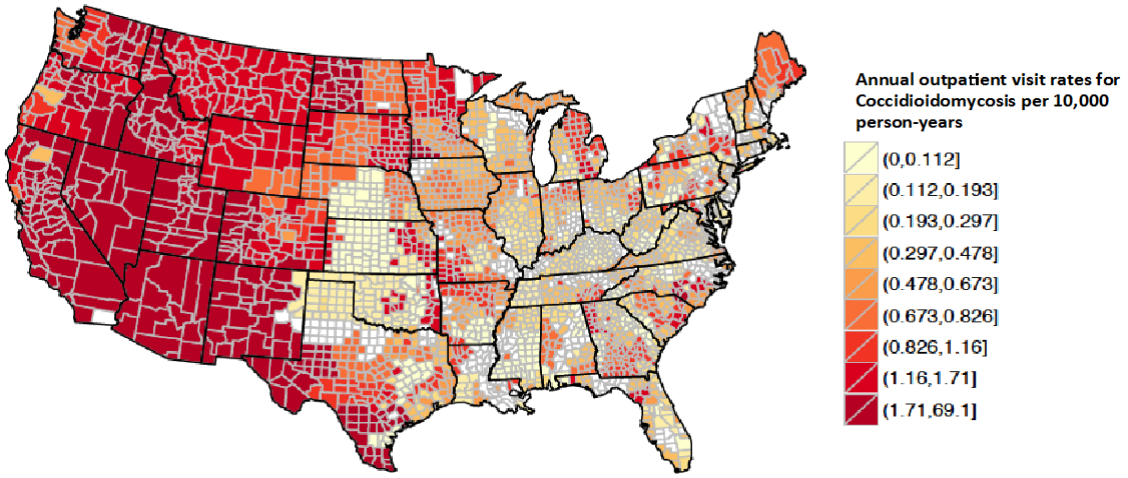
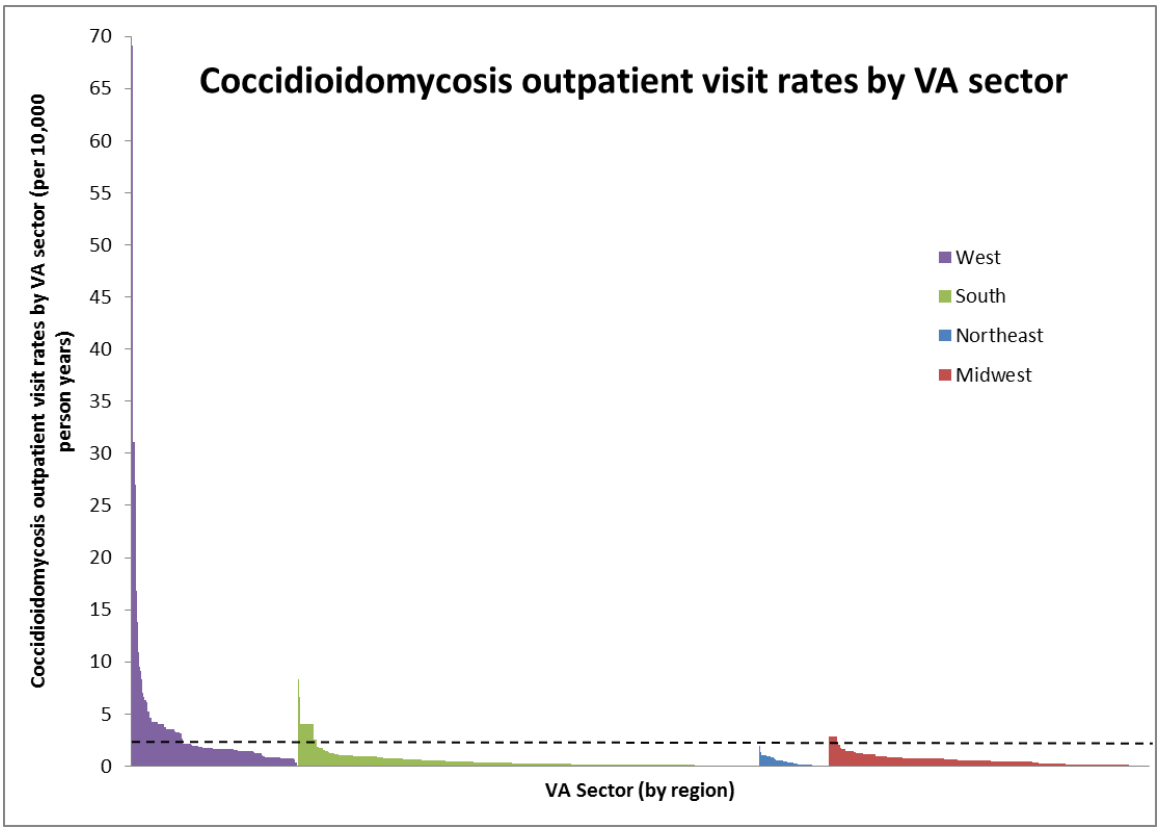


Figure 4: Average annual Coccidioidomycosis outpatient visit rates by VHA sector per 10,000 person- years for fiscal years 2005-2015, grouped by US Census regions



CHAPTER 3- The effect of geographic variation in histoplasmosis endemicity on the detection of non-urgent indeterminate pulmonary nodules

Abstract

Objective

Prior fungal lung infections, such as histoplasmosis, can result in scar tissue or granulomas that mimic cancerous pulmonary nodules leading to poor diagnostic accuracy among patients in endemic areas. The purpose of this study is to examine if greater histoplasmosis endemicity across the US is associated with increased detection of non-urgent pulmonary nodule findings on diagnostic chest-CT scans.

Methods

Among 189,121 patients who underwent diagnostic chest CT imaging (CPT: 71250, 71260, or 71270) in the Veterans Health Administration (VHA) in FY2011 we restricted our analysis to a cohort of 83,544 patients with no previous history of lung or other malignancies, and without an urgent or immediately suspicious finding on their CT scan. We developed an administrative algorithm to determine whether a non-urgent pulmonary nodule finding was identified on their first (index) CT scan in 2011 based on the type and timing of an individual's first follow-up procedure after their index scan using Fleischner guidelines. Once we identified how frequently non-urgent nodule findings were present, we followed patients to assess lung cancer diagnosis up to 24 months.

Geographic variation in histoplasmosis endemicity was based on geographic rates of outpatient visits for histoplasmosis in the VHA over a 10-year period (2005-2015). Each

patient was assigned an endemicity level based on their address at the time of the index chest CT scan.

Logistic regression models were then used to report adjusted risk ratios, adjusting for demographic and clinical characteristics including pre-existing comorbidity and smoking history, to calculate the likelihood of an individual having a suspicious non-urgent nodule finding and separately the likelihood of being diagnosed with lung cancer for each of the quartiles of histoplasmosis endemicity.

Results

Our administrative algorithm determined that 27,024/189,121 (14.3%) patients who underwent diagnostic chest CT imaging in FY2011 had a non-urgent pulmonary nodule finding. Focusing on the cohort of patients without a history of cancer or urgent findings (83,544), three groups were identified using our administrative algorithm: 12,819/83,544 (15.3%) who had follow-up consistent with a pulmonary condition such as pulmonary embolism; 43,701/83,544 (52.3%) had no significant nodule finding requiring surveillance and 27,024/83,544 (32.3%) were identified with indeterminate pulmonary nodule findings based on their surveillance patterns. This varied from 30.5% among residents from the lowest quartile areas of histoplasmosis endemicity to 34.6% among residents of the highest quartile areas. The likelihood of having an indeterminate non-urgent finding increased slightly across quartiles of histoplasmosis endemicity. The adjusted risk ratio (ARR) for the 25th, 50th, and 75th quartile of histoplasmosis relative to the lowest quartile was 1.02 (CI: 0.99-1.05); 1.06 (CI: 1.03-1.09); and 1.05 (CI: 1.03-1.08), respectively.

Among those with a non-urgent pulmonary nodule, 1,393/27,024 (5.2%) were diagnosed with lung cancer within 24 months, which varied from a cancer yield of 4.7% in the lowest quartile of histoplasmosis endemicity to 5.2% in the highest quartile.

Conclusions

Histoplasmosis endemicity had a minor influence on the frequency of indeterminate pulmonary nodules identified on diagnostic chest CT imaging. Variation in histoplasmosis exposure appears to be a minor contributing factor to variation in this national cohort.

Introduction

Chest CT scans are commonly used for a range of diagnostic purposes including a variety of non-specific symptoms such as shortness of breath, chest pain, and suspected pulmonary embolism. A 2009 study found that additional imagining recommended after diagnostic chest CT scans were associated with a high diagnostic yield of clinically relevant findings; in fact, one in every thirteen diagnostic chest CT scans yielded a previously unknown malignancy.[1]

Chest CT scans allow radiologists to obtain a more detailed and thorough image than chest x-rays and frequently detect suspicious pulmonary nodules. Non-urgent indeterminate nodules are usually defined as a single nodule (or an abnormality) that are less than 1 centimeter in diameter and have the appearance of malignancies but remain unchanged. Although most of these non-urgent indeterminate pulmonary nodules never progress to lung cancer, clinical guidelines call for surveillance with repeat imaging for up to two years after detection to determine the stability of the nodule and likelihood of lung cancer.[2–5] Estimates of suspicious pulmonary nodule findings requiring surveillance or follow-up care have widely ranged from 16% to 60% in cohorts of individuals undergoing diagnostic or screening chest CT imaging. [3,6,7] In the National Lung Screening Trial (NLST) study, 21.7% of the study population had non-urgent suspicious abnormal chest CT findings requiring follow-up imaging; less than 3% of those individuals actually went on to be diagnosed with lung cancer within two years.[8,9] A large number of individuals who have diagnostic chest CT scans may undergo unnecessary follow-up procedures for nodules that are not associated with lung cancer.[8–12] Pinsky found that radiologists show considerably more variability in chest CT

follow-up recommendations for non-urgent indeterminate nodules than compared to larger more urgent suspicious nodules.[7] Studies have examined possible factors contributing to the variability in these rates.[6,7,12–14]

One question that has been raised is the role of endemic fungal lung infections, specifically histoplasmosis, in contributing to the variability of false-positive results.[12,13,15] Granuloma inflammation and scarring caused by histoplasmosis can look identical to cancerous tissue on a chest-CT scan. In fact, histoplasmosis granuloma inflammation can have all of the hallmarks of a cancerous nodule including growth on repeated CT scans and lack of calcification.[16]

Fifty million individuals in the US are estimated to have been or are currently infected with histoplasmosis.[17,18] Because histoplasmosis causing spores are found in nitrogen rich soil, particularly soil that contains avian or bat feces, histoplasmosis is endemic across the Ohio, Mississippi, Missouri, Tennessee, and St. Lawrence River valleys.[19–21] In endemic areas, up to 80% of the area population may have been infected irrespective of imaging status. However, the majority of individuals infected with histoplasmosis are either asymptomatic or experience such mild symptoms that they do not realize they are infected.[19,22]

Detection of non-urgent indeterminate pulmonary nodules leading to unnecessary follow-up may be exacerbated in histoplasmosis endemic areas. There is risk that a patient could go through a cascade of unnecessary follow-up procedures, including surgery, and experience an iatrogenic injury or even death. A 2011 study found that in areas with high prevalence of histoplasmosis, 54% of chest CT scans were

found to positive for a suspicious non-urgent indeterminate nodule (nodule size 1-4mm), but of those, less than 4% were later diagnosed with lung cancer.[12]

The purpose of this study is to examine whether variation in histoplasmosis endemicity across the US is associated with detection of non-urgent indeterminate pulmonary nodules on diagnostic chest-CT scans, and whether histoplasmosis endemicity is associated with variation in lung cancer detection rates.

Methods

Data Source

Data for this retrospective cohort study were extracted from the Veterans Health Administration (VHA) Corporate Data Warehouse (CDW),[23] a repository of all health care utilization data, including dates of service, diagnoses, and procedures conducted by VHA health care providers and documented in the VHA's electronic medical records (EMR).

Inpatient and outpatient radiology, surgical, and biopsy procedures were extracted for 24 months following the date of the first (index) chest CT each individual received during the study period. The CDW also provided information on patient demographics, VHA medical facility and geocoded address, lung cancer diagnosis, and dates of death.

Data were collected between FY 2011 and FY2014; analyses were conducted in calendar year 2015-2016.

Population

The study population included individuals between ages 40 and 80 who had a diagnostic chest CT scan (CPT codes: 71250, 71260 and 71270) between October 1,

2010 and September 30, 2011. We used age cut off points with our patient cohort because guidelines for non-urgent chest CT scan nodule findings differ for those who are younger (less than 40 years old) and older (over 80 years old). Non-urgent indeterminate pulmonary nodule findings in younger patients may be more aggressively followed; while for older patients, findings may be due to accumulation of comorbidities and may not be followed more aggressively when weighing follow-up procedure options, side effects, and life expectancy.

We excluded individuals with any history of lung cancer and other cancers (ICD-9 codes: 140-239) prior to the date of their earliest FY2011 CT scans. Other exclusions included individuals with incomplete or errors in their EMR data (including missing data), those with CTs other than chest CTs (i.e., abdomen and pelvic CTs), and missing histoplasmosis outpatient rates.

To restrict our study population to only those individuals with non-urgent pulmonary findings, we excluded all patients immediately diagnosed with lung cancer (n=2,144) within 60 days of their index chest CT. Furthermore, patients with procedures after their index chest CT scan that indicated a non-pulmonary metastatic diagnosis, and patients who underwent immediate (urgent) pulmonary procedures after their index chest CT scan were excluded (n=19,633). These procedures and their groupings are based on procedures reported in the NLST study associated with diagnostic evaluation of suspicious findings for malignancy and are listed in Table 1 of the appendix.[8] The final study population included 83,544 cancer-free patients who underwent diagnostic chest CT imaging at 130 VHA Medical Centers in FY2011 and who did not have a highly suspicious pulmonary finding from their index chest CT scan.

Measures

Detection of non-urgent indeterminate pulmonary nodules from index CT

From the study population of 83,544 individuals, we identified those with suspected non-urgent indeterminate pulmonary nodules based on imaging follow-up sequence. Because coding of non-urgent indeterminate pulmonary nodules is not available electronically, we developed an administrative algorithm to determine and categorize the frequency of non-urgent findings based on the date and type of the individual's first follow-up procedure after their index scan. This algorithm was based on the Fleischner guidelines for managing small pulmonary nodules detected on CT scans.[24] From each patient's index CT, we assigned follow-up categories for the first surveillance imaging based on the type and timing of follow-up procedures of interest: short interval surveillance (2-4 months) imaging, mid-interval surveillance (5-9 months) imaging, and long interval surveillance (10-16 months) imaging (Appendix Table 1). Procedures such as chest x-rays, pulmonary function tests, and unspecified pulmonary procedures were not considered for categorization into these surveillance groupings. The remainder of the study population was categorized as follows:

Group 1. Individuals assumed to have pulmonary conditions other than a pulmonary nodule who received follow-up procedures (n=12,819)

Group 2. Individuals with no suspected pulmonary nodule findings (n=43,701)

Individuals were considered to have unknown pulmonary conditions (group 1) if they received a procedure of interest but at a time interval outside of what would be considered appropriate follow-up based Fleischner guidelines for an individual with a suspected non-urgent indeterminate suspicious nodule. These individuals either: do not

have nodules and have other pulmonary diseases motivating the care/procedures they received, or have a nodule and received follow-up procedures/imaging not in accordance with recommended guidelines (Appendix Table 1). Individuals were considered to have no suspicious pulmonary nodule findings (group 2) if they only had follow-ups with chest x-rays or other procedures within 2 years of their index chest CT scan. These groups were later combined for statistical analysis informing the reference group.

Lung cancer diagnosis

We identified lung cancer diagnosis up to 24 months following a patient's index CT using three different sources within VHA: Veterans Affairs Central Cancer Registry (VACCR), oncology records in the CDW, and ICD-9 codes included in EMR.[25] To ensure ICD-9 diagnosis codes reflected diagnosis of cancer, we used an administrative algorithm that required an ICD-9 diagnosis of (162.9) to appear in at least two unique visits within 60 days.[26–28] The earliest date of diagnosis of lung cancer identified among the three data sources was considered to be the date of diagnosis. Eighty percent of diagnosis data were obtained from ICD-9 diagnosis codes from EMR records.

Histoplasmosis Exposure

Geographic variation in histoplasmosis endemicity was based on geographic rates of outpatient visits in the VHA over a 10-year period. These visit rates were calculated by taking ICD-9 diagnosis counts of unique VHA users with at least one outpatient histoplasmosis visit between fiscal years 2005-2015. Five hundred four VHA planning sectors, consisting of one or more US counties, were used as the primary unit of geographic analysis. An average rate for each sector was calculated as the total

number of histoplasmosis outpatient cases in each sector divided by the total number of unique outpatient VHA users in each sector during the study period. This reflects a person-year approach with the assumption that an individual treated in one year would be at risk of treatment in subsequent years. On average, there were 27,465 patients each year with an outpatient visit for histoplasmosis, ranging from 24,412 in 2006 to 27,589 in 2015. The average national rate of histoplasmosis outpatient visits was 7.99 per 10,000 person-years during this time period.

We grouped our study population into four (quartile) groups across the distribution of histoplasmosis endemicity levels based on their geographic VHA sector (based on their individual zip codes). The patients in the lowest quartile were from areas where the average national outpatient visit rate across VHA from 2005-2015 for a histoplasmosis infection was 1.46 per 10,000 person-years, and the patients in the in the highest quartile were from areas where the average outpatient visit rate was 19.92 per 10,000 person-years. Patients in the geographic VHA sector with the highest histoplasmosis outpatient visit rate (67.5 per 10,000 person-years) consisted of the following seven counties in Ohio state: Adams, Clinton, Fayette, Highland, Pike, Ross, and Scioto. The geographic distribution of histoplasmosis outpatient visit rates were high in the mid-Western and Southern states along the Mississippi and Ohio River valleys.[1,2,4,5] Higher outpatient visit rates were also found in the eastern parts of Oklahoma and Nebraska and in sectors in Montana and other western states in the Columbia River valley.

Statistical Analysis

Descriptive analyses of the population were calculated across the primary outcome – whether or not a patient was identified with a suspicious non-urgent indeterminate pulmonary nodule finding. VHA sector histoplasmosis outpatient visits rates were grouped into deciles and graphed by the frequency of suspicious non-urgent indeterminate findings in order to visualize any trends in rates by histoplasmosis endemicity. Deciles were used to visualize VHA sector histoplasmosis outpatient visits rates while quartiles were used for regression modeling.

A logistic regression model was used to measure the likelihood of an individual having a suspicious non-urgent indeterminate nodule finding for each of the quartiles of histoplasmosis endemicity. This model was adjusted for demographic and clinical characteristics thought to influence the relationship between the likelihood of suspicious non-urgent indeterminate findings and histoplasmosis endemicity; those include: age, gender, race, smoking status, rurality setting, and Charlson comorbidity[29]. For statistical and interpretation purposes, adjusted risk ratios were calculated post-estimation and reported.[30,31]

The secondary outcome was the association of non-urgent indeterminate suspicious pulmonary nodule findings and lung cancer diagnosis within 24 months of the index CT scan. Trends in lung cancer rates were visualized among those who did and did not have any suspicious non-urgent indeterminate nodule findings by histoplasmosis endemicity; VHA sector histoplasmosis outpatient visits rates were grouped into deciles and graphed by the frequency of lung cancer diagnoses. A second logistic regression model was used to measure the likelihood of being diagnosed with

lung cancer among those who had a suspicious non-urgent indeterminate finding for each of the quartiles of histoplasmosis endemicity. This model was also adjusted for the following demographic and clinical characteristics: age, gender, race, smoking status, rurality setting, and Charlson comorbidity. Again, adjusted risk ratios were calculated post-estimation and reported.

All statistical analyses were preformed using Stata statistical software, version 14.0 (StataCorpLP). Institutional Review Board (IRB) approval for the study was obtained from both the University of Washington and the VHA Puget Sound Health Care System.

Results

Our administrative algorithm determined that 27,024/189,121 (14.3%) patients who underwent diagnostic chest CT imaging in FY2011 had a non-urgent pulmonary nodule finding. Focusing on the cohort of patients without a history of cancer or urgent findings, 27,024/83,544 (32.3%) were identified with indeterminate pulmonary nodule findings based on their surveillance patterns (Table 1 & 2). Overall, the majority of the selected cohort (n=83,544) was white (73.5%), male (95.4%), and 55-64 years old (43.0%). 42.9% were current smokers, 39.0% were former smokers, 12.0% were never smokers, and 6.2% had unknown smoking status (Table 2).

When we categorize histoplasmosis endemicity into deciles, we saw a slight increase in individuals with a suspicious non-urgent indeterminate pulmonary nodule finding in more endemic histoplasmosis areas (Figure 2). The percent of patients having a suspicious non-urgent indeterminate nodule finding varied from 30.5% in the lowest decile of histoplasmosis endemicity to 34.6% in the highest decile.

After adjusting for demographic and clinical characteristics including pre-existing comorbidity and smoking history, the adjusted risk ratio for the likelihood of having a suspicious non-urgent pulmonary nodule finding for the 25th, 50th, and 75th quartile of histoplasmosis relative to the bottom quartile was 1.02 (CI: 0.99-1.05); 1.06 (CI: 1.03-1.09); and 1.05 (CI: 1.03-1.08), respectively (Table 4). This can be interpreted as after adjusting for demographic and clinical characteristics, those patients living in the highest quartile of histoplasmosis endemicity had a 5% increase in risk of having a suspicious non-urgent indeterminate lung nodule finding compared to those living in the lowest quartile of endemicity. Patients older than 55, all had a 21% or more increase risk of having a suspicious non-urgent indeterminate pulmonary nodule finding compared to those 55 years or younger. Individuals who were a current smoker or a former smoker both had a 11% increase in risk of having a suspicious non-urgent indeterminate pulmonary nodule finding compared to a never smoker. Those with two pre-existing comorbidities had a 12% higher risk of having a suspicious non-urgent indeterminate pulmonary nodule finding compared to someone with no pre-existing comorbidities.

Among those with a suspicious non-urgent indeterminate pulmonary nodule finding 5.2% (n=1,393) were diagnosed with lung cancer within 24 months (Table 5) and the overall positive predicted value (PPV) was 0.05. When we categorize histoplasmosis endemicity into deciles, we saw a slight increase in individuals diagnosed with lung cancer after receiving a follow-up procedure for a suspicious pulmonary nodule finding in more endemic histoplasmosis areas (Figure 3). Lung cancer rates among those who had a suspicious non-urgent lung nodule finding (PPV) varied from 0.047 in the lowest decile of histoplasmosis endemicity to 0.052 in the

highest decile. Four hundred six patients, who were assumed to have pulmonary conditions other than a lung nodule who received follow-up procedures , and 549 patients, who were categorized as not having a pulmonary nodule surveillance procedure within 12 months, were found to have a lung cancer diagnosis 24 months after their initial chest-CT scan. The negative predicted value, the lung cancer rate among these individuals who did not have any suspicious non-urgent indeterminate lung nodule findings, varied from 0.016 to 0.021 from lowest to highest decile of histoplasmosis (Figure 5).

After adjusting for demographic and clinical characteristics including pre-existing comorbidity and smoking history, the adjusted risk ratio for the likelihood of being diagnosed with lung cancer 24 months after having a suspicious non-urgent indeterminate lung nodule finding for each the 25^{th}, 50^{th} and 75^{th} quartile of histoplasmosis relative to the lowest quartile was 1.14 (CI: 0.99-1.33); 1.17 (CI: 1.01-1.35); 1.15 (CI: 0.99-1.33), respectively (Table 6). For the 4^{th} quartile of histoplasmosis endemicity, we can interpret that after adjusting for demographic and clinical characteristics, those patients living in the highest level of histoplasmosis endemicity who were found to have a non-urgent indeterminate suspicious nodule findings had a 15% greater chance of having a lung cancer diagnosis compared to those living in the lowest quartile of endemicity. Patients older than 55, all had a statistically significant increasing risk of having a lung cancer diagnosis after a suspicious non-urgent indeterminate pulmonary nodule finding. Among patients who were found to have a non-urgent suspicious indeterminate nodule finding, current smokers, former smokers,

and patients with unknown smoking status all had a statistically significant increase in risk of having an eventual lung cancer diagnosis compared to never smokers.

Discussion

Based on our findings, histoplasmosis endemicity was associated with a minor increase in the likelihood of an individual being identified with a non-urgent indeterminate pulmonary nodule in this national cohort of patients. After adjusting for demographic and clinical characteristics, those patients living in the highest quartile of histoplasmosis endemicity had a 5% increase in the likelihood of having a suspicious non-urgent indeterminate lung nodule detected. Also, patients living in the highest level of histoplasmosis endemicity, who were found to have a suspicious non-urgent indeterminate nodule, had a 15% greater chance that this nodule would eventually be found to be malignant leading to a lung cancer diagnosis.

Estimates of the rate of suspicious pulmonary findings in prior cohorts of patients undergoing diagnostic chest CT imaging have ranged from 16-60%, and our overall rate was 14.3%.[3,6,7] A prior study, using the NLST population and looking at variability in CT chest imaging results, did not find histoplasmosis to be a statistically significant factor in the variability of chest CT imaging findings.[7] In contrast, our study unexpectedly shows that residing in a high histoplasmosis area is a minor contributing factor in the likelihood of being identified with a non-urgent indeterminate pulmonary nodule. This difference may be influenced by a number of factors, including the way we have defined histoplasmosis endemicity. First, we were not able to adjust for patient covariates due to data limitations. Additionally, we were not able to use small area estimation analysis methods when we calculated histoplasmosis endemicity. Therefore, there is a risk of

ecological fallacy since we are transferring aggregated rates, VHA sector level rates, of endemicity to individuals.[15,20]

There was an overall increase in cancer yield among individuals with non-urgent indeterminate nodule findings in all quartiles compared to the lowest histoplasmosis endemicity quartile. One possible explanation for this finding may be due to restricting our study population to non-urgent suspicious indeterminate nodule findings. Our study is not examining a general population sample where everyone is at equal risk; patients in this study were selected into our cohort because they had a diagnostic chest CT scan. It is possible that radiologist behavior varies by region, and those radiologists in histoplasmosis endemic areas more frequently use a 'wait and see' approach and may be more likely to recommend additional surveillance rather than recommend an immediate invasive diagnostic procedure. Such behavior would lead to more patients from areas with high histoplasmosis being included in our analysis with non-urgent indeterminate suspicious nodule findings that other radiologists from areas with lower histoplasmosis endemicity would have recommended for immediate diagnostic evaluation. This could explain some of the increase in risk we see in our cohort of patients from areas with high histoplasmosis endemicity. In addition, clinically higher risk patients, those older patients with a history of smoking and comorbidities, may be preferentially selected into the diagnostic cohorts in the histoplasmosis endemic areas and are being followed because of a symptom or an earlier finding on chest imaging. These selection processes may have enriched those areas with slightly higher cancer risk.

Interestingly, the trend in lung cancer yield decreased as histoplasmosis endemicity increased in the higher quartiles. One possible explanation is that residents in areas of highest endemicity also have the highest likelihood of receiving surveillance imagining; therefore, due to the difficulty of distinguishing histoplasmosis from lung cancer, also have a higher rate of false positives.

These data should be reassuring to policy makers and providers in areas with high histoplasmosis endemicity. There is concern that the interpretation of CT chest imaging results is worse in these areas; however, these data suggest that non-urgent indeterminate nodule differentiation is only mildly different-- there are more diagnostic procedures and more false positives, but not needlessly so, because the cancer yield is also slightly higher.

There are limitations to this study. We relied on timing of follow-up procedures (via VHA EMR) to make inferences about nodule findings because non-urgent indeterminate suspicious nodule findings are not currently routinely recorded in the EMR. Due to this, there is possibility of misclassification. If patients did not get the follow-up that was recommended, we may be undercounting the actual number of non-urgent indeterminate suspicious nodules that were found. While we tried our best to narrow our population to those who were receiving diagnostic chest CT scans for cases of new suspicious non-urgent indeterminate lung nodules, because we used VHA EMRs and did not look at individual physician notes, we may have included some individuals with recurrent lung cancers. Furthermore, our reference group (those individuals with unknown pulmonary conditions who received follow-up procedures and imaging of interest not in accordance with Fleischner guidelines and individuals with other or no

suspected pulmonary nodule findings) may contain individuals who in fact had non-urgent indeterminate pulmonary nodules or may in some other way be misclassified. Misclassification may bias our results, the direction of which is indeterminable.

There may be other factors contributing to the variability that is not being measured in our model, including radiologist and facility variability. Assessing how radiologists read and interpret scans in endemic and non-endemic areas is a logical next step to assess variability in indeterminate nodule findings and lung cancer rates. This is because evaluation of nodules includes assessments of changes in size, attenuation, and contour, all of which may be subjective and can be influenced by the radiologist and the environment of the facility in which they work at. [7,12] Further studies should also try to measure variability in rates of suspicious non-urgent indeterminate findings in terms of individual-measured environmental exposures. We can see that patient factors represent a small portion of the wide variability observed in diagnostic chest CT imagining results and the frequency of suspicious findings. This suggests that variability can be reduced with radiology quality improvement initiatives. With the recent recommendation by the US Preventive Services Task Force to offer lung cancer screening to high-risk smokers, efforts should focus on monitoring and improving imaging performance.

References

1. Harvey HB, Gilman MD, Wu CC, et al. Diagnostic yield of recommendations for chest CT examination prompted by outpatient chest radiographic findings. *Radiology*. 2015;275(1):262-271. doi:10.1148/radiol.14140583.
2. Moyer V. Screening for lung cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(5):330-338.
3. Black W. Computed tomography screening for lung cancer: review of screening principles and update on current status. *Cancer*. 2007;110(11):2370-2384. doi:10.1002/cncr.23059.
4. Wahidi M, MGovert J, Gouda R, McCrory D. American College of Chest Physicians Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132:94S-107S.
5. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: When is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 SUPPL):e93S-e120S. doi:10.1378/chest.12-2351.
6. Silvestri G. Screening for lung cancer: it works, but does it really work? *Ann Intern Med*. 2011;155(8):537-540.
7. Pinsky PF, Gierada DS, Nath PH, Kazerooni E, Amorosa J. National lung screening trial: variability in nodule detection rates in chest CT studies. *Radiology*. 2013;268(3):865-873. doi:10.1148/radiol.13121530.
8. Church TR, Black WC, Aberle DR, et al. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med*. 2013;368:1980-1991. doi:10.1056/NEJMoa1209120.
9. Black WC, Gareen IF, Soneji SS, et al. Cost-Effectiveness of CT Screening in the National Lung Screening Trial. *N Engl J Med*. 2014;371(19):1793-1802. doi:10.1056/NEJMoa1312547.
10. Gohagan JK, Marcus PM, Fagerstrom RM, et al. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. *Lung Cancer*. 2005;47:9-15. doi:10.1016/j.lungcan.2004.06.007.
11. Patz EF, Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med*. 2014;174(2):269-274. doi:10.1001/jamainternmed.2013.12738.
12. Singh S, Pinsky P, Fineberg N, Gierada D. Evaluation of reader variability in the interpretation of follow-up CT scans at lung cancer screening. *Radiology*. 2011;259(1):263-270. doi:10.1148/radiol.10101254/-/DC1.
13. Starnes SL, Reed MF, Meyer C a, et al. Can lung cancer screening by computed tomography be effective in areas with endemic histoplasmosis? *J Thorac Cardiovasc Surg*. 2011;141(3):688-693. doi:10.1016/j.jtcvs.2010.08.045.
14. Marshall HM, Bowman R V., Yang I a., Fong KM, Berg CD. Screening for lung cancer with low-dose computed tomography: A review of current status. *J Thorac Dis*. 2013;5. doi:10.3978/j.issn.2072-1439.2013.09.06.
15. Salhab KF, Baram D, Bilfinger T V. Growing PET positive nodule in a patient with histoplasmosis: case report. *J Cardiothorac Surg*. 2006;1:23. doi:10.1186/1749-

8090-1-23.
16. Sharma P, Mukherjee A, Karunanithi S, Bal C, Kumar R. Potential Role of 18F-FDG PET/CT in Patients With Fungal Infections. *Am J Roentgenol*. 2014;203(1):180-189. doi:10.2214/AJR.13.11712.
17. Chu JH, Feudtner C, Heydon K, Walsh TJ, Zaoutis TE. Hospitalizations for endemic mycoses: a population-based national study. *Clin Infect Dis*. 2006;42(6):822-825. doi:10.1086/500405.
18. Baddley J, Winthrop K. Geographic distribution of endemic fungal infections among older persons, United States. *Emerg Infect Dis*. 2011;17(9):7-12.
19. Lenhart S, Schafer M, Singal M, Hajjeh R. *Histoplasmosis: Protecting Workers at Risk*.; 2004.
20. Miller W. Thoracic Fungus Infections. In: *A Radiologic Approach to Disease of the Chest*. ; 1997:481-501.
21. Smith JA KC. Pulmonary fungal infections. *Respirology*. 2012;(17):913-926.
22. Gurney JW, Conces DJ. Pulmonary histoplasmosis. *Radiology*. 1996;199(212):297-306. doi:10.1136/thx.5.4.333.
23. Maynard C, Chapko MK. Data Resources in the Department of Veterans Affairs. *Diabetes Care*. 2004;27:B22-B26. doi:10.2337/diacare.27.suppl_2.B22.
24. MacMahon H, John M Austin BH, Gamsu G, et al. Guidelines for Management of Small Pulmonary Nodules Detected on CT Scans: A Statement from the Fleischner Society. *Radiology*. 2005;237:395-400. doi:10.1148/radiol.2372041887.
25. U.S. Department of Veterans Affairs. U.S. Department of Veterans Affairs Washington, D.C: VHA Directive 2003–034 National Cancer Strategy.
26. Friedlin J, Overhage M, Al-Haddad MA, Waters JA, Aguilar-Saavedra JJ, Kesterson J SM. Comparing methods for identifying pancreatic cancer patients using electronic data sources. *AMIA Annu Symp Proc*. 2010:237–241.
27. Gold H. Evaluation of three algorithms to identify incident breast cancer in Medicare claims data. *Health Serv Res*. 2007;42(5):2056-2069.
28. Ramsey S, Scoggins J, Blough D, McDermott C, Reyes C. Sensitivity of administrative claims to identify incident cases of lung cancer: a comparison of 3 health plans. *J Manag Care Spec Pharmarcy*. 2009;15(8):659-668.
29. Sharabiani, Mansour; Aylin, Paul; Bottle A. Systematic review of comorbidity indices for administrative data. *Med Care Res Rev*. 2012;50(12):1109-1118.
30. Kleinman L., Norton E. What's the Risk? A simple approach for estimating risk ratios from nonlinear models including logistic regression. *Health Serv Res*. 2009;44(1):288-302.
31. Cummings P. The relative merits of risk ratios and odds ratios. *Arch Pediatr Adolesc Med*. 2009;71(2):139-150.
32. Robinson WS. Ecological correlations and the behaviors of individuals. *Am Sociol Rev Relig Res*. 1950;15(January):351-357. doi:10.1093/ije/dyn357.
33. Subramanian S V., Jones K, Kaddour A, Krieger N. Revisiting Robinson: The perils of individualistic and ecologic fallacy. *Int J Epidemiol*. 2009;38(2):342-360. doi:10.1093/ije/dyn359.

Tables and Figures

Figure 1: Study population exclusion/inclusion criteria

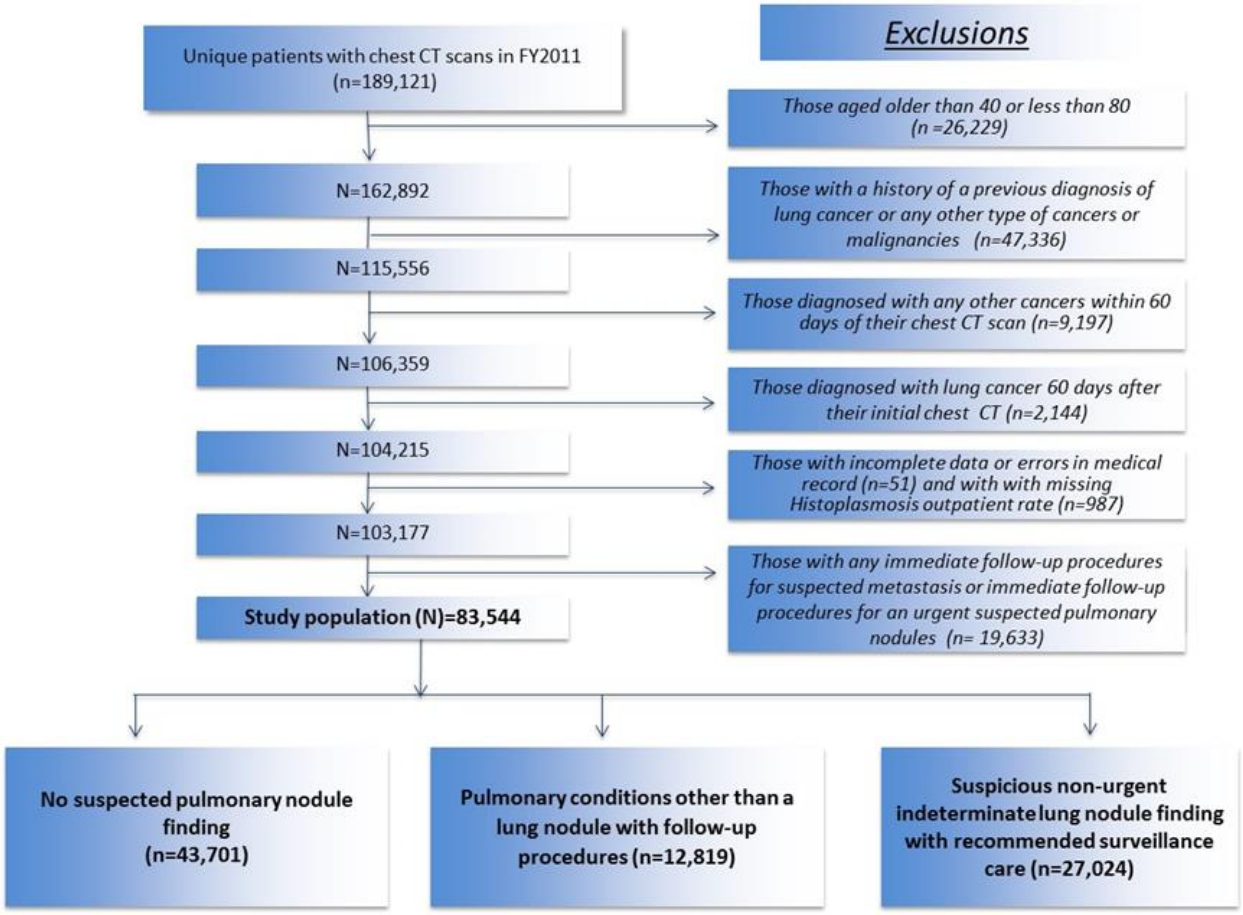


Table 1: Categorization of index CT scan findings based on Fleischner algorithm for timing of follow-up (n=83,544)

Suspicious non-urgent indeterminate pulmonary nodule finding with recommended surveillance care (n=27,024)	**N**	**%**
Short interval surveillance imaging – 2-4 months	8,632	10.3
Mid-interval surveillance imaging – 5-9 months	10160	12.2
Long interval surveillance imaging – 10-16 months	8,232	9.9
Pulmonary conditions other than a lung nodule with follow-up procedures	12,819	15.3
No suspected pulmonary nodule finding (n=43,701)		
Non-surveillance procedures (e.g. chest x-ray)	23,798	28.5
No procedures within 12-months	19,903	23.8
Total	**83,544**	100.0

Table 2: Study population demographics

	Overall n=83,544		Suspicious non-urgent indeterminate pulmonary nodule finding with recommended surveillance care n=27,024		Pulmonary conditions other than a lung nodule with follow-up procedures n=12,819		No suspected pulmonary nodule finding n=43,701		p-value
	N	%	N	%	N	%	N	%	
Age									<0.05
<55	13,668	16.4	3,452	12.8	2,255	17.6	7,961	18.2	-
55-64	35,886	43.0	11,650	43.1	5,782	45.1	18,454	42.2	-
65-74	24,683	29.5	8,665	32.1	3,428	26.7	12,590	28.8	-
=>75	9,307	11.1	3,257	12.1	1,354	10.6	4,696	10.8	-
Gender									<0.05
Male	79,734	95.4	26,008	96.2	12,052	94.0	41,674	95.4	-
Female	3,810	4.6	1,016	3.8	767	6.0	2,027	4.6	-
Race									<0.05
White	61,442	73.5	20,896	77.3	9,242	72.1	31,304	71.6	-
Black	12,513	15.0	3,328	12.3	2,256	17.6	6,929	15.9	-
Other	9,589	11.5	2,800	10.4	1,321	10.3	5,468	12.5	-
Marital Status									<0.05
Married	41,500	49.7	14,101	52.2	5,981	46.7	21,418	49.0	-
Not married	41,898	50.2	12,902	47.7	6,827	53.3	22,169	50.7	-
Unknown	146	0.2	21	0.1	11	0.1	114	0.3	-
Smoking status									<0.05
Current smoker	35,825	42.9	11,873	44.0	5,812	12.1	18,140	41.5	-
Former smoker	32,542	39.0	11,110	41.1	4,874	45.3	16,558	37.9	-
Never smoker	9,961	12.0	2,856	10.6	1,554	38.0	5,551	12.7	-
Unknown	5,216	6.2	1,185	4.4	579	4.5	3,452	7.9	-
Patient residence rurality setting									<0.05
Urban	68,652	82.2	22,086	81.7	10,784	84.1	35,782	81.9	-
Suburban	7,277	8.7	2,364	8.8	969	7.6	3,944	9.0	-
Rural	7,569	9.1	2,558	9.5	1,059	8.3	3,952	9.0	-
Unknown	46	0.1	16	0.1	7	0.1	23	0.1	-
Charlson comorbidity score									<0.05
0	24,168	29.0	7,162	26.5	3,069	24.0	13,937	31.9	-
1	10,750	12.9	3,204	11.9	1,669	13.0	5,877	13.5	-
2	23,018	27.6	8,160	30.2	3,310	25.8	11,548	26.4	-
>=3	25,608	30.7	8,498	31.5	4,771	37.2	12,339	28.2	-

Table 3: Histoplasmosis endemicity rate [a] by type of follow-up procedures performed after index chest CT-scan

	Mean	Median	Standard Deviation
Overall (n=83,544)	7.6	4.0	9.5
Suspicious non-urgent indeterminate pulmonary nodule finding with recommended surveillance care (n=27,024)	7.8	4.1	9.6
Pulmonary conditions other than a lung nodule with follow-up procedures (n=12,819)	7.4	3.8	9.3
No suspected pulmonary nodule finding (n=43,701)	7.9	4.1	9.7

a. Histoplasmosis endemicity rates are sector rates per 10,000

Figure 2: Percent of population with a suspicious non-urgent indeterminate pulmonary nodule finding with recommended surveillance care by Histoplasmosis endemicity

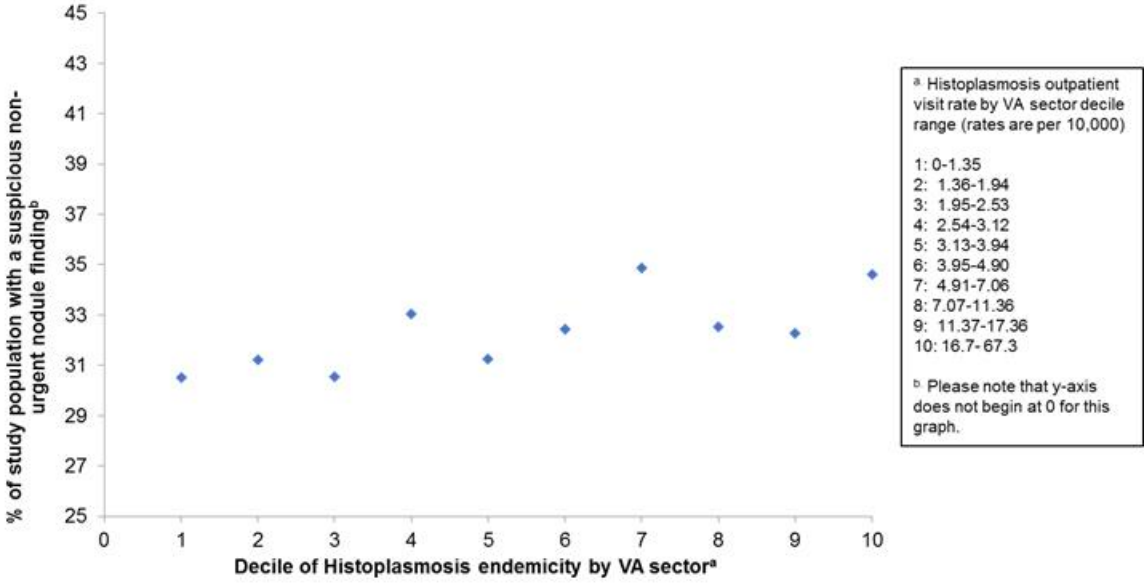


Table 4: Adjusted risk ratios for the likelihood of detection of a non-urgent indeterminate pulmonary nodule finding (n=83,544)

Variables	Adjusted risk ratio	95% Confidence Interval
Histoplasmosis		
1st Quartile (Reference; n=20,999)	-	-
2nd Quartile (n=20,939)	1.02	0.99,1.05
3rd quartile (n=20,784)	1.06*	1.03,1.09
4th quartile (n=20,822)	1.05*	1.03,1.08
Age		
<55 (Reference)	-	-
55-64	1.21*	1.17,1.25
65-74	1.29*	1.25,1.33
=>75	1.28*	1.23,1.32
Gender		
Female (Reference)	-	
Male	1.10*	1.04,1.16
Race		
White (Reference)	-	
Black	0.83*	0.80,0.85
Other	0.88*	0.85,0.91
Smoking Status		
Never smoker (Reference)	-	
Current smoker	1.11*	1.08, 1.15
Former smoker	1.11*	1.07, 1.15
Unknown	0.77*	0.73, 0.82
Patient residence rurality setting		
Urban (Reference)	-	
Suburban	0.98	0.94,1.01
Rural	1.01	0.97,1.04
Unknown	1.10	0.75,1.63
Charlson comorbidity score		
0 (Reference)	-	
1	0.97	0.93,1.00
2	1.12*	1.09,1.15
>=3	1.03*	1.01,1.06

* rate ratios have p-value<0.05

Table 5: Lung cancer yield by type of follow-up procedures performed after index chest CT-scan

Type of follow-up procedures performed	**Lung Cancer Diagnosis within 2 years (n=2,348)**	
	N	%
Suspicious non-urgent indeterminate pulmonary nodule finding with recommended surveillance care (n=1,393)		
Short interval surveillance imaging – 2-4 months	311	13.2
Mid-interval surveillance imaging – 5-9 months	429	18.3
Long interval surveillance imaging – 10-16 months	653	27.8
Pulmonary conditions other than a lung nodule with follow-up procedures	406	17.4
No suspected pulmonary nodule finding (n=549)		
Non-surveillance procedures (e.g. chest x-ray)	375	16.0
No procedures within 12-months	174	7.4
Total	**2,348**	100.0

Figure 3: 24-month lung cancer rate among those who had a non-urgent indeterminate pulmonary nodule finding with recommended surveillance care (PPV) by Histoplasmosis endemicity

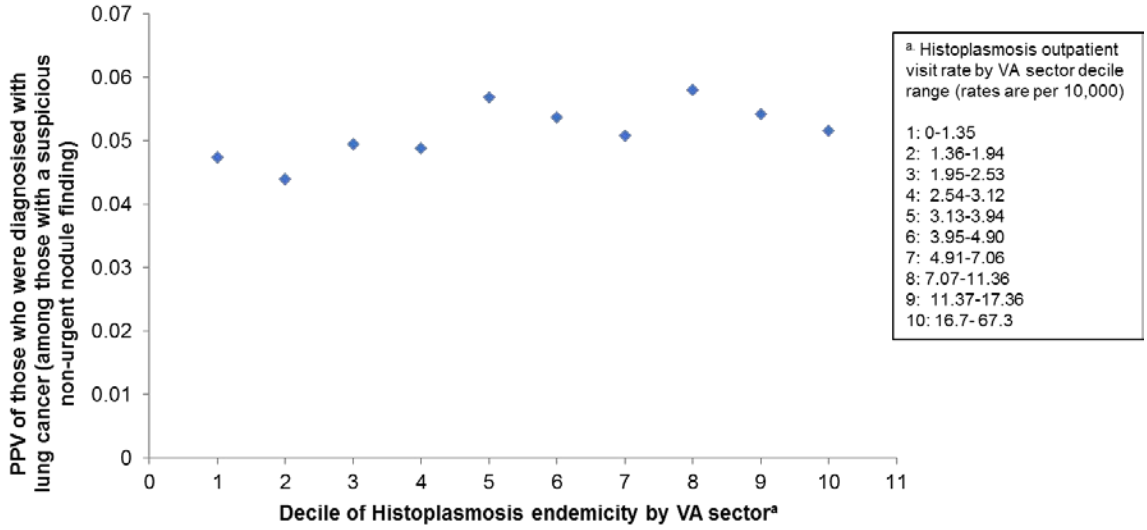


Figure 4: 24-month lung cancer rate among those who did not have a non-urgent indeterminate pulmonary nodule finding with recommended surveillance care (NPV) by Histoplasmosis endemicity

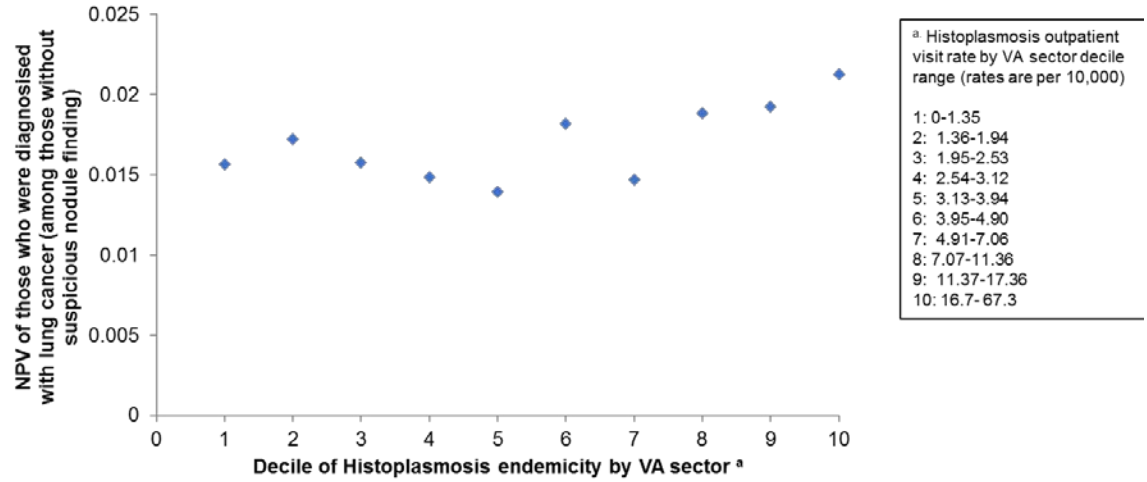


Table 6: Adjusted risk ratio of lung cancer diagnosis (after 24 months) among those detected with a suspicious non-urgent indeterminate pulmonary nodule finding (n=27,024)

Variables	Adjusted risk ratio	95% Confidence Interval
Histoplasmosis [a]		
1st Quartile (Reference; n= 6,750)	-	-
2nd Quartile (n=6,564)	1.14	0.99,1.33
3rd quartile (n=7,166)	1.17*	1.01,1.35
4th quartile (n=6,544)	1.15	0.99,1.33
Age		
<55 (Reference)	-	-
55-64	2.23*	1.78,2.79
65-74	3.04*	2.44,3.79
=>75	3.68*	2.94,4.60
Gender		
Female (Reference)	-	
Male	1.21	0.86,1.70
Race		
White (Reference)	-	
Black	1.12	0.96,1.32
Other	0.87	0.73,1.05
Smoking Status		
Never smoker (Reference)	-	
Current smoker	3.80*	2.93,4.92
Former smoker	2.01*	1.54,2.62
Unknown	2.80*	2.04,3.85
Patient residence rurality setting		
Urban (Reference)	-	
Suburban	1.01	0.85,1.21
Rural	0.95	0.79,1.13
Charlson comorbidity score		
0 (Reference)	-	
1	0.89	0.72,1.10
2	1.45*	1.26,1.68
>=3	1.44*	1.25,1.66

* rate ratios have p-value<0.05

a. 1st quartile rate range: 0-2.32; 2nd quartile rate range: 2.33-4.08; 3rd quartile rate range: 4.09-10.19; 4th quartile rate range: 10.25-67.25

Appendix Table 1: List of follow-up procedures (with CPT codes and descriptions) and their follow-up classification

		Excluded as immediate procedure for suspected non-pulmonary metastasis (within 60 days)	Excluded as immediate pulmonary procedure (within 60 days)	Classified as short interval imaging 2-4 months	Classified as mid-interval surveillance imaging: 5-9 months	Classified as long interval surveillance imaging:10-16 months	Classified as unknown pulmonary conditions with follow-up procedures
Head PET							
78609	Brain imaging (pet)	X					X
Head CT							
70450	Ct head/brain w/o dye	X					X
70460	Ct head/brain w/dye	X					X
70470	Ct head/brain w/o & w/dye	X					X
Head MRI							
70551	Mri brain w/o dye	X					X
70552	Mri brain w/dye	X					X
70553	Mri brain w/o & w/dye	X					X
Pulmonary surgical procedure							
32110 32120 32140 32141 32150 32151 32160	Thoracotomy		X				X

		Excluded as immediate procedure for suspected non-pulmonary metastasis (within 60 days)	Excluded as immediate pulmonary procedure (within 60 days)	Classified as short interval imaging 2-4 months	Classified as mid-interval surveillance imaging: 5-9 months	Classified as long interval surveillance imaging:10-16 months	Classified as unknown pulmonary conditions with follow-up procedures
Pulmonary surgical procedure							
32440 32442 32445 32480 32482 32484 32486 32488 32491	Removal of lung		X				X
32601-32608	Thoracoscopy, diagnostic with/without biopsy (ies)		X				X
32650-32659	Thoracoscopy, surgical		X				X
39010	Mediastinotomy with exploration, drainage, removal of foreign body, or biopsy; transthoracic approach, including either transthoracic or median sternotomy		X				X
32661 - 32668	Thoracoscopy, surgical; with therapeutic wedge resection		X				X

		Excluded as immediate procedure for suspected non-pulmonary metastasis (within 60 days)	Excluded as immediate pulmonary procedure (within 60 days)	Classified as short interval imaging 2-4 months	Classified as mid-interval surveillance imaging: 5-9 months	Classified as long interval surveillance imaging:10-16 months	Classified as unknown pulmonary conditions with follow-up procedures
Pulmonary surgical procedure							
32501	Resection and repair of portion of bronchus (bronchoplasty) when performed at time of lobectomy or segmentectomy		X				X
32505 - 32507	Thoracotomy, w/ wedge resection		X				X
32096 - 32100	Thoracotomy, with/without diagnostic biopsy(ies)		X				X
32800	Repair lung hernia through chest wall		X				X
Pulmonary biopsy							
32400	Needle biopsy chest lining		X				X
32405	Biopsy, lung or mediastinum		X				X
10021	Fine needle aspiration w/o image		X				X
10022	Fine needle aspiration w/image		X				X
77012	Ct scan for needle biopsy		X				X
39400	Mediastinoscopy, includes biopsy(ies), when performed		X				X

		Excluded as immediate procedure for suspected non-pulmonary metastasis (within 60 days)	Excluded as immediate pulmonary procedure (within 60 days)	Classified as short interval imaging 2-4 months	Classified as mid-interval surveillance imaging: 5-9 months	Classified as long interval surveillance imaging:10-16 months	Classified as unknown pulmonary conditions with follow-up procedures
Pulmonary biopsy							
32141	Remove treat lung lesions (thoractomy)		X				X
Bronchoscopy with biopsy							
31625	Bronchoscopy w/biopsy(s)		X				X
31628	Bronchoscopy /lung bx, each		X				X
31629	Bronchoscopy/needle bx, each		X				X
31632	Bronchoscopy/lung bx, addl		X				X
31633	Bronchoscopy/needle bx addl		X				X
31640	Bronchoscopy w/tumor excise		X				X
Bronchoscopy							
31622	Dx bronchoscope/wash		X				X
31623	Dx bronchoscope/brush		X				X
31624	Dx bronchoscope/lavage		X				X
31630	Bronchoscopy dilate/fx repair		X				X

		Excluded as immediate procedure for suspected non-pulmonary metastasis (within 60 days)	Excluded as immediate pulmonary procedure (within 60 days)	Classified as short interval imaging 2-4 months	Classified as mid-interval surveillance imaging: 5-9 months	Classified as long interval surveillance imaging:10-16 months	Classified as unknown pulmonary conditions with follow-up procedures
Bronchoscopy							
31635	Bronchoscopy w/fb removal		X				X
31636	Bronchoscopy, bronch stents		X				X
31637	Bronchoscopy, stent add-on		X				X
31638	Bronchoscopy, revise stent		X				X
31643	Diag bronchoscope/catheter		X				X
31645	Bronchoscopy, clear airways		X				X
Full body PET/PET-CT							
78811	Tumor imaging (pet), limited		X	X			
78812	Tumor image (pet)/skull-thigh		X	X			
78813	Tumor image (pet) full body		X	X			
78814	Tumor image pet/ct, limited		X	X			
78815	Tumor image pet/ct skull-thigh		X	X			
78816	Tumor image pet/ct full body		X	X			

		Excluded as immediate procedure for suspected non-pulmonary metastasis (within 60 days)	Excluded as immediate pulmonary procedure (within 60 days)	Classified as short interval imaging 2-4 months	Classified as mid-interval surveillance imaging: 5-9 months	Classified as long interval surveillance imaging:10-16 months	Classified as unknown pulmonary conditions with follow-up procedures
Chest MRI							
71550	Mri chest w/o dye		X	X			
71552	Mri chest w/o & w/dye		X	X			
Chest CT							
71250	Diagnostic ct w/o contrast / ct low dose helical screening ct exam / ct thorax w/o dye		X	X	X	X	
71260	Diagnostic ct w/contrast / ct thorax w/dye		X	X	X	X	
71270	Diagnostic ct w/o then w/contrast / ct thorax w/o & w/dye		X	X	X	X	

CHAPTER 4- Histoplasmosis exposure and costs of follow-up among patients undergoing diagnostic chest CT imaging

Abstract

Objective

Residing in areas with high levels of histoplasmosis exposure influences the results of diagnostic chest CT imaging. The objective of this study is to assess if living in a higher histoplasmosis endemic area leads to more follow-up procedures and thus higher follow-up procedure costs over a 2-year follow-up period.

Methods

We identified a national cohort of 70,725 individuals who either had a non-urgent lung nodule finding (27,024, 38%) or no suspicious pulmonary finding (43,701, 62%) on a diagnostic chest CT at 130 VHA Medical Centers in FY2011. Categorization was based on an administrative algorithm accounting for the timing of follow-up procedures a patient received. Patients undergoing CT imaging for specific pulmonary conditions, for a previously diagnosed cancer, or who had a finding for suspected malignancy immediately after their diagnostic chest CT were excluded. We assessed relevant follow-up procedures including additional chest CT scans, pulmonary biopsies, and surgical procedures within 24 months of the index diagnostic chest CT scan.

The rates of geographic variation in histoplasmosis exposure (calculated in Chapter 2) were used to assign an endemicity level based on residential zip code at the time of the patient's index scan. A 2-part cost model was used to estimate the differences in cost associated with histoplasmosis endemicity adjusting for other clinical and demographic factors.

Results

Overall, this cohort incurred $128,596,305 in costs attributable to follow-up procedures over the 24-month period following a diagnostic chest CT with a mean cost of $1,818 per person ($909 per person per year). Twenty-eight percent of the cohort (n=19,903) incurred zero cost after their index chest CT scan. The majority of costs (90%) were incurred among patients who had a non-urgent nodule identified on the index CT (average per individual= $4,111.) compared to patients with no pulmonary findings (average per individual= $400). Pulmonary biopsies, bronchoscopies and chest CTs were the procedures with the highest corresponding costs ($39,646,916; $34,872,571; $19,497,480 respectively). Increasing quartile of histoplasmosis endemicity, increasing age, current or former smoking status, and increasing number of comorbidities all increased the likelihood of having any costs.

Across quartiles of histoplasmosis endemicity, overall average individual costs ranged from $1,685 to $1,981. .After adjusting for individual demographic and clinical characteristics, patients living in areas with the highest levels of histoplasmosis endemicity (quartile 4) had costs that were $263 (95% CI: $58 - $475) higher compared to patients in areas with the lowest endemicity levels (quartile 1).

Conclusions

Histoplasmosis endemicity influenced the number and cost of follow-up procedures following diagnostic chest CT imaging. Variation in histoplasmosis exposure appears to be a small contributing factor to increased costs in this large national cohort.

Introduction

Non-urgent indeterminate nodules are nodules (or abnormalities) that are less than 1 centimeter in diameter and have the appearance of malignancies but may be

benign. Although most non-urgent indeterminate pulmonary nodules never progress to lung cancer, some clinical guidelines call for surveillance with repeat imaging for up to 24 months after detection to determine the stability of the nodule and likelihood of lung cancer.[1–4] Estimates of suspicious pulmonary nodule findings requiring surveillance or follow-up care have widely ranged from 16% to 60% in cohorts of individuals undergoing diagnostic or screening chest CT imaging. [1,5,6] In the National Lung Screening Trial (NLST) study, 21.7% of the study population had a non-urgent suspicious abnormal chest CT finding requiring follow-up imaging; less than 3% of those individuals actually went on to be diagnosed with lung cancer within two years.[7,8] A large number of individuals who have diagnostic chest CT scans may undergo unnecessary follow-up procedures for nodules that are not associated with lung cancer.[7–11]

Prior studies show that endemic fungal lung infections, specifically histoplasmosis, contribute to the variability in follow-up procedures.[11–13] Granuloma inflammation and scarring caused by histoplasmosis can look identical to cancerous tissue on a chest-CT scan. In fact, histoplasmosis granuloma inflammation can have all of the hallmarks of a cancerous nodule including growth on repeated CT scans and lack of calcification.[14]

Detection of non-urgent indeterminate pulmonary nodules leading to a substantial number of follow-up procedures may be exacerbated in histoplasmosis endemic areas. If true, this may result in unnecessary utilization of healthcare resources and wasteful healthcare expenditures. The objective of this study is to assess if living in a higher histoplasmosis endemic area leads to more follow-up procedures and

subsequently higher follow-up procedure costs over a 2-year follow-up period, compared to those living in lower endemic areas.

Methods

Data Sources

Data for this study were extracted from the Veterans Health Administration (VHA) Corporate Data Warehouse (CDW),[15] a repository of all health care utilization data, including dates of service, diagnoses, and procedures conducted by VHA health care providers and documented in the VHA's electronic medical records (EMR). Inpatient and outpatient radiology, surgical, and biopsy procedures were extracted for 24 months following the date of the first (index) chest CT each individual received during the study period. Twenty- four months was used because it is in accordance with the clinical guidelines which recommend follow-up for up 2 years. The CDW also provided information on patient demographics, VHA medical facility and geocoded address, lung cancer diagnosis, and dates of death.

Outpatient procedure costs were estimated based on the prices reported in the NLST study which used the 2009 Physician Fee Schedule for both professional and technical components of all outpatient procedures.[8] Inpatient procedure costs were aggregated from the Health Economics Resource Center (HERC) inpatient average discharge cost dataset. Details on these data have been described previously in other studies.[15] The specific cost assignment method used for this study is described below.

Data were extracted between FY 2014 and FY2015 analyses were conducted in calendar years 2015-2017.

Population

The study population included individuals between ages 40 and 79 who had a diagnostic chest CT scan (CPT codes: 71250, 71260 and 71270) between October 1, 2010 and September 30, 2011. This time period corresponds to the US Preventive Services Task Force's focus on the prevention of lung cancer and the release of new recommendations around screening. This study focused on those between ages 40 and 79 since providers may not necessarily follow guidelines for atypical younger patients or older patients with additional comorbidity. The focus of the study was not on how providers manage these outlier/unique patients but on typical patients with non-urgent chest CT scan nodule findings.

We excluded individuals with any history of lung cancer and other cancers (ICD-9 codes: 140-239) prior to the date of their earliest FY2011 CT scans (n=47,336). Other exclusions included individuals with incomplete or errors in their EMR data (including missing data; n=51) and missing histoplasmosis outpatient rates (n=987).

To restrict our study population to only those individuals with non-urgent pulmonary findings, we excluded patients immediately diagnosed with lung cancer (n=2,144) within 60 days of their index chest and patients who underwent immediate (urgent) pulmonary procedures after their index chest CT scan were excluded (n=19,633). These procedures and their groupings are listed in Table 1 of the Appendix.[7]

Individuals assumed to have pulmonary conditions other than a pulmonary nodule, who received follow-up procedures consistent with management of a pulmonary condition such as pulmonary embolism (n=12,819), were also excluded. These individuals either: do not have nodules and have other pulmonary diseases motivating

the care/procedures they received, or have a nodule and received follow-up procedures/imaging not in accordance with recommended guidelines (Appendix Table 1).

The final study population included 70,725 cancer-free patients who underwent diagnostic chest CT imaging at 130 VHA Medical Centers in FY2011 and who did not have a highly suspicious pulmonary finding from their index chest CT scan.

Measures

Detection of non-urgent indeterminate pulmonary nodules from index CT

From the study population of 70,725 individuals, we identified those with suspected non-urgent indeterminate pulmonary nodules based on imaging follow-up sequence. Because coding of non-urgent indeterminate pulmonary nodules is not available electronically, we developed an administrative algorithm to determine and categorize the frequency of non-urgent findings based on the date and type of the individual's first follow-up procedure after their index scan. This algorithm was based on the Fleischner guidelines for managing small pulmonary nodules detected on CT scans.[16] From each patient's index CT, we assigned follow-up categories for the first surveillance imaging based on the type of follow-up procedures of interest (Appendix Table 1). Individuals were considered to have no suspicious pulmonary nodule findings (n=43,701) if they only had follow-ups with procedures such as chest x-rays, pulmonary function tests, and unspecified pulmonary procedures within 2 years of their index chest CT scan.

Histoplasmosis Exposure

As detailed in Chapter 2, geographic variation in histoplasmosis endemicity was based on geographic rates of outpatient visits in the VHA over a 10-year period. These visit rates were calculated by taking ICD-9 diagnosis counts of unique VHA users with at least one outpatient histoplasmosis visit between fiscal years 2005-2015. Five hundred four VHA planning sectors, consisting of one or more US counties, were used as the primary unit of geographic analysis. An average rate for each sector was calculated as the total number of histoplasmosis outpatient cases in each sector divided by the total number of unique outpatient VHA users in each sector during the study period. This reflects a person-year approach with the assumption that an individual treated in one year would be at risk of treatment in subsequent years. On average, there were 27,465 patients each year with an outpatient visit for histoplasmosis, ranging from 24,412 in 2006 to 27,589 in 2015. The average national rate of histoplasmosis outpatient visits was 7.99 per 10,000 person-years during this time period.

We grouped our study population into four (quartile) groups across the distribution of histoplasmosis endemicity levels based on their geographic VHA sector (based on their individual zip codes). The patients in the lowest quartile were from areas where the average national outpatient visit rate across VHA from 2005-2015 for a histoplasmosis infection was 1.46 per 10,000 person-years, and the patients in the in the highest quartile were from areas where the average outpatient visit rate was 19.92 per 10,000 person-years.

Cost Assignment

Costs were assigned to type of follow-up procedures based on their outpatient or inpatient setting. As stated previously, outpatient procedure costs were assigned based

on prices reported in the NLST study.[8] The NLST study used 2009 Physician Fee Schedule prices. For our study, we adjusted the 2009 prices to 2011 dollars using the consumer price index (CPI).

Inpatient costs were calculated using HERC inpatient average discharge costs[17]. These costs are estimated based on Diagnosis Related Group, overall length of stay, and days in intensive care. Estimates are also based on analysis of cost-adjusted charges in the Medicare funded stays of veterans in non-VA hospitals. These costs are adjusted in order to correspond to national VA expenditures for each type of care and are calculated assuming that all encounters with the same observed characteristics have the same average cost.[17] A crosswalk of CPT codes and HERC median costs was generated and is reported in Table 2 Appendix.

Statistical Analysis

Descriptive analyses of the population were calculated across the primary exposure – the histoplasmosis endemicity level of their residence, as well as whether a patient was identified with a non-urgent pulmonary nodule. Total counts per procedure of interest were calculated and categorized based on pulmonary findings and histoplasmosis endemicity. The Cochran–Armitage test for trend was conducted to assess the association between quartiles of histoplasmosis endemicity and count of procedures. This test is a modified version of the Pearson chi-squared test to assess the effects of the ordering of categories.[18] Total costs and mean costs per individual were calculated and categorized based on pulmonary findings and histoplasmosis endemicity. In addition, total costs per procedure of interest were calculated and categorized based on pulmonary findings and histoplasmosis endemicity.

A 2-part cost model was conducted. Two-part models allow for more flexibility in modeling of costs; it allows for inclusion of observations with zero costs and corrects for skewed or kurtotic distributions, and heteroscedastic errors in the data. In addition, it allows for the calculation of the effect of interest on the additive scale. We first modeled the probability of any follow up cost (part 1); then modeled the cost given histoplasmosis endemicity among those that have non-zero costs (part 2), to obtain the incremental cost of residing in increasing quartiles of histoplasmosis endemicity.

Part 1 of the 2-part cost model utilized a logistic regression model to measure the likelihood of an individual having any cost given their nodule findings. In addition to including histoplasmosis endemicity level, this model was adjusted for demographic and clinical characteristics including age, gender, race, smoking status, rurality setting, and Charlson comorbidity.[19]

Part 2 of the 2-part model used a generalized linear model (GLM) approach. The GLM framework requires a link function that relates the conditional mean to the covariates and a distribution to specify the relationship between the variance and the mean. For this study, the link function and appropriate distribution for our GLM model was determined based on diagnostic tests.[20,21] Based on these tests, we used a log link and a gamma distribution in our GLM to estimate adjusted cost. The incremental costs were calculated using counterfactual regression predictions where we gave an attributable cost based on the difference between the entire sample residing in each sequential quartile (2-4) of histoplasmosis endemicity and residing in quartile 1 of histoplasmosis endemicity.[22] 95% confidence intervals were generated post-estimation using the 'boot' package in R with 10,000 iterations.[23]

All statistical analyses were preformed using Stata statistical software, version 14.0 (StataCorpLP) and R version 3.2.22.[24] The Puget Sound VA Medical Center IRB approved this study.

Results

Of our national VA cohort of 70,725 cancer-free patients who underwent diagnostic chest CT imaging in FY2011 and did not have urgent findings or other pulmonary conditions, 27,024 (38%) were identified as having a non-urgent pulmonary nodule finding (Table 1). Those with non-urgent pulmonary nodule findings underwent 90% of the follow-up procedures of interest that occurred within the 24-month period following a diagnostic chest CT scan.

Chest CTs, advanced imaging, and pulmonary biopsy procedures were the three most frequently performed procedures (59,799, 12,618, and 2,006 respectively) (Table 2a). The number of follow-up chest CT procedures varied slightly among patients residing in areas with high and low histoplasmosis endemicity, ranging from 14,700 in quartile 1 to 14,972 in quartile 4 of histoplasmosis endemicity (p-value <0.05). Similar trends in the number of follow up procedures were observed for pulmonary biopsies (473 – 551; p-value <0.05). Among individuals with non-urgent pulmonary nodules, these trends were comparable (p-value <0.05). Among those in the no suspected pulmonary nodule group, the number of follow-up chest CT procedures and pulmonary biopsies remained relatively stable across quartiles of histoplasmosis endemicity. Other procedures of interest did not exhibit clear trends of increasing counts of follow-up procedures across quartiles of histoplasmosis endemicity, overall or when categorized by pulmonary findings. (Table 2b)

Overall, this cohort incurred $128,596,305 in costs of follow-up procedures over the 24-month period following a diagnostic chest CT with a mean cost of $1,818 per individual ($909 per person per year) (Table 3). Twenty-eight percent of the cohort (n=19,903) incurred zero cost after their index chest CT scan. The majority of costs were incurred among individuals with non-urgent pulmonary nodule findings ($111,095,197; average per individual= $4,111). Across quartiles of histoplasmosis endemicity, overall average individual costs ranged from $1,685 to $1,981 (Table 3).

Pulmonary biopsies, bronchoscopies and chest CTs were the procedures with the highest corresponding costs ($39,646,916; $34,872,571; $19,497,480 respectively). (Table 4) Overall, the total costs for Chest CTs and pulmonary biopsies increased slightly across quartiles of histoplasmosis endemicity (Table 4).

Increasing quartile of histoplasmosis endemicity, increasing age, current or former smoking status, and increasing number of comorbidities all increased the likelihood of having any costs. The most notable result was among individuals with three or greater comorbidities for which the odds of having any costs were 2.4 (95% CI 2.3 – 2.5) times more likely compared to individuals with no comorbidities. (Appendix Table 3) After adjusting for individual demographic and clinical characteristics, patients living in areas with the highest levels of histoplasmosis endemicity (quartile 4) had costs that were $263 (95% CI: $56 - $475) higher compared to patients in areas with the lowest endemicity levels (quartile 1).

Discussion

Histoplasmosis endemicity has a minor association with the number and costs of follow-up procedures performed after diagnostic chest CT imaging in this national cohort of patients in unadjusted and adjusted analyses.

Studies have raised the question of how or if histoplasmosis affects follow-up and costs among those with non-urgent pulmonary nodules, specifically, if histoplasmosis contributes to the variability of false positive results and subsequent follow-up recommendations.[8,11,13,25] These studies have found follow-up to be more common in areas with a high prevalence of histoplasmosis.[6,13] In this study, across quartiles of histoplasmosis endemicity average individual costs ranged from $1,685 to $1,981; thus, our findings suggest that residing in a high histoplasmosis region does not greatly impact follow-up care after diagnostic chest CT imaging. However, chest CTs and pulmonary biopsies were found to increase across quartiles of histoplasmosis endemicity, and were two of the main drivers of the overall costs.

There are some limitations to our study. Our study population focused on individuals with non-urgent pulmonary nodule findings or no nodules; thus we excluded those patients with more urgent suspicious pulmonary findings. We are unable to examine how residing in a histoplasmosis endemic region influences more urgent findings. We excluded patients with more urgent findings, so the number of procedures and costs in our cohort do not represent the full spectrum incurred for all patients undergoing diagnostic CT imaging. Another potential limitation is that we relied on follow-up procedures to make inferences about the presence of a nodule identified on the index diagnostic CT scan. We may have misclassified some individuals because radiology coding about nodules was not routinely reported and we were not able to

access individual patient medical records. Lastly, the method by which inpatient costs were assigned using HERC data assumes that all encounters that share the same characteristics receive the same average cost estimate. This assumption is unable to be verified and could bias our findings and result in either an overestimation of underestimation of the true costs. Furthermore, the prices reported are truly not equal to costs, but are prices that payers, such as private insurers, would reimburse for a procedure.

The incremental increase in cost in our study was small thus other factors, aside from Histoplasmosis exposure, may also contribute to the variability observed. In intermediate analyses, we found that increasing age, smoking status, and increasing number of comorbidities all increased the likelihood of an individual having any costs. Other factors that were not measured in our study may contribute to additional variability; thus we would recommend further research in this area to focus on variability resulting from factors such as radiologist or clinic practices.[11] In order to confirm the generalizability of our findings, future research should be undertaken in a different population, since our population mostly consisted of older male veterans.

References

1. Black W. Computed tomography screening for lung cancer: review of screening principles and update on current status. *Cancer*. 2007;110(11):2370-2384. doi:10.1002/cncr.23059.
2. Wahidi M, MGovert J, Gouda R, McCrory D. American College of Chest Physicians Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer?: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*. 2007;132:94S-107S.
3. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: When is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 SUPPL):e93S-e120S. doi:10.1378/chest.12-2351.
4. Moyer V. Screening for lung cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(5):330-338.
5. Silvestri G. Screening for lung cancer: it works, but does it really work? *Ann Intern Med*. 2011;155(8):537-540.
6. Pinsky PF, Gierada DS, Nath PH, Kazerooni E, Amorosa J. National lung screening trial: variability in nodule detection rates in chest CT studies. *Radiology*. 2013;268(3):865-873. doi:10.1148/radiol.13121530.
7. Church TR, Black WC, Aberle DR, et al. Results of initial low-dose computed tomographic screening for lung cancer. *N Engl J Med*. 2013;368:1980-1991. doi:10.1056/NEJMoa1209120.
8. Black WC, Gareen IF, Soneji SS, et al. Cost-Effectiveness of CT Screening in the National Lung Screening Trial. *N Engl J Med*. 2014;371(19):1793-1802. doi:10.1056/NEJMoa1312547.
9. Gohagan JK, Marcus PM, Fagerstrom RM, et al. Final results of the Lung Screening Study, a randomized feasibility study of spiral CT versus chest X-ray screening for lung cancer. *Lung Cancer*. 2005;47:9-15. doi:10.1016/j.lungcan.2004.06.007.
10. Patz EF, Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med*. 2014;174(2):269-274. doi:10.1001/jamainternmed.2013.12738.
11. Singh S, Pinsky P, Fineberg N, Gierada D. Evaluation of reader variability in the interpretation of follow-up CT scans at lung cancer screening. *Radiology*. 2011;259(1):263-270. doi:10.1148/radiol.10101254/-/DC1.
12. Salhab KF, Baram D, Bilfinger T V. Growing PET positive nodule in a patient with histoplasmosis: case report. *J Cardiothorac Surg*. 2006;1:23. doi:10.1186/1749-8090-1-23.
13. Starnes SL, Reed MF, Meyer C a, et al. Can lung cancer screening by computed tomography be effective in areas with endemic histoplasmosis? *J Thorac Cardiovasc Surg*. 2011;141(3):688-693. doi:10.1016/j.jtcvs.2010.08.045.
14. Sharma P, Mukherjee A, Karunanithi S, Bal C, Kumar R. Potential Role of 18F-FDG PET/CT in Patients With Fungal Infections. *Am J Roentgenol*. 2014;203(1):180-189. doi:10.2214/AJR.13.11712.
15. Maynard C, Chapko MK. Data Resources in the Department of Veterans Affairs. *Diabetes Care*. 2004;27:B22-B26. doi:10.2337/diacare.27.suppl_2.B22.

16. MacMahon H, John M Austin BH, Gamsu G, et al. Guidelines for Management of Small Pulmonary Nodules Detected on CT Scans: A Statement from the Fleischner Society. *Radiology*. 2005;237:395-400. doi:10.1148/radiol.2372041887.
17. Wagner T, Chow A, Su P BP. *Guidebook: HERC's Average Cost Datasets for VA Inpatient Care, FY1998-FY2016*. Menlo Park, CA. VA Palo Alto
18. Agresti A. *Categorical Data Analysis (Second Ed.)*. Wiley.; 2002.
19. Sharabiani, Mansour; Aylin, Paul; Bottle A. Systematic review of comorbidity indices for administrative data. *Med Care Res Rev*. 2012;50(12):1109-1118.
20. Manning W, Mullahy J. Estimating log models : to transform or not to transform ? *J Health Econ*. 2001;20(June 1999):461-494.
21. Manning W, Basu A, Mullahy J. Generalized modeling approaches to risk adjustment of skewed outcomes data. *J Health Econ*. 2005;24:465-488.
22. Coughlan D, Yeh ST, O'Neill C, Frick KD. Evaluating direct medical expenditures estimation methods of adults using the medical expenditure panel survey: An example focusing on head and neck cancer. *Value Heal*. 2014;17(1):90-97. doi:10.1016/j.jval.2013.10.004.
23. Canty A RB. Bootstrap R (S-Plus) functions. 2012.
24. R Core Team. R: A language and environment for statistical computing. 2016.
25. Marshall HM, Bowman R V., Yang I a., Fong KM, Berg CD. Screening for lung cancer with low-dose computed tomography: A review of current status. *J Thorac Dis*. 2013;5. doi:10.3978/j.issn.2072-1439.2013.09.06.
26. Chu JH, Feudtner C, Heydon K, Walsh TJ, Zaoutis TE. Hospitalizations for endemic mycoses: a population-based national study. *Clin Infect Dis*. 2006;42(6):822-825. doi:10.1086/500405.
27. Baddley J, Winthrop K. Geographic distribution of endemic fungal infections among older persons, United States. *Emerg Infect Dis*. 2011;17(9):7-12.
28. Kurowski R, Ostapchuk M. Overview of histoplasmosis. *Am Fam Physician*. 2002;66(12):2247-2252.

Tables and Figures

Figure 1: Study Population exclusion/inclusion criteria and lung cancer diagnosis

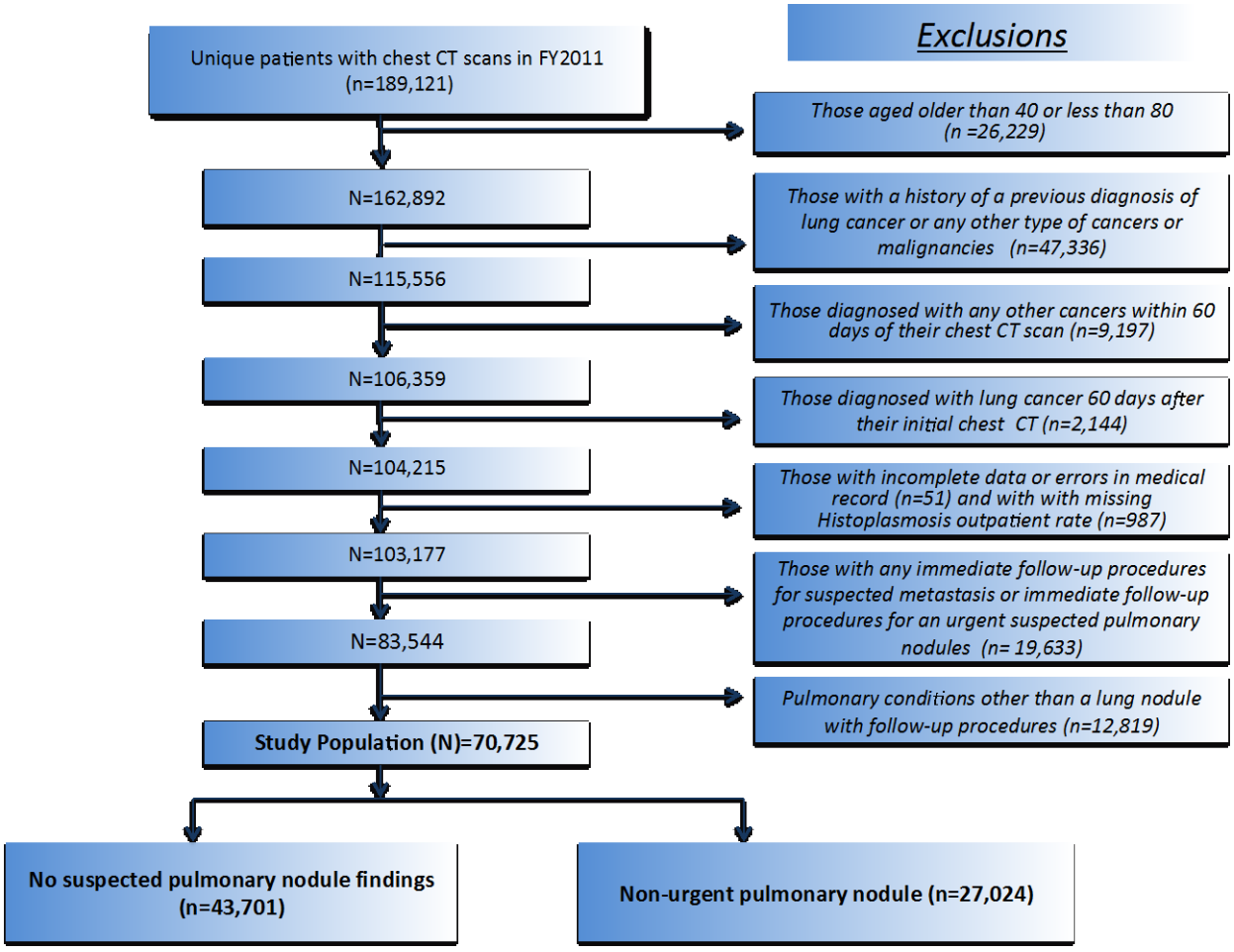


Table 1: Study population demographics

	Overall n=70,725		Non-urgent pulmonary nodule n=27,024		No suspected pulmonary nodule findings n=43,701		p-value
	N	%	N	%	N	%	
Age							<0.05
<55	11,413	16.1	3,452	12.8	7,961	18.2	-
55-64	30,104	42.6	11,650	43.1	18,454	42.2	-
65-74	21,255	30.1	8,665	32.1	12,590	28.8	-
=>75	7,953	11.2	3,257	12.1	4,696	10.8	-
Gender							<0.05
Male	67,682	95.7	26,008	96.2	41,674	95.4	-
Female	3,043	4.3	1,016	3.8	2,027	4.6	-
Race							<0.05
White	52,200	73.8	20,896	77.3	31,304	71.6	-
Black	10,257	14.5	3,328	12.3	6,929	15.9	-
Other	8,268	11.7	2,800	10.4	5,468	12.5	-
Marital Status							<0.05
Married	35,519	50.2	14,101	52.2	21,418	49	-
Not married	35,071	49.6	12,902	47.7	22,169	50.7	-
Unknown	135	0.2	21	0.1	114	0.3	-
Smoking status							<0.05
Current smoker	30,013	42.4	11,873	44	18,140	41.5	-
Former smoker	27,668	39.1	11,110	41.1	16,558	37.9	-
Never smoker	8,407	11.9	2,856	10.6	5,551	12.7	-
Unknown	4,637	6.6	1,185	4.4	3,452	7.9	-
Patient residence rurality setting							<0.05
Urban	57,868	81.8	22,086	81.7	35,782	81.9	-
Suburban	6,308	8.9	2,364	8.8	3,944	9	-
Rural	6,510	9.2	2,558	9.5	3,952	9	-
Unknown	39	0.1	16	0.1	23	0.1	-
Charlson comorbidity score							<0.05
0	21,099	29.8	7,162	26.5	13,937	31.9	-
1	9,081	12.8	3,204	11.9	5,877	13.5	-
2	19,708	27.9	8,160	30.2	11,548	26.4	-
>=3	20,837	29.5	8,498	31.5	12,339	28.2	-

Table 2a: Type and count of follow up procedures performed after index chest-CT scan

	Chest-CT's [a]	Advanced imaging	Pulmonary surgical procedure	Pulmonary Biopsy	Bronchoscopy with Biopsy	Bronchoscopy
	Total [b]	**Total**	**Total**	**Total**	**Total**	**Total**
	Type of nodule finding					
Overall (n=70,725)	59,799	12,618	52	2,006	820	1,705
Non-urgent pulmonary nodule (n=27,024)	55,601	9,346	51	1,767	734	1,495
No suspected pulmonary nodule finding (n=43,701)	4,198	3,272	1	239	86	210

a. List of procedure CPT codes are listed in Appendix
b. Total= Total number of procedures 24 months after index chest-CT

Table 2b: Type and count of follow up procedures performed after index chest-CT scan by Histoplasmosis endemicity

	Chest-CTs [a]		Advanced imaging		Pulmonary surgical procedure		Pulmonary Biopsy		Bronchoscopy with Biopsy		Bronchoscopy	
	Total [b]	p-value	Total	p-value	Total	p-value	Total	p-value	Total	p-value	Total	p-value
	Overall (n=70,725)											
1st Quartile [c] (n=18,640)	14,700	<0.05	3,217	<0.05	12	0.92	473	<0.05	189	0.57	429	0.68
2nd Quartile (n=17,436)	14,160	-	3,089	-	14	-	426	-	237	-	475	-
3rd Quartile (n=18,237)	15,967	-	3,322	-	17	-	556	-	205	-	372	-
4th Quartile (n=16,412)	14,972	-	2,990	-	9	-	551	-	189	-	429	-
	Non-urgent pulmonary nodule (n=27,024)											
1st Quartile (n=6,750)	13,599	<0.05	2,354	0.38	11	0.85	414	<0.05	158	0.67	366	0.41
2nd Quartile (n=6,564)	13,124	-	2,278	-	14	-	358	-	214	-	421	-
3rd quartile (n=7,166)	14,907	-	2,513	-	17	-	489	-	186	-	339	-
4th quartile (n=6,544)	13,971	-	2,201	-	9	-	506	-	176	-	369	-
	No suspected pulmonary nodule finding (n=43,701)											
1st Quartile (n=11,890)	1,101	0.60	863	0.10	1	0.20	59	0.75	31	<0.05	63	0.96
2nd Quartile (n=10,872)	1,036	-	811	-	0	-	68	-	23	-	54	-
3rd quartile (n=11,071)	1,060	-	809	-	0	-	67	-	19	-	33	-
4th quartile (n=9,868)	1,001	-	789	-	0	-	45	-	13	-	60	-

a. List of procedure CPT codes are listed in Appendix
b. Total= Total number of procedures 24 months after index chest-CT
c. Quartile rate range (per 10,000 person-years): 1st quartile: 0-2.32; 2nd quartile: 2.33-4.08; 3rd quartile: 4.09-10.19; 4th quartile: 10.25-67.25

Table 3: Follow-up care performed after index chest-CT scan total and average costs per individual

Type of nodule finding		
	Total Costs	**Average cost per individual (SD)**
Overall (n=70,725)	$ 128,596,305	$1,818 ($9,955)
Non-urgent pulmonary nodule (n=27,024)	$ 111,095,197	$4,111 ($15,055)
No suspected pulmonary nodule finding (n=43,701)	$ 17,501,109	$400 ($3,868)
Histoplasmosis endemicity		
Overall (n=70,725)		
1st Quartile (n=18,640)	$ 31,410,107	$1,685 ($9,260)
2nd Quartile (n=17,436)	$ 32,040,629	$1,838 ($11,267)
3rd Quartile (n=18,237)	$ 32,626,062	$1,789 ($8,968)
4th Quartile (n=16,412)	$ 32,519,509	$1,981 ($10,267)
Non-urgent pulmonary nodule (n=27,024)		
1st Quartile [d] (n=6,750)	$ 26,530,348	$3,930 ($13,946)
2nd Quartile (n=6,564)	$ 27,399,494	$4,174 ($17,319)
3rd quartile (n=7,166)	$ 28,592,197	$3,990 ($13,426)
4th quartile (n=6,544)	$ 28,573,158	$4,366 ($15,399)
No suspected pulmonary nodule finding (n=43,701)		
1st Quartile (n=11,890)	$ 4,879,759	$410 ($4,420)
2nd Quartile (n=10,872)	$ 4,641,135	$427 ($4,149)
3rd quartile (n=11,071)	$ 4,033,864	$364 ($3,263)
4th quartile (n=9,868)	$ 3,946,351	$400 ($3,436)

a. Quartile rate range (per 10,000 person-years): 1st quartile: 0-2.32; 2nd quartile: 2.33-4.08; 3rd quartile: 4.09-10.19; 4th quartile: 10.25-67.25

Table 4: Type and cost of follow up procedures performed after index chest CT scan

	Chest-CTs [a]	Advanced imaging	Pulmonary surgical procedure	Pulmonary Biopsy	Bronchoscopy with Biopsy	Bronchoscopy
	Total [c]	**Total**	**Total**	**Total**	**Total**	**Total**
	Type of nodule finding					
Overall (n=70,725)	$19,497,480	$7,696,635	$747,032	$39,646,916	$16,236,584	$34,872,571
Non-urgent pulmonary nodule (n=27,024)	$18,028,902	$6,222,093	$733,057	$34,953,217	$14,529,806	$30,568,076
No suspected pulmonary nodule finding (n=43,701)	$1,468,578	$1,474,542	$13,975	$4,693,699	$1,706,778	$4,304,495
	Histoplasmosis endemicity					
	Overall (n=70,725)					
1st Quartile (n=18,640)	$4,794,337	$2,027,415	$172,562	$9,342,678	$3,791,596	$8,681,268
2nd Quartile (n=17,436)	$4,812,764	$1,974,101	$200,954	$8,423,519	$4,624,421	$9,729,421
3rd Quartile (n=18,237)	$5,213,351	$2,002,161	$244,647	$10,966,955	$4,063,085	$7,694,152
4th Quartile (n=16,412)	$4,852,115	$1,692,958	$128,869	$10,913,764	$3,757,482	$8,767,730
	Non-urgent pulmonary nodule (n=27,024)					
1st Quartile [d] (n=6,750)	$4,413,586	$1,610,736	$158,587	$8,188,579	$3,187,796	$7,402,429
2nd Quartile (n=6,564)	$4,274,082	$1,591,349	$200,954	$7,094,316	$4,160,954	$8,590,817
3rd Quartile (n=7,166)	$4,839,222	$1,649,458	$244,647	$9,636,044	$3,676,924	$7,012,128
4th Quartile (n=6,544)	$4,502,013	$1,370,550	$128,869	$10,034,278	$3,504,132	$7,562,702
	No suspected pulmonary nodule finding (n=43,701)					
1st Quartile (n=11,890)	$380,751	$416,678	$13,975	$1,154,099	$603,800	$1,278,839
2nd Quartile (n=10,872)	$363,596	$382,752	-	$1,329,203	$463,467	$1,138,604
3rd Quartile (n=11,071)	$374,129	$352,703	-	$1,330,911	$386,161	$682,024
4th Quartile (n=9,868)	$350,102	$322,408	-	$879,486	$253,350	$1,205,028

a. List of procedure CPT codes are listed in Appendix
b. Total= Total cost of procedures 24 months after index chest-CT
c. Quartile rate range (per 10,000 person-years): 1st quartile: 0-2.32; 2nd quartile: 2.33-4.08; 3rd quartile: 4.09-10.19; 4th quartile: 10.25-67.25

Table 5: Adjusted average costs differences across histoplasmosis endemicity for follow up procedures performed after index chest CT scan (n= 70,725)

	Average adjusted incremental cost due to histoplasmosis endemicity	95% Confidence Interval
1st Quartile[a] (reference) (n=18,640)	-	
2nd Quartile (n=17,436)	$ 148	-$62 - $368
3rd Quartile (n=18,237)	$ 83	-$104 - $273
4th Quartile (n=16,412)	$ 263	$56 - $475

a. Quartile rate range (per 10,000 person-years): 1st quartile: 0-2.32; 2nd quartile: 2.33-4.08; 3rd quartile: 4.09-10.19; 4th quartile: 10.25-67.25

Appendix Table 1: List of follow-up procedures (with CPT codes and descriptions) and their follow-up classification

		Excluded as immediate procedure for suspected non-pulmonary metastasis (within 60 days)	Excluded as immediate pulmonary procedure (within 60 days)	Classified as non-urgent pulmonary nodule
Head PET				
78609	Brain imaging (pet)	X		
Head CT				
70450	Ct head/brain w/o dye	X		
70460	Ct head/brain w/dye	X		
70470	Ct head/brain w/o & w/dye	X		
Head MRI				
70551	Mri brain w/o dye	X		
70552	Mri brain w/dye	X		
70553	Mri brain w/o & w/dye	X		
Pulmonary surgical procedure				
32110 32120 32140 32141 32150 32151 32160	Thoracotomy		X	

		Excluded as immediate procedure for suspected non-pulmonary metastasis (within 60 days)	Excluded as immediate pulmonary procedure (within 60 days)	Classified as non-urgent pulmonary nodule
Pulmonary surgical procedure				
32440 32442 32445 32480 32482 32484 32486 32488 32491	Removal of lung		X	
32601-32608	Thoracoscopy, diagnostic with/without biopsy (ies)		X	
32650-32659	Thoracoscopy, surgical		X	
39010	Mediastinotomy with exploration, drainage, removal of foreign body, or biopsy; transthoracic approach, including either transthoracic or median sternotomy		X	
32661 - 32668	Thoracoscopy, surgical; with therapeutic wedge resection		X	

		Excluded as immediate procedure for suspected non-pulmonary metastasis (within 60 days)	Excluded as immediate pulmonary procedure (within 60 days)	Classified as non-urgent pulmonary nodule
Pulmonary surgical procedure				
32501	Resection and repair of portion of bronchus (bronchoplasty) when performed at time of lobectomy or segmentectomy		X	
32505 - 32507	Thoracotomy, w/ wedge resection		X	
32096 - 32100	Thoracotomy, with/without diagnostic biopsy(ies)		X	
32800	Repair lung hernia through chest wall		X	
Pulmonary biopsy				
32400	Needle biopsy chest lining		X	
32405	Biopsy, lung or mediastinum		X	
10021	Fine needle aspiration w/o image		X	
10022	Fine needle aspiration w/image		X	
77012	Ct scan for needle biopsy		X	
39400	Mediastinoscopy, includes biopsy(ies), when performed		X	

		Excluded as immediate procedure for suspected non-pulmonary metastasis (within 60 days)	Excluded as immediate pulmonary procedure (within 60 days)	Classified as non-urgent pulmonary nodule
Pulmonary biopsy				
32141	Remove treat lung lesions (thoractomy)		X	
Bronchoscopy with biopsy				
31625	Bronchoscopy w/biopsy(s)		X	
31628	Bronchoscopy /lung bx, each		X	
31629	Bronchoscopy/needle bx, each		X	
31632	Bronchoscopy/lung bx, addl		X	
31633	Bronchoscopy/needle bx addl		X	
31640	Bronchoscopy w/tumor excise		X	
Bronchoscopy				
31622	Dx bronchoscope/wash		X	
31623	Dx bronchoscope/brush		X	
31624	Dx bronchoscope/lavage		X	
31630	Bronchoscopy dilate/fx repair		X	

		Excluded as immediate procedure for suspected non-pulmonary metastasis (within 60 days)	Excluded as immediate pulmonary procedure (within 60 days)	Classified as non-urgent pulmonary nodule
Bronchoscopy				
31635	Bronchoscopy w/fb removal		X	
31636	Bronchoscopy, bronch stents		X	
31637	Bronchoscopy, stent add-on		X	
31638	Bronchoscopy, revise stent		X	
31643	Diag bronchoscope/catheter		X	
31645	Bronchoscopy, clear airways		X	
Full body PET/PET-CT				
78811	Tumor imaging (pet), limited		X	X
78812	Tumor image (pet)/skull-thigh		X	X
78813	Tumor image (pet) full body		X	X
78814	Tumor image pet/ct, limited		X	X
78815	Tumor image pet/ct skull-thigh		X	X
78816	Tumor image pet/ct full body		X	X

		Excluded as immediate procedure for suspected non-pulmonary metastasis (within 60 days)	Excluded as immediate pulmonary procedure (within 60 days)	Classified as non-urgent pulmonary nodule
Chest MRI				
71550	Mri chest w/o dye		X	X
71552	Mri chest w/o & w/dye		X	X
Chest CT				
71250	Diagnostic ct w/o contrast / ct low dose helical screening ct exam / ct thorax w/o dye		X	X
71260	Diagnostic ct w/contrast / ct thorax w/dye		X	X
71270	Diagnostic ct w/o then w/contrast / ct thorax w/o & w/dye		X	X

Appendix Table 2: List of inpatient follow-up procedures (with CPT codes and descriptions) and their HERC median cost assignment

Description	CPT Code	HERC Cost (Median cost)
Thoracotomy, with/without diagnostic biopsy(ies)	32096-32098; 32100	$ 24,278
Thoracotomy	32110 32120 32140 32141 32150 32151 32160	$ 24,278
Thoracotomy, w/ wedge resection	32505 - 32507	$ 24,278
Removal of lung	32440 32442 32445 32480 32482 32484 32486 32488 32491	$ 14,472
Resection and repair of portion of bronchus (bronchoplasty) when performed at time of lobectomy or segmentectomy	32501	$ 14,472
Mediastinotomy with exploration, drainage, removal of foreign body, or biopsy; transthoracic approach, including either transthoracic or median sternotomy	39010	$ 13,975
Thoracoscopy, diagnostic with/without biopsy (ies)	32601- 32609	$ 14,417
Thoracoscopy, surgical	32650- 32659	$ 14,417
Thoracoscopy, surgical; with therapeutic wedge resection	32661 - 32668	$ 14,417
Pulmonary biopsy		
Needle biopsy chest lining	32400	$ 26,922
Biopsy, lung or mediastinum	32405	$ 19,456
Remove treat lung lesions (thoractomy)	32141	$ 24,278
Mediastinoscopy, includes biopsy(ies), when performed	39400	$ 23,001
Ct scan for needle biopsy	77012	$ 19,996
Fine needle aspiration w/o image	10021	$ 16,638
Fine needle aspiration w/image	10022	$ 19,456
Bronchoscopy with biopsy		
Bronchoscopy w/biopsy(s)	31625	$ 20,240
Bronchoscopy /lung bx, each	31628	$ 18,679
Bronchoscopy/needle bx, each	31629	$ 19,585
Bronchoscopy/lung bx, addl	31632	$ 17,385
Bronchoscopy/needle bx addl	31633	$ 30,173
Bronchoscopy w/tumor excise	31640	$ 13,443

Bronchoscopy		
Dx bronchoscope/wash	31622	$ 20,324
Dx bronchoscope/brush	31623	$ 19,638
Dx bronchoscope/lavage	31624	$ 20,310
Bronchoscopy dilate/fx repair	31630	$ 41,331
Bronchoscopy w/fb removal	31635	$ 23,987
Bronchoscopy, bronch stents	31636	$ 70,097
Bronchoscopy, stent add-on	31637	$ 41,144
Bronchoscopy, revise stent	31638	$ 4,341
Diag bronchoscope/catheter	31643	$ 20,171
Bronchoscopy, clear airways	31645	$ 13,561

Appendix Table 3: 2-Part Model Intermediate Results (odds of having any costs)

	Odds Ratio	P-value	95% Confidence Interval	
Histoplasmosis endemicity				
1st Quartile	Reference	-	-	-
2nd Quartile	1.06	0.02	1.01	1.11
3rd Quartile	1.09	<0.05	1.04	1.14
4th Quartile	1.25	<0.05	1.19	1.31
Age				
<55	Reference	-	-	-
55-64	1.23	<0.05	1.00	1.11
65-74	1.19	<0.05	1.04	1.14
=>75	1.19	<0.05	1.19	1.31
Gender				
Female	Reference	-	-	-
Male	0.98	0.59	0.90	1.06
Race				
White	Reference	-	-	
Black	1.00	0.98	0.95	1.05
Other	0.78	<0.05	0.74	0.82
Smoking status				
Current smoker	Reference	-	-	-
Former smoker	1.19	<0.05	1.13	1.26
Never smoker	1.17	<0.05	1.11	1.24
Unknown	0.81	<0.05	0.75	0.88
Charlson comorbidity score				
0	Reference	-	-	-
1	1.19	<0.05	1.12	1.25
2	1.78	<0.05	1.70	1.86
>=3	2.42	<0.05	2.31	2.53

CHAPTER 5- Conclusions

Summary of findings

In this dissertation, we explored the relationship between environmental exposures and diagnostic chest CT outcomes. Paper 1 more precisely quantified levels of exposure of Histoplasmosis and Coccidioidomycosis than previously reported through the use of VA planning sectors. Paper 2 examined if greater Histoplasmosis endemicity is associated with increased detection of suspicious non-urgent indeterminate pulmonary nodule findings and explored the association in lung cancer detection rates and Histoplasmosis endemicity. Paper 3 assigned costs to follow-up procedures among those with suspicious non-urgent indeterminate pulmonary nodules and explored if costs were great for those living in higher Histoplasmosis endemic areas.

We found in Paper 1, that between 2006 and 2015 the overall national average outpatient visit rate for Histoplasmosis was 7.99 per 10,000 person years and 0.99 per 10,000 person years for Coccidioidomycosis. Using outpatient visit data allowed us a novel way to quantify endemicity of fungal lung infections. There was considerable geographic variation in endemicity of both fungal lung infections within county based areas in the US. Interestingly, rates varied considerably within an individual state, even in traditionally known endemic states. Results from this study give more precise geographical estimated endemicity rates compared to prior studies. This allows healthcare providers to identify patients living in endemic areas so that they can more thoroughly understand patients' possible exposure and risks.

Paper 2 showed that histoplasmosis endemicity had a minor influence on the likelihood of an individual being identified with a non-urgent indeterminate pulmonary nodule. After adjusting for demographic and clinical characteristics, those patients living in the highest quartile of histoplasmosis endemicity had a 5% increase in the likelihood of having a suspicious non-urgent indeterminate lung nodule detected. Also, patients living in the highest level of histoplasmosis endemicity, who were found to have a suspicious non-urgent indeterminate nodule, had a 15% greater chance that this nodule would eventually be found to be malignant leading to a lung cancer diagnosis. There was prior concern that the interpretation of CT chest imaging results is worse in areas with higher Histomplamosis endemicity, however, these results suggest that suspicious non-urgent indeterminate nodule differentiation is only mildly different-- there are more diagnostic procedures and more false positives, but not needlessly so, because the cancer yield is also slightly higher.

In Paper 3 we found that the overall the study population incurred $128,596,305 in follow-up procedure costs over a 24-month period following a diagnostic chest CT with a mean cost of $1,818 per person ($909 per person per year). Pulmonary biopsies, bronchoscopies and chest CTs were the procedures with the highest corresponding costs ($39,646,916; $34,872,571; $19,497,480 respectively). Across quartiles of histoplasmosis endemicity, overall average individual costs ranged from $1,685 to $1,981. After adjusting for demographic factors, histoplasmosis endemicity had only a slight influence on the number and cost of follow-up procedures following diagnostic chest CT imaging. Due to the small incremental increase in costs observed in this study, other factors, aside from Histoplasmosis exposure, may contribute to the

variability in follow-up procedures occurring after imaging for suspicious non-urgent indeterminate pulmonary nodules.

Implications

One major implication from paper 1 is that there is variability in endemicity within a state, even within a previously defined endemic state.[26–28] There needs to be careful consideration before assuming that exposure to fungal lung infection causing spores is consistent in areas that are considered endemic. The findings from this paper also highlight the need to focus on fungal lung infections at a more individual and granular level. Future research can use these more detailed estimated rates to further explore individuals' risks of health outcomes that are impacted by exposure to these fungal lung infections.

Paper 2 results illustrate that histoplasmosis endemicity has a minor influence in variability of suspicious non-urgent indeterminate pulmonary nodule findings from diagnostic chest CT imaging. While the increase in risk was small, our results are similar to other studies assessing the frequency of nodule detection. These small but statistically significant findings indicate that histoplasmosis may be one of many factors influencing the variability we see in previous studies.[6,11,13] Further studies should attempt to assess the variability in rates of suspicious findings in terms of individual-measured environmental exposures and facility-level and radiologist level trends.[6,11] Trends in how radiologists read and interpret chest CT scans in endemic and non-endemic areas may be a logical next research step.

Paper 3 findings show that histoplasmosis may not have as significant of an influence on the variability in the number and costs of follow-up procedures as previously thought. However, chest CTs and pulmonary biopsies were found to increase

across quartiles of histoplasmosis endemicity, and were two of the main drivers of the overall costs. Other factors aside from Histoplasmosis exposure should be considered. Once again, further research in this area to focus on variability resulting from radiologist or clinic practices is recommended.

References

1. Chu JH, Feudtner C, Heydon K, Walsh TJ, Zaoutis TE. Hospitalizations for endemic mycoses: a population-based national study. *Clin Infect Dis*. 2006;42(6):822-825. doi:10.1086/500405.
2. Baddley J, Winthrop K. Geographic distribution of endemic fungal infections among older persons, United States. *Emerg Infect Dis*. 2011;17(9):7-12.
3. Kurowski R, Ostapchuk M. Overview of histoplasmosis. *Am Fam Physician*. 2002;66(12):2247-2252.
4. Singh S, Pinsky P, Fineberg N, Gierada D. Evaluation of reader variability in the interpretation of follow-up CT scans at lung cancer screening. *Radiology*. 2011;259(1):263-270. doi:10.1148/radiol.10101254/-/DC1.
5. Pinsky PF, Gierada DS, Nath PH, Kazerooni E, Amorosa J. National lung screening trial: variability in nodule detection rates in chest CT studies. *Radiology*. 2013;268(3):865-873. doi:10.1148/radiol.13121530.
6. Starnes SL, Reed MF, Meyer C a, et al. Can lung cancer screening by computed tomography be effective in areas with endemic histoplasmosis? *J Thorac Cardiovasc Surg*. 2011;141(3):688-693. doi:10.1016/j.jtcvs.2010.08.045.
7. Moyer V. Screening for lung cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;160(5):330-338.