**Effect of Asbestos Fibers and the Association with Pneumonia Mortality**

by

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**Abstract**

Asbestos fibers have a well-researched chronic impact on the immune system, they cause scarring and thickening of the lining associated with the lungs. Asbestos also affects the immunological response in the pulmonary system, due to constant inflammation as a result of the attempted phagocytosis by alveolar macrophages. Around the body, asbestos fibers can cause the suppression of the killing activity done by Natural Killer and Cytotoxic T-Lymphocytes cells, which makes the host more vulnerable for other infections such as pneumonia. The public health relevance lies with the elderly population, as due to the long latency period of the diseases associated with asbestos, elderly individuals are more at risk for experiencing a decrease in the efficiency of their immune system. With this decrease, they are also more at risk for pneumonia infections due to their age alone, it makes them more susceptible to pneumonia mortality. Given that Allegheny County has elderly population makes up almost a fifth of the total population, they are more at risk to experience the pneumonia related deaths. The primary focus pneumonia related deaths should be on the elderly population and those in the asbestos field in Allegheny County. The secondary focus should be on updating any training materials and policies that are used by the Allegheny County Health Department (ACHD) Asbestos Department for training incoming Inspectors, so that they are able to protect themselves efficiently and so the Department can standardize any medical surveillance system they create to protect their exposed employees.

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# Definitions

**Alveolar Macrophages**: Phagocytes that reside in the lung system of a host, and are able to kill bacteria and release cytokines to signal for an inflammatory response during an infection.

**Asbestosis**: Pulmonary fibrosis that results from the exposure and inhalation to asbestos fibers

**Idiopathic Interstitial Pneumonia**: A lung disease that is caused by scarring, or fibrosis, of the lungs.

**Mesothelioma**: A malignant cancer of the lining of the chest wall, that is significantly associated with exposure to asbestos fibers

**Occupational Exposure**: Contact with asbestos fibers that are a result of conducting employee duties

**Pleural Effusion**: The buildup of fluid in the space between the lungs and chest wall, also known as the pleura, that is caused by either infectious or non-infectious agents.

**Pleural Plaques**: Small areas of thickening pleura, or lining, of the lungs that is due to prolonged exposure to asbestos fibers.

**Pleural Thickening**: Thickening of the pleural surface of the inner visceral lung, it is beneath the pleura and is associated more closely with the organs.

**Pneumonia**: Lung inflammation that is a result of infection, either bacterial, viral, or fungal and effects the air sacs.

**Pneumoconiosis**: An interstitial lung disease that is caused by breathing in dust particles that damage the lungs and is associated with occupational exposure to the irritants, and is also related to asbestosis.

# Acknowledgements

This is made in conjunction with the Asbestos Inspector Manual that is currently in review by the Allegheny County Health Department.

# Background

## What is Asbestos?

Asbestos is a natural occurring mineral fibers that has been used in the past for its characteristics: flexibility, heat resistance, chemical resistance, and tensile strength. There are two categories of fiber types: Chrysotile and Amphibole, Chrysotile fibers have been found to be more toxic due to the bio-persistence in the body. The bio-persistence in the body modifies the immune response to both chronic diseases and infectious disease. In terms of chronic diseases, specifically cancer, it is the chronic damage to the lungs that can cause mutations to rise and leads to an increase risk to develop the condition. In terms of infectious disease, specifically pneumonia, it is the change in the immune response that will leave individual at a higher risk of pneumonia especially because the infection takes place in the same area as asbestos fibers may settle. However, in 1970, it has been decided by the Environmental Protection Agency (EPA) that all asbestos fibers are carcinogenic[[1]](#footnote-2). Asbestos fibers can vary in length, however fibers greater than 10 µm are more likely to be carcinogenic, because they are more difficult for the lungs to clear out physically and immunologically. Asbestos is associated with a dose-response relationship with any potential health effects, meaning that the larger and more sustained individuals experience an exposure the more likely that they will encounter a severe health outcome[[2]](#footnote-3). Most health effects of asbestos have an extensive latency period that can range from 10-50 years[[3]](#footnote-4), which by that time an individual may be an elderly person and may suffer from other co-morbidities that impact their fragile immune system.

## What is Pneumonia?

According to the Centers for Disease Control and Prevention (CDC), there are multiple causes of pneumonia and these can involve multiple organisms such as viruses, bacteria, and fungi[[4]](#footnote-5). There is also an association between pneumonia mortality along with other factors such as smoking and other co-morbidities[[5]](#footnote-6), that may be more prevalent among elderly adults. The most common bacterial cause of pneumonia is *Streptococcus pneumoniae,* and it is the leading cause of death among elderly individuals in the United States[[6]](#footnote-7). This bacterium can also cause a more severe and invasive disease called Meningitis, which is an infection of the tissue associated with the brain and spinal cord. There are multiple risk factors for bacterial pneumonia infections, the primary risks are smoking status and age. Regarding age as a risk factor for an infection compared to those 49 and younger, people in the 60-64-year old range have 2.8 times rate of pneumonia and those 70 and older have 4.2 times the rate of infection[[7]](#footnote-8). The fungal species that can cause pneumonia is *Pneumocystis jirovecii*, it is an infection that primarily affects those who are immunocompromised or have a weakened immune system[[8]](#footnote-9). Lastly, the viral form of pneumonia is caused by the Respiratory Syncytial Virus (RSV) and it mainly affects children under the age of one and those who are 65 and older with some respiratory co-morbidities[[9]](#footnote-10).

## Public Health Importance

In 2018, the age-adjusted mortality rate of Influenza and Pneumonia in Pennsylvania was 15.5 per 100,000 individuals[[10]](#footnote-11). In addition, the mortality rate from mesothelioma in PA is one of the highest in the US, out of the top 50 counties with the highest malignant mesothelioma rates there are 6 counties from PA[[11]](#footnote-12). Historically Allegheny county was a very industrial population with coal mining, iron, steel, car manufacturing, all industries that have an association with a high exposure to asbestos and its fibers[[12]](#footnote-13), these industries lead to a very high risk population in which older males in Allegheny County may be very susceptible to a possible synergistic effect of these multiple risk factors on a vulnerable population. The age-adjusted mortality rate from mesothelioma in older adults in PA is 0.1 per 100,000 individuals[[13]](#footnote-14). In Allegheny County alone approximately 19% of the total population are 65 and older[[14]](#footnote-15), and there are numerous old houses that are being demolished or renovated that may contain asbestos in some form. Inspectors from the ACHD are charged with inspecting the facilities before, during, and after an asbestos abatement takes place to ensure that all safety protocols provided by the EPA and the National Institute for Occupational Safety and Health (NIOSH) are followed to protect public safety. However, asbestos inspectors may be unknowingly exposed to the fibers, and that could lead to the future development of asbestos-related diseases. Another vulnerable population are the elderly adults, especially among males, that may have been previously exposed to asbestos fibers either environmentally or occupationally. The occupations at a higher risk are those that interact with asbestos-containing materials such as: construction, mechanics, and shipyard workers[[15]](#footnote-16). In 2016 alone, among males the age adjusted mortality rate specific for influenza and pneumonia was 17.7 per 100,000 and for females it was 11.4 per 100,000[[16]](#footnote-17). This may be due to the occupational exposure that is more common among males than females. There is an association between an asbestos-related symptom known as pleural effusion and the risk of developing pneumonia, however there are multiple respiratory conditions caused by asbestos that contribute to the development of a pleural effusion.

# Methods

A literature search was conducted using Google and the University of Pittsburgh Health Science Library System (HSLS). Within the HSLS, the databases: National Center for Biotechnology Information (NCBI), PubMed, and PubMed Central (PMC) were used in order to conduct the searches. The following phrases were used in order to search through the HSLS databases: asbestos AND pneumonia, asbestos AND infectious disease, asbestos AND lung, asbestos-induced interstitial pneumonia, occupational exposure AND infectious pneumonia, asbestos AND pleural effusion, asbestos AND respiratory disease, pneumoconiosis AND pneumonia, pneumoconiosis AND asbestos, pleural effusion AND pneumonia AND mortality, pleural effusion AND pneumonia mortality, “benign pleural effusion” AND “asbestos”, “benign asbestos pleural effusion”, “BAPE” AND “asbestos”, (“asbestos” OR “asbestosis”) AND (“correlation” OR “association” OR “relation” OR “relationship”) AND (“pneumonia” OR “pneumonia mortality”), "TNF-α" and "IL-1β" AND "asbestos", "pleural effusion" AND "pneumonia mortality". A search criterion used was the articles could not before 1990, and this resulted in 70 articles. For exclusion criteria, articles were excluded if they exclusively discussed mesothelioma and lung cancer mortality. This excluded 44 articles, which left 26 articles for full review. The three phrases used to search on Google was “Allegheny county public health department mortality report”, “causes of pneumonia”, and “CDC pneumonia mortality”.

# Health Effects of Asbestos Exposure

## Diseases Caused

All of the diseases that are associated with asbestos exposure have a latency period that varies from 10 years to 40 years, with the more severe diseases having a longer latency period. There are multiple diseases that has been associated with asbestos exposure: lung cancer, mesothelioma, pleural plaques, diffuse pleural thickening, asbestosis, and pleural effusions. Mesothelioma is a rare cancer of the pleural lining, and is almost exclusively associated with asbestos exposure, however the 5-year survival rate is less than five percent[[17]](#footnote-18), which makes this malignant cancer very deadly. In the United Kingdom, in 2007, lung cancer has a prevalence of 2,000 to 3,000 deaths per year associated with asbestos exposure and has been shown to have an increased association with an individual suffering from asbestosis[[18]](#footnote-19). Asbestosis refers to a chronic lung disease that is due to continuous damage to the lungs specifically caused by exposure to asbestos fibers[[19]](#footnote-20), however it does resemble other idiopathic lung disease. Pleural plaques and diffuse pleural thickening are similar in that they both causes scarring, or fibrosis, within the respiratory system, however the extent of fibrosis and location are different between the two diseases. Diffuse Pleural Thickening, otherwise known as DPT, refers to fibrosis that only affects the tissues associated on the surface of the lungs. DPT is associated with more severe symptoms than pleural plaques, such as respiratory failure[[20]](#footnote-21).

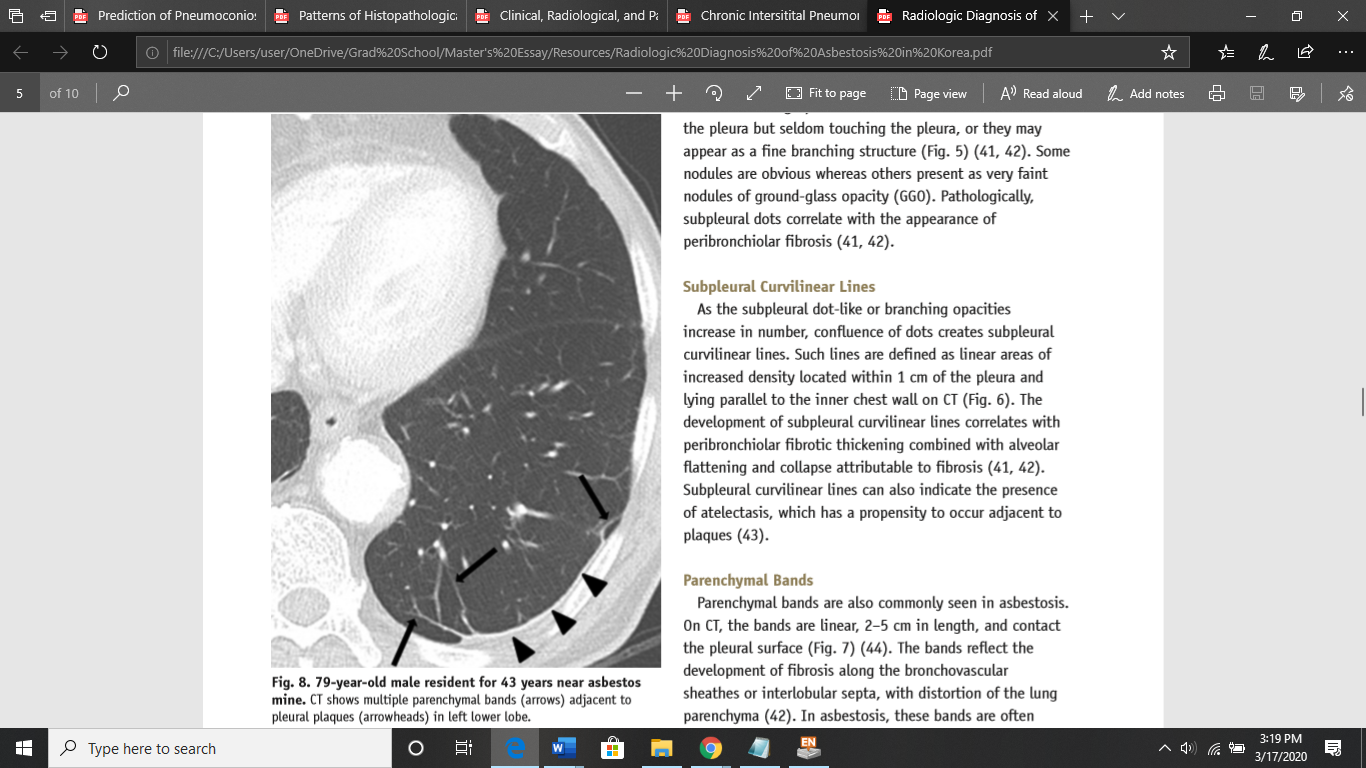
Pleural plaques refer to smaller areas of fibrosis that is associated with the pleura, or lining, of the

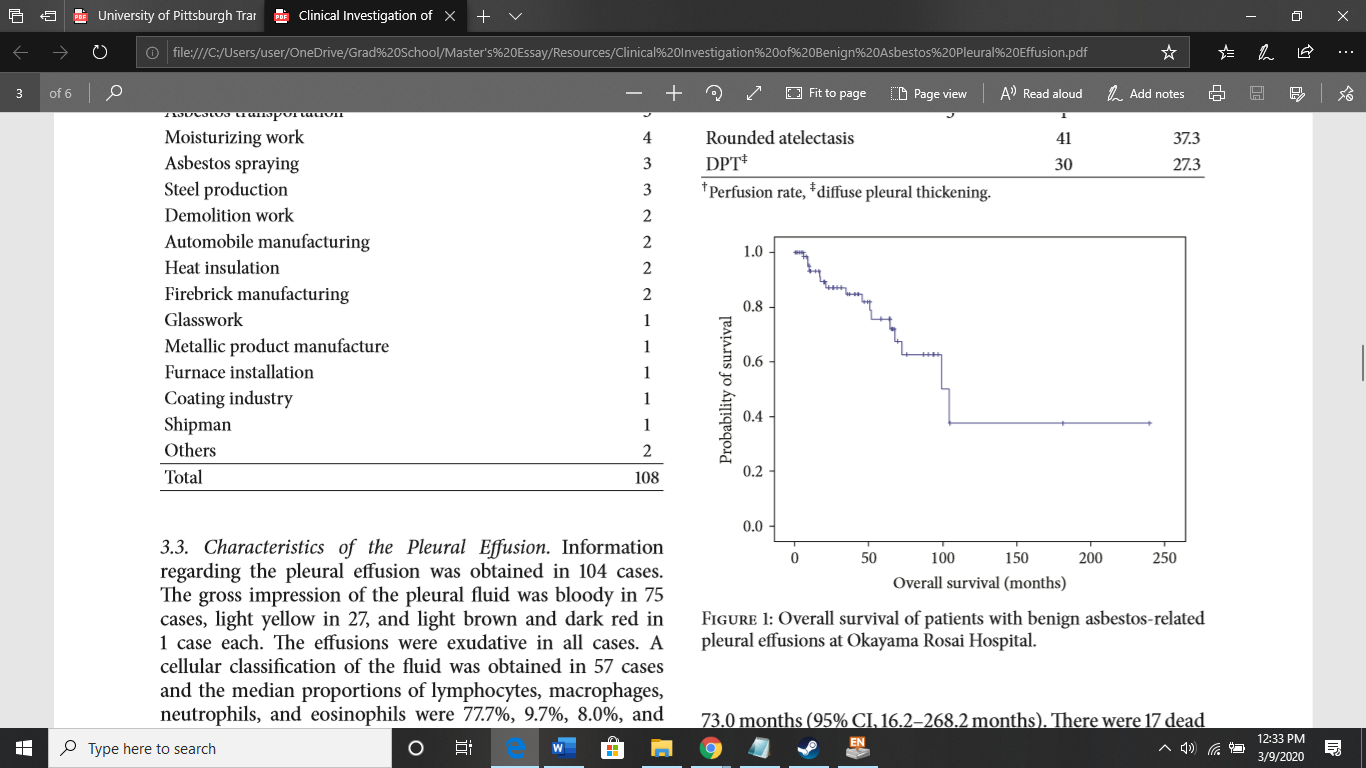
Figure 1 Example of Fibrosis and Pleural Plaques

According to “Radiological Diagnosis of Asbestosis in Korea”, a CT scan of an elderly patient with over 40 years of asbestos exposure was taken, there are noticeable changes in the physical structure of the lungs that are associated with asbestos fibers exposure. The thick arrows shows the pleural thickening that is visible in the scan, and the arrows show the fibrosis or scarring that is visible on the lungs which is a symptom of DPT ([Yoon Ki Cha, 2016](#_ENREF_32)).

chest cavity. Pleural effusions are the accumulation of fluid between the lungs and the chest cavity and can be caused by chronic exposure to asbestos fibers[[21]](#footnote-22). These symptoms have a potential to impact asbestos-related mortality and pneumonia mortality due to their physical impact on the respiratory system and the immunological impact that compound on each other.

Figure 2 Pleural Plaque Mortality

According to “Clinical Investigation of Benign Asbestos Pleural Effusion”, the graph of the probability of survival of benign pleural effusions over time. Based on the graph there is a noticeable decrease in survival as months pass, however the cause of death among those involved in this study varied ranging from respiratory failure and septic shock ([Nobukazu Fujimoto, 2015](#_ENREF_17)).



## Molecular and Immunological Effects

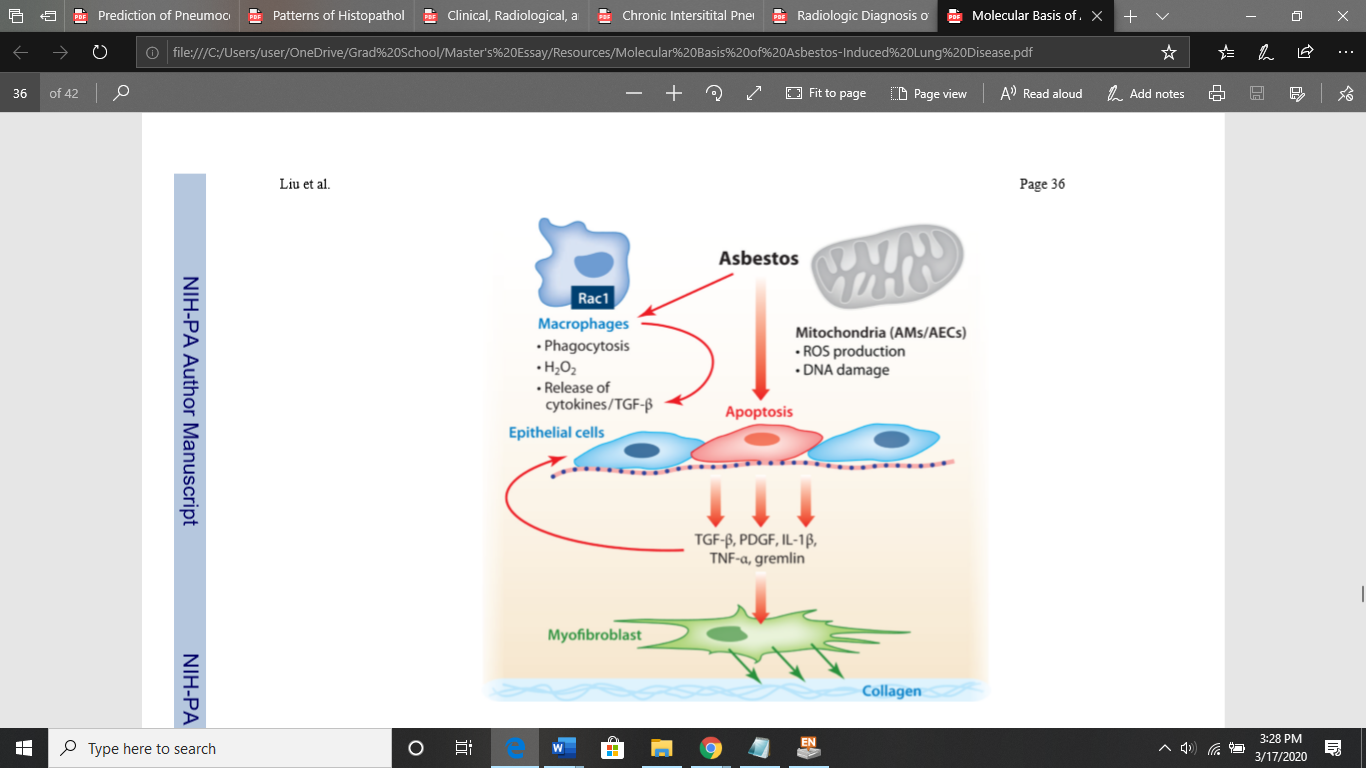
After there has been an exposure to asbestos fibers, there are some immunological response to any fibers that have entered the lungs. However, most of the damage to the lungs is caused by chronic exposure to asbestos fibers, due to the accumulation of immunological cells. There is evidence that there is a dose-response relationship with duration and the severity of the exposure of asbestos fibers, and this affects the type of immunological response that is mounted. A short duration of a large amount of fibers elicits a neutrophil inflammation response, while a long exposure of small amount of fibers elicits a chronic alveolar macrophage inflammation response2. In the lungs, the cells that are responsible for primary defense against invading pathogens and substances are the alveolar macrophages. These cells function as normal macrophages, however they are specialized to protect the pulmonary system. When short fibers enter the lungs, alveolar macrophages can phagocytize the fibers, however this causes an increased production of two specific cytokines in the immunological system. Cytokines are signaling molecules produced by cells that when received on the correct receptor, can influence the behaviors of other cells[[22]](#footnote-23). After an asbestos exposure, the two cytokines that are increased in production are TNF-α and IL-1β which are both produced by macrophages, which also includes alveolar macrophages. The cytokines both take part in the inflammatory process, IL-1β is used to activate other macrophages and T-cells while TNF-α is used to activate the epithelial cells in that area. Studies have shown that an increase in TNF-α and IL-1β is associated with being exposed to asbestos, which promotes the inflammatory response by alveolar macrophages and epithelial cells[[23]](#footnote-24). It is the constant inflammation that causes the extensive and progressive damage to the lungs, due to the asbestos fibers that are unable to be cleared by the alveolar macrophages. There is also a protein that is essential to the toxicity of the asbestos fibers in the lungs, known as p53, which has a transcriptional function for the genome2. The function of p53 is to suppress the accumulation of DNA damaging mutations, however any changes in the expression of the protein can cause the protein to not prevent the damage, this is seen in pulmonary fibrosis diseases such as asbestosis.

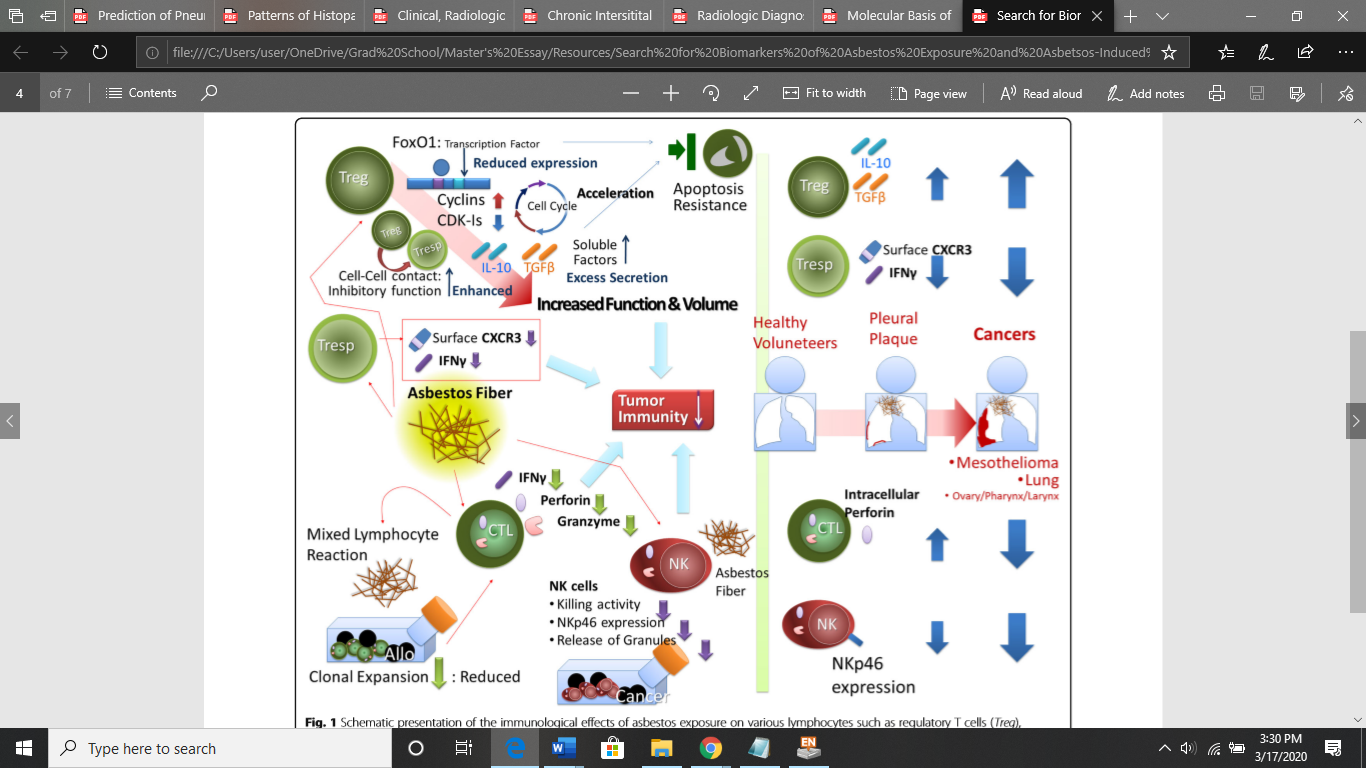
Figure 3 Immunological Response to Asbestos

According to “Molecular Basis of Asbestos-Induced Lung Disease “, this is a model that shows the impact on alveolar macrophages and alveolar epithelial cells. The most influential cytokines are TNF-α and IL-1β, they are released by both the macrophages and epithelial cells. TNF-α and IL-1β are responsible for promoting the inflammation response, which is prolonged due to the consistent exposure to asbestos fibers that become embedded into the lungs. This constant inflammation is what causes the extensive damage to the lungs results in in fibrosis and thickening of the lungs known specifically as asbestosis or pneumoconiosis ([Gang Liu, 2013](#_ENREF_6)).

When asbestos fibers enter the lungs, the larger fibers can be lodged in the lungs and are difficult to get rid from the body which leads to the physical fibrosis that can be seen in the lungs. However, it is the smaller fibers that can cause the inflammation response to cause chronic damage to the lungs, and immunological cells, making it difficult for the tumor-suppressive mechanisms to function properly especially among the Cytotoxic t-lymphocytes (CTL) and Natural Killer (NK) cells.

Figure 4 Effects of Asbestos on NK and CTL Functions

When the immune system is exposed to asbestos fibers there is a significant impact on the Natural Killer (NK) and Cytotoxic T lymphocytes (CTL) cells when performing their primary function. NK cells function to kill both tumor and infected cells and are part of the innate immune system ([Murphy, 2012](#_ENREF_16)). CTL cells function to protect the host by killing other abnormal or infected cells, and are essential for the adaptive immune system ([Murphy, 2012](#_ENREF_16)). According to “Search for Biomarkers of Asbestos Exposure and Asbestos-Induced Cancers in Investigations of the Immunological Effects of Asbestos” the presence of asbestos fibers causes the NK cells killing activities to be reduced, as well as a suppression in the NK cell activation receptor which also decreases the NK cells activities ([Hidenori Matsuzaki, 2017](#_ENREF_7)). For CTL cells the exposure effects the ability for clonal expansion in order to generate a multitude of cells that can target the same microorganism without also targeting any of the host cells ([Hidenori Matsuzaki, 2017](#_ENREF_7)). Without clonal expansion that host immune system can become easily overwhelmed because the cells have not been trained to target the invader. With both immunological cells, these changes affect the tumor cells suppression system that is regulated throughout the body, and it makes the host more susceptible to common illnesses that would otherwise be easier to clear, such as pneumonia.



# Asbestos Exposure and Autoimmunity

The presence of asbestos fibers in the lungs, can cause the development of self-reacting immunological cells, which is a major concern for all those who are exposed to the fibers. Immunological cells, due to their functions throughout multiple sites in the body, are generated with varying degrees of specificity for their antigens. A major component of the immune system relies on potential self-recognizing lymphocytes to be eliminated in order to ensure that there is no cross-reactivity of the immune system with any component of cells that are naturally present in the body, this is known as clonal expansion22. Based on animal and human models, there is some association between the presence of asbestos fibers and autoantibody production, especially those autoantibodies related to rheumatoid arthritis[[24]](#footnote-25). These autoantibodies do not function as normal antibodies, typically antibodies would target non-host identification points such as a non-normal cell envelope, unrecognized proteins, etc. However, with autoantibodies, they recognize targets that are present in the host which causes unnecessary attacks on host structures by immune cells and can cause damage and inflammation in those areas.

# Relationship to Pneumonia Mortality

## Age

Elderly people are more at risk for pneumonia infections and pneumonia mortality, both community-acquired, and hospital acquired, due to their waning immune system and other co-morbidities. In the presence of other co-morbidities, there is an increased risk of pneumonia mortality, especially among those who have developed pleural plaques5. Given that elderly people are more likely to suffer from pneumonia infections based on age, there is an increased risk for hospitalization if there is a known prior history of the infection[[25]](#footnote-26). With all these factors taken into account, elderly individuals are at a severe disadvantage in defending against the infection, without the presence of pleural effusions. However, the presence of a pleural effusion can increase their risk immensely.

## Pleural Effusion

Among those patients that are hospitalized for pneumonia, 40% of those patients also suffer from a pleural effusion[[26]](#footnote-27). A pleural effusion can be caused by infectious and non-infectious diseases, after asbestos exposure it most often results in Benign Asbestos Pleural Effusion[[27]](#footnote-28) (BAPE). Overall, a pleural effusion is present in 9% of individuals with a pulmonary infection, and annually at least 1,500,000 people are diagnosed with this condition[[28]](#footnote-29). A pleural effusion is when fluid fills the pleural space between the lungs and the lining of the chest wall, and when it is present in the case of Community-Acquired Pneumonia (CAP) it increases the risk of mortality[[29]](#footnote-30). There are multiple levels of severity of the condition and more severe cases are associated with more severe outcomes, especially if it is a malignant pleural effusion. The two different forms of pleural effusion, benign and malignant, differs in the presence of neoplastic cells in the pleural space brought in by the pleural fluid28.

## Asbestos Fibers

Asbestos exposure has a long latency period for asbestos-related diseases, this means that these diseases are seen more commonly among elderly people with a previous exposure history. A pleural effusion can be caused by the exposure to asbestos fibers, BAPE, and has an increased 30-day mortality rate especially in the presence of CAP[[30]](#footnote-31). Given that the presence of asbestos fibers can cause changes in the immunological response in the respiratory system, this is a major concern for individuals’ susceptibility to pneumonia. Immunological cells from both the innate and adaptive immune system are not able to perform their primary functions, eliminating abnormal or infected cells, this allows any potential viruses to replicate within cells. After replication, the immune system would not be able to clear out both the virus and infected cells, thus the immune system would be overwhelmed which would lead to hospitalization or severe outcomes.

# Conclusion

Exposure to asbestos fibers can cause chronic damage in the lungs by impacting the cytokine production of immunological cells, causing chronic damage to the lungs that lead to scarring. This can cause a change in the physical structure of the lungs and the lung capacity due to the scarring. However, other immunological cells are affected that do not have a specialization for the lungs, such as Natural Killer cells and Cytotoxic T Lymphocytes. These cells are necessary for the innate and adaptive immune system, respectively, to function correctly by attacking and killing abnormal and infected cells in the body. The presence of asbestos fibers can cause a decrease in the killing activity that the cells can do, and creates a vulnerability in the hosts’ immune system, where normally a bacterial infection such as pneumonia may be easily cleared is more difficult to clear and may overwhelm the body. There is also evidence to suggest that asbestos fibers are a cause of pleural effusions, which has an increased risk associated with pneumonia mortality.

Given all the evidence, there is a relationship between the exposure to asbestos fibers and an increased risk of pneumonia mortality, especially among the elderly population. The increased risk is a culmination of numerous factors: age, co-morbidities, presence of pleural plaques, and most important the presence of a pleural effusion.

# Future Directions

With the Asbestos Inspector Manual currently in review by the ACHD, this review has showcased important information that would be beneficial to consider adding to the Manual. With asbestos fibers causing some immunological damage within the lungs, it would be beneficial for those who go through Inspector training to have information regarding the relationship between risk of pneumonia, asbestos exposure, and asbestos related diseases. Another future direction may be to research the relationship between mycobacterium infections, which can cause Tuberculosis disease, and asbestosis which is as a result of consistent damage to the lungs by asbestos fibers. Lastly, to provide protection for all of those in the elderly population, especially those with an exposure history to asbestos, promoting the use of the Pneumococcal vaccination should be a major focus of the health department going forward*.* The vaccination has proven to be an effective tool to prevent the infection of the bacterium especially among younger populations, however it would still benefit the elderly population and may decrease the amount of pneumonia related deaths.

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