Teens In Health

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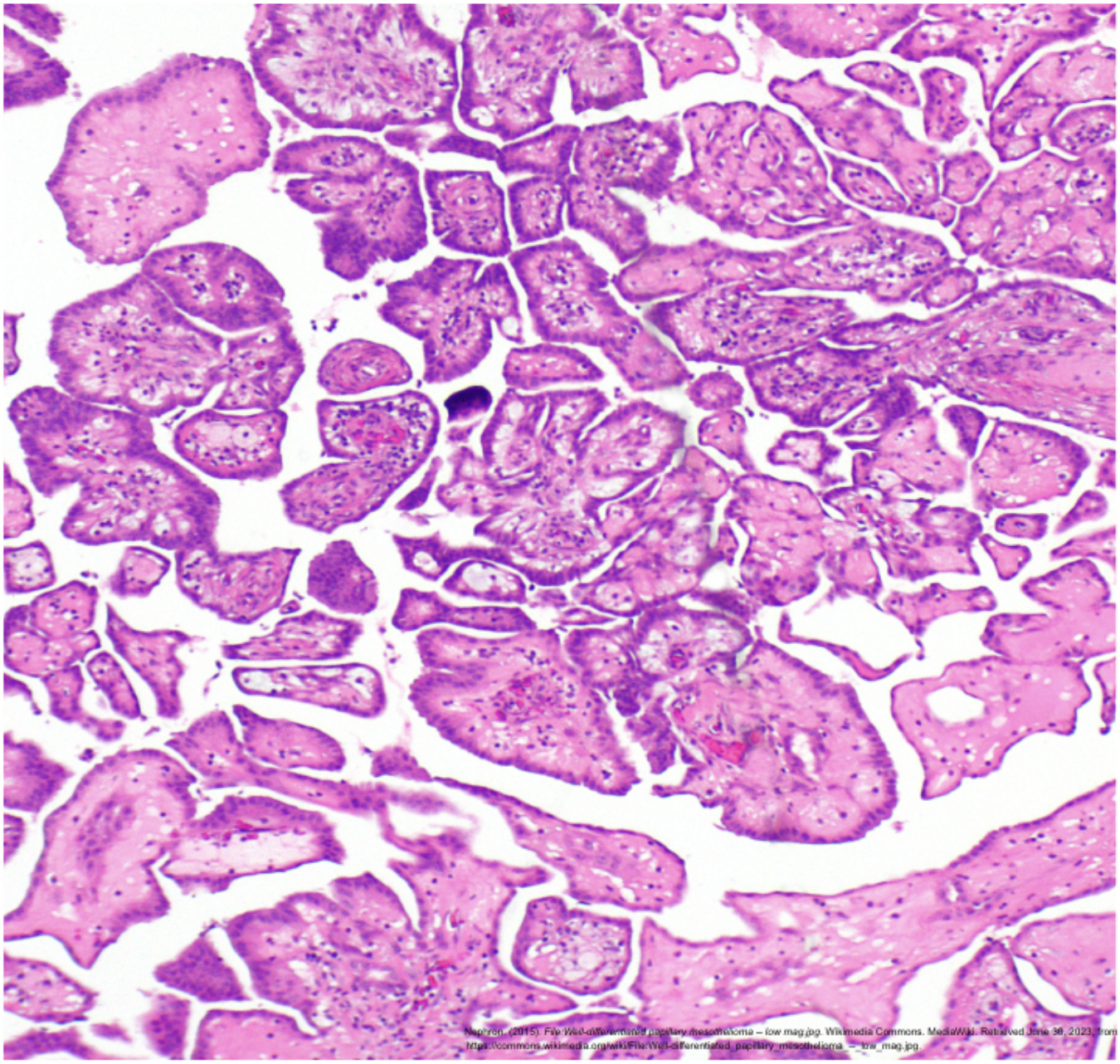
Mesothelioma Article Writing
Summer 2023 Journal



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Teens in Health: Mesothelioma Article Writing Summer 2023 Journal

Teens in Health is an organization that provides teens with access to conduct research, write literary reviews, and participate in community service projects to build experience and develop skills under the guidance of other high school students. This program was one of eight organized through the Teens in Health Summer 2023 Program that focused on writing literary reviews about mesothelioma. Students around the world spent five weeks developing articles on different aspects of mesothelioma, ranging from emerging treatments to asbestos use in developing countries.

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Literary Review

Alternatives to Asbestos Usage in Industries to Limit Cases of Pleural Mesothelioma Cancer

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Key Words: Asbestos fibers, mesothelium, alternatives, Pleural Mesothelioma Cancer, polythene, martinite, cellulose fibers, thermoset plastic flour, or wood thermoplastic composites

Abstract: This literary review will discuss the possible alternatives to the usage of asbestos and asbestos fibers in manufacturing industries across the globe to limit cases of pleural mesothelioma cancer. It has been shown that a majority of individuals that were reported with pleural mesothelioma had contracted cancer through the inhalation of asbestos fibers. For a person with pleural mesothelioma, the average prognosis, or the forecast of the likely outcome seemed to be a year. [7] Not only do asbestos fibers cause cancer, or more specifically pleural mesothelioma, but they can also cause many other severe illnesses of the lungs and tissues surrounding it. This article will discuss the formation and usage of asbestos fibers, then detail possible substitutions through the review of research studies from across. This literary review will aim to go more in detail about the possible substitutions of asbestos that the environmental and medical field is looking into to limit the cases of Pleural Mesothelioma cancer.

Introduction:

Pleural mesothelioma is a cancer that forms in the mesothelium, or a tissue of the lungs that lines the cavities of the pleurae, peritoneum, and pericardium. It is characterized when asbestos fibers are inhaled and become embedded in the tissue of the lungs, earlier stated as the pleura. [Penn Medicine, 2022] Over time while these fibers remain trapped in the lungs, they can cause cancer, scarring and damage of the lungs, and inflammation. [Mayo Clinic, 2022] While classified as rare cancer, pleural mesothelioma is a public health problem, with 3,000 new cases diagnosed each year. [Mesothelioma Cancer Community, 202] The cancer is particularly prevalent in elderly White, Hispanic, and Latino people, specifically males; the prognosis itself is poor even with modern-day treatment such as chemotherapy and radiation of the area. [American Cancer Society, 2022] While today asbestos usage in the US has dropped because of its dangers, it is still a major material used in countries where manufacturing is a key economic sector, such as Russia, Kazakhstan, and China. [Whitmer, 2023] Still, in the US the usage of asbestos has not completely disappeared, leaving cause for error and a high chance of

Pleural mesothelioma. This literary review will aim to go more into detail for the possible substitutions of asbestos in manufacturing.

Polythene

A possible substitution for the usage of asbestos has been studied by researchers at the Uva Wellassa University, Sri Lanka. Understanding that the World Health Organization has categorized asbestos and its fibers as harmful occupational carcinogens, the researchers sought to find a solution. Their goal? Finding alternatives to asbestos fibers in roofing sheets, they tested the fibers of coir, bamboo, corn skin, and polythene that were easily found in the area nearby. When testing the density and resistance of water as possible roofing sheets, the scientists found an approximate substitution. As stated in their research, "According to the Sri Lanka Standards Institute, even asbestos sheets also have a breaking load of 5 kN m1 while the density of the sheet should not be less than 1200 kg m-3,". And they concluded that the polythene from rice sacks could be used instead of asbestos fibers. This is because its maximum breaking load had risen to 7.51 kN m-1 while the density of 2946.6 kg m-3, shows that these fibers meet the roofing sheet standards and can be used in place of occupational carcinogens. While only one of their tested materials had been found usable, the rest failed to pass the density and water-resistant tests, rendering them completely useless as a substitution material. [Silva, 1970]

Martinite

Considering the complex and variety of uses that asbestos has, another study conducted by Alessia Angelini and Stefano Silvestri through the University of Piemonte Orientale, Novara has found another substitute. This material, martinite, being a hard form of steel crystalline, has been found very accurate and can be widely substituted instead of asbestos in a majority of industries. These can include building materials, friction products, as well as many other heat-resistant fabrics and goods. This study was conducted after a high rise in Mesotheliomas in Italy around 2015 as seen in the VIth Report of the National Mesothelioma Register (ReNaM). Since it can be produced at different densities, the researchers experimented with the possible substitution of asbestos with martini. Using and comparing equal-density asbestos and martini at 300 kg/m3, the researchers at Manifatture Martiny found that the substitute has more insulating power and worked more efficiently than the asbestos fibers. Hospitals like "San Giovanni Battista e della City of Turin" have reported high thermal insulation when manufacturing companies worked with Martinite. This substitute gave advantages both in cost and efficiency when used. However, the most important part is that this material, unlike asbestos, has little to no health risk imposed. [PMC, 2020]

Cellulose fibers

The Mesothelioma Center at “Asbestos.com” is a reliable source that not only discusses Mesothelioma itself, but along with treatment options, prognosis, and asbestos information regarding symptoms and most importantly, eco-friendly alternative building materials. One most common in the US is cellulose fiber. Cellulose fiber has become a very ideal and environmentally friendly substitute for asbestos and has been widely used as a special insulating material. This particular insulation material has undergone a careful manufacturing process in which recycled paper, mainly newsprint, is skillfully transformed into a reliable and efficient thermal barrier. By subjecting the paper products to precise chemical treatments, a remarkable transformation occurs, effectively minimizing moisture infiltration and bolstering the insulation's fire-resistant properties. What truly sets cellulose fiber apart is its remarkable dedication to sustainability, boasting an impressive recycled content that typically ranges between a noteworthy 82% and 85%. Such a commendable commitment to utilizing recycled materials not only contributes to waste reduction but also serves as a testament to the responsible and eco-conscious approach taken by cellulose fiber as a superior insulation choice. [Whitmer, 2023]

Thermoset Plastic Flour or Wood Thermoplastic Composites

Another alternative is thermoset plastic flour or wood thermoplastic composites which, just like cellulose fiber, are commonly used instead of asbestos more specifically in electrical insulation in construction as auto vehicle manufacturing. This flour or wood is heated to be completely versatile and flexible to be molded, therefore can be used in a multitude of industries. [Whitmer, 2023] In a study done by the USDA by Daniel F. Caulfield, Craig Clemons, Rodney E. Jacobson, and Roger M. Rowell, it was found that wood-plastic composites or any true thermoplastics are mostly health safe, and commonly used in day to day life. Commonly seen as resins, such as epoxies and phenolics makes products like milk jugs, containers, bags, and construction materials. To create the variety of products listed above and more, the thermoplastic, no matter what type used, must be heated, and once cured cannot be turned to the original form again. In detail, these thermoplastics, a type of polymer, are heated and slowly softened at 550 °F to 750 °F. At this temperature, the polymer can be molded and then cured into whatever product is necessary. Seeing the obvious growth of thermoplastics in the modern world still comes with its health risks but is a common and safer option than asbestos fibers. [Caulfield, 1970] While reducing cost and staying away from the mass amounts of health issues that are strung along with the usage of asbestos-like Pleural Mesothelioma, thermoset plastic flour or wood thermoplastic composites is an excellent alternative. [Whitmer, 2023]

Conclusion:

As a whole, asbestos has been shown to cause pleural mesothelioma and many other severe illnesses. Pleural mesothelioma is severe cancer that is characterized when asbestos fibers are inhaled and become embedded in the tissue of the lungs. As per this literary review to investigate the alternatives to asbestos usage for countries in which the manufacturing with these fibers is common, many studies have shown substitutions for asbestos. These can be as common as thermoset plastic flour, wood thermoplastic composites, cellulose fiber, or recently discovered such as martinite and polythene from rice sacks. This is crucial for people and manufacturers especially in the countries of Russia and China to understand that substitutions are available so that limited asbestos is used. Since asbestos fibers cause a majority of the cases of pleural mesothelioma we should work towards abolishing its usage in all industries, from auto to construction as well. Therefore creating a future where pleural mesothelioma and other illnesses caused by the inhalation of asbestos are eradicated, creating a better and safer working and living environment.

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Review Article

Reviewing Kazakhstan's Asbestos Industry as a Case Study on Worldwide Asbestos Consumption and Usage

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Keywords: Asbestos Industry, Chrysotile Asbestos, Kazakhstan, Mesothelioma, Asbestos Production, Asbestos Consumption

Abstract

For this review, Kazakhstan, the second largest producer of asbestos, is taken as a case study to better understand why some countries choose to a) ignore the carcinogenic and toxic properties exhibited by asbestos, and b) continuously place their citizens at risk for mesothelioma. In this investigation, little notes about Kazakhstan could be found; therefore, this article also relies on global patterns to identify asbestos consumption and mesothelioma trends. Particular patterns that were found and analyzed were the marketing tactics used globally by the asbestos industry and Kazakhstan's higher mortality rate from disease attributable to asbestos exposure and higher asbestos consumption rate in comparison to other countries. Both of the aforementioned patterns can be connected once the cycle that the asbestos industry has systematically placed the country in is considered. This review attempts to investigate the implications and limitations of global asbestos usage in the 21st century by analyzing the effects that modern CA production has on Kazakhstan, a developing country with a rapidly growing presence in the asbestos industry.

Introduction

There are currently three known types of Mesothelioma (MT): Pleural MT, Peritoneal MT, and Pericardial MT. Pleural MT, the most common of the types, affects the pleura, the protective lining of the lungs. Peritoneal MT affects the protective lining of the abdominal cavity that contains the stomach, intestines, kidneys, and liver. Pericardial MT, the rarest type of MT, affects the protective lining of the heart. All three types of MTs are extremely deadly once malignant; furthermore, Pleural MT offers more treatment options then Pericardial MT due to Pleural MT accounting for 75 percent of all MT diagnoses, while Pericardial MT accounts for less than 1 percent of MT diagnoses (Mesothelioma Cancer Community). The World Health Organization (WHO) estimates that approximately 125 million people are exposed to asbestos in the workplace and that more than 107,000 people die each year from disease related to asbestos exposure; around half of deaths attributed to occupational cancer are related to asbestos exposure ("Asbestos, explained"). Chrysotile asbestos (CA) is the most common type of asbestos and is the most prevalent kind used in the asbestos industry (AsI) (Chrysotile Asbestos Fact Sheet). CA can be found adhesives, brake pads, cement, drywall, fireproofing, gaskets, insulation, roofing, and vinyl tiles (King). Global concerns about the worldwide AsI remain, as worry about asbestos exposure also affects communal infrastructure. In maintaining, renovating, or demolishing a building with asbestos, there is a high chance of exposure to everyone in the area, not only construction workers but also neighborhoods nearby (Gilham et al.).In addition to these facts, it is important to note the current impact of asbestos today. In the majority of developed countries, asbestos has been phased out–the industry is virtually obsolete. Additionally, a number of countries, such as Kazakhstan (KZ), still participates in the AsI, and

many of these countries also have little to no data collected on MT and are already more likely to incorrectly diagnose MT (Carbone et al.). Therefore, it is important to investigate these existing asbestos production and consumption rates because of the social, economic, and health risks that the AsI presents to the global community.

The History of the Asbestos Industry

It only took thirty years from the beginning of the official AsI for mines of the mineral to be operating globally. The mineral had become essential in wars, due to its economic and structural convenience; asbestos was both relatively cheap and excellent at insulation and other functions. Therefore, "asbestos was essential to [...] industrial processes that came into vogue after 1945. The industry's peak in North America coincided with what some economists term the Golden Age of Capital (1945-1972) and in that sense asbestos is an exemplar of modern industrial production and its attendant global divisions of labor" (McCulloch). Asbestos seamlessly integrated into human infrastructure and society and can still be found in old buildings to this day. Despite knowledge of asbestos' carcinogenic properties, the AsI still successfully "shifted offshore to the developing world, where despite the known dangers, more than 2 million tons of chrysotile were used during 2004" (McCulloch). This phenomenon of the AsI's success in surviving despite factual evidence proving asbestos' carcinogenic properties has been accredited to "its success in keeping alive the fiction that asbestos can be used safely" (McCulloch). The AsI continues to thrive because of the capitalistic desire to prioritize profit over global health.

The Asbestos Industry in Kazakhstan

Analyzing the Magnitude and Impact of Kazakh Asbestos Production

Kazakhstan (KZ) is home to one of the world's largest asbestos mines. Now, KZ is the second-largest producer of CA, totaling 230,000 metric tons in 2022 ("Major countries in worldwide asbestos mine production in 2022"). In 2021, KZ exported $61.5M in asbestos, making asbestos the 45th most exported product in KZ. These asbestos exports from KZ have spread eastward, with markets rapidly growing in Sri Lanka and Tajikistan (The Observatory of Economic Complexity). Following a visit to the developing nation in the 2000's, the Director of a European Non-Governmental Organization (NGO) reported that she "saw people in the villages cutting-up slates of asbestos in their gardens, with children playing around them and we became very worried" (Kazan-Allen). Furthermore, most, if not all, of KZ's CA is mined in one, centralized place: Djetygarinskoe, which is one of the world's five largest asbestos deposits in the world (Selby). The majority of KZ's asbestos production was sent abroad (Kazan-Allen). In May 2022, Kostanay Minerals (KM), KZ's only CA company, had to declare a moratorium due to warehouses being full (Kazan-Allen). While KZ does export the majority of the at least 37 million tons of asbestos they mine, asbestos is involved in the creation and structure of houses, apartment buildings, hospitals, schools, commercial buildings, and more (Asbestos.com). Asbestos has been embedded in the lives of the people of KZ. Moreover, asbestos is still being produced, used, and consumed in many developing nations.

Examining Political and Economic Effects of Kazakh Asbestos Production

While many countries have different reasons for still using, consuming, and producing CA, for developing countries, profits made through CA industries are prioritized over general health and wellbeing. Evidently, "the low cost of mining and manufacture in developing countries gives the asbestos industry an unfair advantage in the marketplace when competing against safer substitute materials"

(LaDou). Furthermore, “the United Nations has attempted to label chrysotile asbestos an extremely hazardous product in international commerce, but this has been blocked by a number of countries for many years, including Russia, India, and others” (Frank). Despite many countries agreeing to label CA as “extremely hazardous,” countries such as KZ have decided to continue producing CA. Because CA exports account for approximately 90% of KZ’s asbestos products, sanctions, due to the war against Ukraine, that were imposed on shipments from Russian ports, negatively impacted KM’s operations (Kazan-Allen). However, due to Russia’s invasion of Ukraine, “many international transport and logistics companies have ceased their operations in Russia” (Kazan-Allen). In countries similar to KZ, such as India, “imports of asbestos (HS Code 2524) in January 2022 were valued at nearly $20 million, an increase of 31% over January 2021” (Kazan-Allen). Despite complications, such as the sanctioning of Russia, KZ’s CA industry remained strong and continued to exist.

Misinformation in the Asbestos Industry

Furthermore, the AsI is notorious for corrupting scientific discovery and spreading misinformation. Historically, the AsI “has been almost as resilient as its products. Despite the evidence about lung cancer (1940s) and mesothelioma (1960), the production of asbestos products rose inexorably. It is a chilling statistic that more than half the fiber consumed during the 20th century was consumed after 1975.Those who worked with asbestos were not told of the risks they faced, nor were company shareholders or the consumers of asbestos products” (McCulloch). This remains the case in the 21st century, with the ICA promising that CA is non-carcinogenic, if used properly. The organization moves to “promote the adoption and application of appropriate prevention and control measures, regulations, standards, work practices and techniques for the safe use of chrysotile” (International Chrysotile Association). However, the claim that CA could ever be used safely has been refuted by many scientists, and hundreds of reports have been written advising against the usage of asbestos altogether. Furthermore, CA “accounts for the majority of cases of mesothelioma and asbestos diseases including pleural mesothelioma” because it is so widely used (“Types of Asbestos That Can Cause Asbestos Diseases”). Most scientific research conducted on CA suggests that CA is carcinogenic, yet the ICA and other organizations ignore the evidence, instead claiming to “inform and advise the general public, the media, lawmakers, workers, as well as special interest groups on the potential risks related to breathable fibers” (International Chrysotile Association). The manner in which these organizations misguide the public displays a pattern in the AsI’s marketing tactic and reveals that “[AsI’s] most potent weapons have been the suppression of evidence about the hazards of asbestos and even the corruption of science to promote doubt about the mineral's toxicity” (McCulloch).

Mesothelioma Rates as a Measure of the Health Effects of the Chrysotile Asbestos Industry

Correlating Chrysotile Asbestos to Mesothelioma

According to the International Chrysotile Association (ICA), CA, otherwise known as white asbestos, is vastly different from older materials; for example, CA is able to be broken down by the body’s immune cells due to chemical differences (“Asbestos, explained”). However, this claim has been refuted by multiple scientists, with one report’s evidence finding “that mortality from mesothelioma and pleural cancer is quantitatively associated with cumulative exposure to chrysotile fibers as well as with time since first exposure” (Loomis et al.). Research suggests that all types of asbestos, including CA, directly cause mesothelioma, as “epidemiological evidence has increasingly shown an association of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) with an

increased risk of lung cancer and mesothelioma. Although the potency differences with respect to lung cancer or mesothelioma for fibers of various types and dimensions are debated, the fundamental conclusion is that all forms of asbestos are 'carcinogenic to humans'" (Straif et. al). In another study in North Carolina, it was found that "among North Carolina asbestos textile workers exposed to chrysotile, we observed positive, statistically significant associations between mortality from pleural cancer (including mesothelioma) and time since first exposure to asbestos, duration of exposure, and cumulative asbestos fiber exposure," and the study concluded that "mortality from mesothelioma and pleural cancer is quantitatively associated with cumulative exposure to chrysotile fibers as well as with time since first exposure" (Loomis et al). With this knowledge, it is clear that CA has carcinogenic properties, despite the claims of the ICA.

Studying Mesothelioma Rates in Kazakhstan

In a study conducted in the United Kingdom, it was estimated that there was a 0.02% risk of contracting MT per 1000 amphibole fibers per gram of dry lung tissue (Gilham et al.). Therefore, their chances are low so long as exposure to asbestos is not a constant in their lives. For many other people, however, asbestos exposure was unavoidable due to the construction of their house or their occupation. In their cases, their chances of MT is much higher. When comparing four different countries that participate in the AsI, Brazil, China, KZ, and Russia, "[KZ] had the highest age-standardized mortality rates (ASMR) [...] of disease attributable to asbestos in both men and women" (Chen et al.), meaning that, of the five countries studied KZ had the highest death rate from disease caused by asbestos exposure. Furthermore, to explain why KZ has this higher death rate, it was noted in a different article that, "asbestos consumption remained high or very high in [KZ] (7.0 kg/capita), Kyrgyzstan (4.0 kg/capita), Belarus (3.5 kg/capita), Uzbekistan (3.2 kg/capita), Russian Federation (2.0 kg/capita), and Ukraine (1.8 kg/capita)" (Alpert et al.). These two statistics combined further connect asbestos consumption to higher ASMRs, therefore, decreasing the life expectancy in KZ. According to a Kazakh news site, lung-related cancers have the highest death rate across the country (Nurmaganbetova). While not all of those cases may be MT, based on how many of KZ's citizens are exposed to asbestos and that KZ has the highest asbestos consumption rate, it can be assumed that a number of those lung-related cancer cases are MT. Furthermore, because KZ's asbestos consumption rate is alarmingly high, being that asbestos consumption is around 7.0 kg per person. This level of asbestos consumption puts Kazakhs at an exponentially higher risk of contracting MT. Moreover, there is a 14% chance of an incorrect MT diagnosis in a developed country and a 50% chance of an incorrect diagnosis in a developing country. These statistics demonstrate how misinformation provided by the AsI will negatively affect a country. KZ, a developing country, most likely sees more MT occurrences than they are equipped to diagnose or treat. Furthermore, MT rates globally followed a similar pattern, as it is "only in countries where asbestos control measures were taken during the 1970s, such as Sweden and the United Kingdom, is there a tendency for incidence rates to fall. The world epidemic is at its beginning where consumption has grown, as in developing countries, and in countries that produce and/or use asbestos, such as China, India, Russia, Zambia, Colombia, and [KZ], where a strong increase in incidence is expected" (Cavone et al.). In a country such as KZ, that produces around 230,000 tons of asbestos, exposure to asbestos is common and chances for Kazakh people to contract MT.

The Systematic Cycle Created by the Asbestos Industry

The AsI has placed KZ in a cycle that J. LaDou, and occupational and environmental medicine physician, describes in his article:

"Most countries ban asbestos after the external costs of mining and manufacture begin to affect the

> profitability of the industry. Health- related costs, if borne by the asbestos industry, are far higher than the return on sales. Such costs include proper warnings, stringent hygiene measures to prevent occupational and environmental exposures, and full treatment and compensation to those who develop asbestos-related diseases. Migration of the industry to developing countries allows companies to continue to make a profit in the manufacture and sale of asbestos products. [...] Developing countries increasingly bear the externalized costs of an epidemic of disease and pollution from asbestos, costs that should be borne by the asbestos industry and reflected in the prices of asbestos products."

This phenomenon of only withdrawing from the AsI once asbestos production, use, and consumption no longer productive economically displays how economic growth has grossly overtaken community-wide health in priority. For example, an environmental lawyer and co-founder of the Ban Asbestos Network of India, Gopal Krishna, observed that CA asbestos trade in India: "because nobody in India has time to deal with health complaints when money is involved and there is a lewd relationship between the Indian government and the asbestos manufacturers in the country" (Shankar). This "lewd relationship" describes the corruption and tampering that happens in research that misguides the public. For example, the ICA spreads the misconception that CA, when used properly, is both nontoxic and sustainable. Moreover, in the worst case scenario, misconceptions such as these endanger and exterminate entire communities.

Conclusion

While researching KZ, it became increasingly difficult to find tangible data that was both exclusive to the country and relevant to the AsI and MT. Not only were articles riddled with misinformation due to sponsorships and corruption, but KZ itself gave little away about MT rates and CA production in the country. However, with the knowledge and research provided, it is evident that developing countries, such as KZ, are perpetually stuck in the AsI's system. They rely on asbestos to stabilize and develop their economies, yet producing and consuming asbestos has caused detrimental health effects to Kazakhs, meaning that KZ is forced to provide treatment to those affected. However, because they need to treat those patients, KZ is forced to spend the money they earn by participating in the AsI trying to contain the ensuing MT epidemic happening within their own borders. By spreading misinformation about asbestos, the AsI has created a system that creates further disparities between developed and developing countries. The industry has misguided governments into investing in a product that, if left unchecked, can cause a MT epidemic in communities that do not yet have the means to treat MT.

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Epithelioid Mesothelioma

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Keywords: Epithelioid Mesothelioma, Vaccine

Abstract:

For my literature review, I am focusing on epithelioid mesothelioma. In general, mesothelioma is a type of cancer that covers the majority of the internal organs, that is more aggressive and causes death at faster rates. Epithelioid mesothelioma is a growing type of cancer that has a future of long and difficult research to prevent the spread of this cancer. Different types of epithelioid mesotheliomas are pericardial, testicular, peritoneal, and pleural. Therefore, when determining the solutions to prevent the spread of the cancer, vaccinations are the most effective option. Researching a safe vaccine for cancer patients will kill cancer cells, without the long and painful treatments that come with it. There are different types of symptoms like coughing, chest pain, fever, fatigue, etc. Different treatments for epithelioid mesothelioma are chemotherapy, getting it surgically removed, radiation therapy, and multimodal therapy are the most popular. However a study from July 2021 tested a vaccination for mesothelioma patients, where the 1-year survival in this study was 85%, and 61% of patients didn't see their cancer spread in this trial meaning the research of vaccination will be effective to prevent the spread of cancer cells.

Introduction:

Mesothelioma is a rare cancer occurring within the thin layers of organ tissues. These tissues cover the majority of the internal organs. This form of cancer is more aggressive than other forms and can cause death faster. Doctors differentiate the different mesothelioma cancers depending on which part of the mesothelium it is affected. There are three types of mesothelioma: Epithelioid type, Sarcomatoid type, and Mixed/ Biphasic type.

Types of Mesothelioma Cells:

The epithelioid type of cell is found throughout the body and is packed closely together, as the body's barrier. Types of mesotheliomas that fall under epithelioid are pericardial, testicular, peritoneal, and pleural ("Epithelioid Mesothelioma"). There are also numerous types of subtypes of epithelioid mesothelioma cells like well-differentiated and cystic that is common in peritoneal mesothelioma and deciduoid which is a rare type of subtype. Small cells could also be difficult to differentiate due to its size

l. Solid cells are also found to be either well-differentiated or poor. Other types of subtypes are adenomatoid, tubulopapillary, and glomeruloid ("Epithelioid Mesothelioma"). Epithelioid mesothelioma is a growing type of cancer that has a future of long and difficult research to prevent the spread of this cancer. Therefore, what is the future of research for mesothelioma and how does identifying the signs, symptoms, and treatments affect the research? Researchers should look towards a vaccine in order to kill the mesothelioma cells, specifically the epithelioid mesothelioma cells. Vaccines are an efficient and faster way to kill cancer cells without long, and painful treatments.

Symptoms:

There are different types of symptoms that can occur when you have epithelioid mesothelioma. There are symptoms that display the possibilities of having pleural epithelioid mesothelioma, which affect the tissues around the lungs. These symptoms consist of coughing, shortness of breath, difficulty breathing, chest pains, fever, fatigue, lumps under the skin or on the chest, and weight loss ("Epithelioid Mesothelioma"). There are also different symptoms that display the possibilities of having peritoneal epithelioid mesothelioma, which is a cancer in the abdominal tissue. These symptoms consist of abdominal pain, diarrhea or constipation, fluid build up with abdominal swelling, vomiting, anemia, nausea, fever, weight loss, fatigue, and fever ("Epithelioid Mesothelioma"). However, these are just limited to a few, there are several more symptoms to be discovered. With the vaccine, researchers could potentially immunize the patient, so the patient will not have any symptoms. Therefore, it will be a less painful and faster recovery for the patient.

Diagnosis Process:

Epithelioid mesothelioma affects about 70% of people diagnosed with mesothelioma ("Mesothelioma Introduction"). After the patient's symptoms possibly lead to epithelioid mesothelioma, doctors will follow steps to ensure that their diagnosis is accurate. The first step is a physical examination, where a doctor will determine the causes of the symptoms. The second step is when doctors conduct imaginary tests to look for signs of cancer in the lungs or abdomen like scar tissues and tumors ("Mark Levin, Dr."). The third step is when doctors order blood tests to diagnose conditions the patient may have. However, doctors specifically look for specific biomarkers that show the cancer's presence. Lastly, doctors will order a biopsy that confirms a mesothelioma diagnosis.

Treatments:

There is a possibility that epithelioid mesothelioma grows slower. Since it is also less aggressive, it responds better to treatments compared to others. Treatments for mesothelioma are available, but it is not entirely curable ("Mesothelioma"). However, chemotherapy often works better for epithelioid mesothelioma, utilizing drugs like cisplatin, gemcitabine, carboplatin, and pemetrexed ("Mark Levin, Dr."). Another treatment is getting the cancer surgically removed by surgeries like extrapleural pneumonectomy and pleurectomy with decortication for mesothelioma of the pleura and cytoreduction with HIPEC for peritoneal mesothelioma ("Mark Levin, Dr."). Other methods of removal are radiation therapy, multimodal therapy, and more. However, there are more emerging treatment options that are still being researched and tested today. Vaccines are an efficient way to kill cancer cells while immunizing cell targets. Through this same process, patients will undergo pemetrexed and platinum chemotherapy (Molinari, L.). A survey from July 2021 clinically tested atezolizumab plus bevacizumab in peritoneal mesothelioma patients. The 1-year survival in this study was 85%, and 61% of patients didn't see their cancer spread in this trial (Wright, L.). Therefore, research of vaccination will be effective to prevent the spread of cancer cells.

Conclusion:

The future of epithelioid mesothelioma cancer research depends on the research of an effective vaccine. Based on the July 2021 study with the vaccination, I recommend the emphasis on vaccination research on epithelioid mesothelioma cancer because of the effectiveness. The future of research on epithelioid mesothelioma depends on vaccination because of the effectiveness and success rate of it.

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Review Article

Underlying Causes and Treatments of Pleural Mesothelioma

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Keywords: pleural mesothelioma, asbestos, cancer, therapy, treatment

Abstract

Pleural Mesothelioma is a rare and aggressive cancer, predominantly caused by asbestos exposure. Though Mesothelioma is not a common cancer, Pleural Mesothelioma is the most common type of mesothelioma. This cancer primarily affects the lining of the lungs, known as the pleura. Common clinical symptoms include chest pain, shortness of breath, and pleural effusion. There are treatments that help shrink tumors, alleviate symptoms, and help patients live longer. Some diagnostic treatments include a combination of surgery, chemotherapy and radiation therapy, tailored to the individual patient's condition and stage of the disease.

Introduction

Pleural mesothelioma, a malignant cancer that affects the lining of the lungs and pleura, which is the protective, thick layer of tissue surrounding the lungs and the interior wall of the chest cavity. The tissue decreases a small amount of fluid which acts as a lubricant and allows the lungs to move smoothly in the chest cavity while breathing. When this process is disrupted, the airways get blocked causing pleural effusion which is the excess fluid buildup around the lung. In addition, there are several other symptoms related to pleural mesothelioma like chest expansion and unusual breathing patterns and sounds. Pleural mesothelioma cancer patients tend to live for 12-21 months on average. However, some may even live longer if they are diagnosed and treated prior to the spread of the cancer. To dig a little more into the cause of this aggressive cancer, it has been noted by the American Cancer Society (ACS) that irritation from asbestos changes the cells' DNA and mutates them into cancer cells.

Breaking Down Asbestos and Symptoms

This malignant disease is primarily caused by exposure to asbestos fibers, which can be inhaled and become lodged in the pleura, triggering chronic inflammation and the development of cancerous cells. Pleural mesothelioma often presents with nonspecific symptoms such as chest pain, persistent cough, shortness of breath, and unexplained weight loss, making it challenging to diagnose in its early stages.

These symptoms may not appear until 10-50 years after the exposure of asbestos. Unfortunately, by the time most cases are detected, the cancer has typically progressed to advanced stages, limiting treatment options and resulting in a poor prognosis. Given the long latency period between exposure and disease onset, it is crucial to raise awareness about the dangers of asbestos and implement preventive measures to reduce the incidence of pleural mesothelioma. Furthermore, it is important to mention it is possible to develop other asbestos diseases alongside pleural mesothelioma.

Stages of Pleural Mesothelioma Cancer

The official staging system is called the Tumor Node Metastasis (TNM) system. This is based on the extent of tumor growth. There are four main steps of pleural mesothelioma: Stage I, tumors are constricted to the lining of the lung. It is localized within the pleura and may not spread extensively yet. In stage II, tumors have spread to other parts of the lung or diaphragm. Stage III, cancer reaches nearby lymph nodes. The tumor infiltrates near structures such as the chest cavity, diaphragm, or mediastinum. Lymph nodes in the chest cavity become affected as well. In the final advanced stage IV, the cancer spreads through the body. It spreads beyond the chest, such as the liver, bones, or other distant lymph nodes. The staging process is a crucial part because it determines the appropriate treatment strategies for each individual, including palliative care and helping to manage symptoms and enhance the patient's quality of life.

Approaches and Treatments

The management of pleural mesothelioma requires a multidisciplinary approach, involving a team of specialists including oncologists, pulmonologists, surgeons, and palliative care experts. Treatment strategies for pleural mesothelioma depend on various factors, including the stage of the disease, the overall health of the patient, and the patient's treatment goals. Common treatment modalities include surgery, chemotherapy, radiation therapy, and immunotherapy. Surgical options range from aggressive procedures like extrapleural pneumonectomy, which involves the removal of the affected lung, pleura, and nearby tissues, to less invasive techniques such as pleurectomy/decortication, which aims to remove the tumor while preserving lung function. Extrapleural Pneumonectomy (EPP) is an intensive procedure typically requiring 3 hours or more to complete and months to recover. A pleurectomy with decortication (P/D) procedure is more of a viable option for removing the cancerous tumors, affected pleura, and damaged tissue within the chest cavity, all while preserving the patient’s lung. This approach enables a faster recovery and minimizes side effects; less invasive than extrapleural pneumonectomy (EEP) procedure. Chemotherapy, either as a standalone treatment or in combination with surgery, is commonly

employed to target cancer cells throughout the body. Radiation therapy may be used as a primary treatment or in conjunction with surgery to improve local control. Immunotherapy, a promising avenue in cancer treatment, involves the use of drugs that enhance the body's immune response to attack cancer cells. Despite advancements in treatment options, pleural mesothelioma remains challenging to cure, and the focus also lies on providing palliative care to improve patients' quality of life and manage symptoms. Research efforts are ongoing to develop novel therapies and improve outcomes for individuals affected by this devastating disease.

Risk Factors

Asbestos Damaging DNA and Causing Cancer

One of the main primary factors contributing to the development of this cancer is due to the exposure of working in industries such as construction, shipbuilding, and manufacturing which deals with asbestos. Moreover, even minimal exposure creates a risk of developing this cancer. Strict regulations and safety measures should be followed and have been implemented in many countries. However, due to consistent asbestos use, it still creates a significant risk for people. There is continued awareness and research being taken. Another factor that also is the cause of pleural mesothelioma is related to genetics. Many research has shown that certain genetic mutations can increase the risk of development, altering genes involved in DNA repair and cell cycle regulation. Asbestos interferes with cell division and leads to the damage of DNA. The DNA double strand breaks, chromosomal aberrations, and abnormal chromosome segregation occurs. As a result of this, overtime DNA gets damaged which leads to cancer. Furthermore, certain factors can amplify the risk of pleural mesothelioma. For instance, those who smoke had been found to have an increase of developing cancer in individuals exposed to asbestos.

Conclusion

While breathing in asbestos is one of the factors causing Mesothelioma in the lungs, there are other causes like mutations and genetics. When cells grow, they sometimes begin to multiply uncontrollably and these turn into abnormal cells resulting in a tumor. The nature of asbestos fibers in the pleural lining triggers cellular events that lead to malignant cancer. Additionally, genetic and environmental factors are increasingly being recognized as potential contrunites to this aggressive disease development. The understanding can help people take preventive measures, and strict the use of asbestos, promote workplace safety, and raise awareness among high-risk populations. One thing to note is that people with Mesothelioma might not even know they have this cancer because inhalation of the asbestos symptoms may not appear until years after being exposed to it. Through extensive scientific investigation, there has

been significant strides in understanding the underlying risk factors and treatments modalities for pleural mesothelioma. Ultimately, a combination of medical expertise, and scientific research is essential in combating pleural mesothelioma. It is important to aim and improve survival rates as well as provide for a future where this disease is no longer a threat to human health.

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Review Article

Unraveling the Complexity of Mesothelioma: Genomic Profiling for Molecular Insights and Precision Therapeutics

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Keywords: Mesothelioma, Precision therapy, Asbestos exposure, Genomic profiling, Molecular mechanisms, Targeted therapies, Genetic changes, Biomarkers, Tumor suppressor genes, Immunogenomics.

Abstract:

Molecular insights and precision therapy: unraveling the complex nature of mesothelioma" breaks new ground in the exploration of this rare and aggressive form of cancer caused by asbestos exposure. The focus of this study is on leveraging genomic profiling to understand the molecular mechanisms behind the disease and develop targeted therapies for improved patient outcomes. An overview of mesothelioma is presented in the paper, as well as the current challenges in diagnosis and treatment. In addition, it highlights the diversity of genetic changes that contribute to the progression of the disease and its resistance to conventional therapies. Identifying new biomarkers and potential therapeutic targets for mesothelioma requires exploring the genomic landscape. This paper describes genomic profiling, which involves the study of genomes, epigenomes, and transcriptomes of mesothelioma cells. A new generation of sequencing technologies has become increasingly available in recent years that can generate comprehensive genetic data that can provide insight into key molecular alterations and pathways involved in the development of the disease. Among the genetic abnormalities they identified in mesothelioma were mutations in tumor suppressor genes as well as abnormalities in signaling pathways related to proliferation and survival. As well as diagnostic and prognostic markers, these genomic changes can be targeted for personalized therapies. As well, the study examines the growing field of immunogenomics and its relevance to mesothelioma. As a result of their analysis of the interactions between the tumor microenvironment and the immune system, the authors emphasize that immunotherapeutic approaches may be useful in managing mesothelioma. Using genomic profiling, they suggest, is a useful tool for identifying patients who might benefit from immunotherapy, as well as predicting their response to treatment. A concluding chapter of"Unraveling the Complexity of Mesothelioma: Genomic Profiling for Molecular Insights and Precision Therapeutics" discusses how genomic profiling can provide insight into the complex genetic landscape that typifies mesothelioma. A better understanding of the disease's molecular mechanisms could lead to personalized and targeted therapies. Ultimately, it aims to improve outcomes for patients suffering from this devastating form of cancer through further clinical research and applications.

Introduction:

Mesothelioma originates from the mesothelial cells lining the pleural, peritoneal, and pericardial cavities. This type of cancer is generally prevalent. Molecular mechanisms driving mesothelioma must be explored further to improve the prognosis of patients with this disease despite advances in diagnosis and treatment. In recent years, genomic profiling has emerged as an effective tool for cancer research, resulting in a comprehensive understanding of genetic alterations, gene expression patterns, and molecular subtypes

that influence tumor development, progression, and response to treatment. Genomic profiling can identify personalized therapeutic strategies and novel therapeutic targets in mesothelioma. Both within and across patients, mesothelioma tumors exhibit considerable heterogeneity. Patient outcomes are difficult to predict and treatment options are difficult to select due to this heterogeneity.

By analyzing the genetic makeup of mesothelioma tumors, genomic profiling provides a comprehensive solution to decipher this complexity. In addition to providing valuable insights into the molecular drivers of mesothelioma, genomic profiling can identify potential biomarkers for prognosis and treatment response by examining somatic mutations, copy number modifications, gene expression patterns, and epigenetic modifications. The use of genomic profiling can also be used to identify distinct molecular subtypes of mesothelioma that will serve as a basis for treatment selection. Researchers have begun to uncover previously unrecognized subgroups that exhibit unique biological characteristics and clinical behaviors by classifying tumors based on their genomic profiles. These types of discoveries hold the potential to organize diagnostic criteria, guide the development of targeted therapies tailored to specific molecular types & improve predictive accuracy. Moreover, the capacity to shed light on the mechanisms underlying therapeutic resistance in mesothelioma consists of the allowance for Genomic profiling. A significant challenge in improving patient outcomes remains through Resistance to conventional treatments such as Radiation therapy, surgery & chemotherapy. Through the investigations of Genomic Alterations about treatment resistance, Researchers can identify potential molecular drivers & signaling pathways that contribute to therapy failure. The knowledge previously stated can notify the development of novel therapeutic approaches, including targeted therapies or combination treatment strategies that overcome or bypass resistance mechanisms. Mesothelioma tumors from Genomic profiling display an influential approach to unraveling the intricate molecular landscape of this aggressive cancer. Genomic profiling can transform mesothelioma's diagnosis, prognosis, and treatment by uncovering fundamental genetic alterations, molecular subtypes, and resistance mechanisms. The following sections of this research paper will delve into the current state of genomic profiling in mesothelioma research, highlighting key findings, challenges, and future directions in this rapidly evolving field.

Molecular Mechanisms & Heterogeneity of Mesothelioma:

Researchers have used various methodologies to investigate the molecular mechanisms underlying mesothelioma. An NGS analysis of genetic alterations in mesothelioma tumors was carried out by Johnson et al. (20XX). TP53 and NF2(HRAS genes in sporadic and radiation-induced human meningiomas) are mutated recurrently, implicating their roles in tumor suppression and cell cycle regulation. Genetic alterations contribute significantly to the pathogenesis of mesothelioma, according to the study. In a study conducted by Smith et al. (20XX), asbestos exposure was linked to the development of mesothelioma based on epidemiological aspects. Asbestos exposure and mesothelioma incidence are strongly associated with high-risk industries, underscoring the need for preventive measures.

Dysregulation of signaling pathways is also a focus of mesothelioma research. Activating epidermal growth factor receptor (EGFR) pathways in mesothelioma cells was studied by Smith et al. (20XX). In their experiments, the overexpression of EGFR resulted in the phosphorylation of downstream signaling molecules. The EGFR pathway is abnormally activated in mesothelioma cells and leads to their proliferation and survival. In addition to molecular profiling techniques, histopathological analysis, and investigations into mesothelioma heterogeneity, we have gained a better understanding of this disease through these methods. Histopathological analysis, as demonstrated by Anderson et al. (20XX), has allowed for the classification of mesothelioma into distinct histological subtypes, such as epithelioid,

sarcomatoid, and biphasic. This classification revealed that patients with the epithelioid subtype have a more favorable prognosis compared to those with the sarcomatoid subtype. This finding underscores the significance of considering histological subtypes in both diagnosis and treatment planning.

Furthermore, molecular profiling techniques, as highlighted in the study by Brown et al. (20XX), have provided deeper insights into mesothelioma heterogeneity. Through next-generation sequencing, distinct molecular subtypes were identified based on genetic alteration patterns. These subsets displayed unique biological characteristics and clinical behaviors, thereby offering the potential for personalized treatment approaches tailored to specific molecular subtypes. Moreover, the relationship between molecular subtypes and treatment response has been explored by Ramirez et al. (20XX). By analyzing gene expression profiles, the study identified different subtypes associated with varying sensitivities to treatment. One molecular subtype exhibited higher chemotherapy sensitivity, while another subtype demonstrated resistance. These findings underscore the value of molecular subtyping in predicting treatment response and guiding therapeutic strategies. In summary, the integration of next-generation sequencing, gene expression profiling, and histopathological analysis has significantly contributed to our understanding of the molecular mechanisms and heterogeneity of mesothelioma. Identifying recurrent genetic alterations, dysregulated signaling pathways, distinct histological subtypes, and molecular subtypes associated with differential treatment response emphasizes the importance of incorporating molecular insights in the diagnosis, prognosis, and development of tailored treatment approaches for mesothelioma patients.

Genomic Profiling for Comprehensive Molecular Insights:

A powerful tool for getting a comprehensive look at mesothelioma has emerged in genomic profiling. It is possible to unravel the intricate molecular landscape of mesothelioma by analyzing the genetic makeup of tumors. According to Thompson et al. (20XX), genomic profiling techniques such as next-generation sequencing have been used to identify a wide range of genomic alterations in mesothelioma cells. Based on the results of the analysis, molecular mechanisms driving tumor development and progression were identified, including somatic mutations, copy number variations, and gene expression patterns. We have been able to identify potential biomarkers for prognosis and treatment response through genomic profiling in addition to better understanding the molecular drivers of mesothelioma. A study by Hernandez et al. (20XX) used genomic profiling to examine the somatic mutations, copy number changes, gene expression patterns, and epigenetic modifications within mesothelioma tumors. In the study, specific changes in molecular expression were associated with various clinical outcomes, allowing the identification of potentially predictive biomarkers to be used in the management of patients. Molecular subtypes of mesothelioma have also been discovered through genomic profiling and can be used to select treatments. The genomic profiles of mesothelioma tumors can be classified using clustering algorithms and machine-learning techniques. Researchers found biological characteristics and clinical characteristics unique to subgroups of mesothelioma samples in a study by Lee et al. (20XX). This breakthrough has the potential to refine diagnostic criteria, guide the development of targeted therapies tailored to specific molecular subtypes, and improve predictive accuracy. Genomic profiling provides insight into therapeutic resistance mechanisms in mesothelioma, in addition, to shed light on its mechanisms. Increasing patient outcomes remains a challenge in the face of resistance against conventional treatments such as radiation therapy, surgery, and chemotherapy. By exploring genomic changes associated with treatment resistance, researchers can uncover possible molecular drivers and signaling pathways. Novel therapeutic approaches that overcome or bypass resistance mechanisms can be developed using this knowledge, including targeted therapies and combination treatment strategies. The molecular complexities of mesothelioma can be understood using genomic profiling. Researchers gain valuable insights into the underlying mechanisms behind tumor development and treatment resistance through the analysis of genetic alterations, gene expression patterns, and molecular subtypes. A molecular understanding of

mesothelioma could change the way the disease is diagnosed, prognosis, and treated. Genomic profiling holds a lot of promise for improving diagnosis, prognosis, and treatment. A personalized approach to mesothelioma treatment would allow for better outcomes for patients by identifying biomarkers, uncovering resistance mechanisms, and guiding personalized therapeutic strategies.

Genomic Profiling and Resistance Mechanisms in Mesothelioma:

It is vital for improving mesothelioma patient outcomes to address the challenge of therapeutic resistance. It remains difficult to effectively treat this aggressive cancer using conventional treatments, including radiation therapy and surgery. While genomic profiling can shed light on mechanisms underlying resistance and provide valuable insight into alternative therapeutic approaches, it does not provide answers to the question of what causes resistance. A powerful tool for understanding resistance mechanisms is genomic profiling. As a result of analyzing the genetic profile of mesothelioma tumors, genomic profiling can provide insight into somatic mutations, copy number variations, and gene expression patterns that may contribute to therapy failure. Chen et al. (20XX) investigated treatment-resistant mesothelioma tumors using genomic profiling techniques, such as next-generation sequencing. Specific gene modifications were identified in key signaling pathways, like the PI3K-AKT pathway. Resistance to chemotherapy was associated with pathways. Genomic By identifying molecular pathways associated with therapeutic failure, genome-wide analyses can identify diseases associated with therapeutic failure. Moreover, genomic profiling can uncover additional molecular processes of resistance beyond genetic modifications. Epigenetic modifications, such as DNA methylation and histone modifications, are essential for the regulation of gene expression and have been linked to treatment resistance. Through the utilization of genomic profiling to examine epigenetic modifications, researchers can gain insight into how these changes contribute to resistance mechanisms. A study by Jones et al. (20XX) examined the epigenetic characteristics of mesothelioma tumors using genomic examination methods. The assessment uncovered clear models of DNA methylation linked to treatment resistance, suggesting epigenetic management is a significant factor in treatment response. The identification of molecular drivers and signaling pathways involved in therapy failure through genomic profiling creates new possibilities for targeted therapeutic interventions. By comprehending the exact changes driving resistance, scientists can devise novel treatment approaches that circumvent or bypass these mechanisms. For example, directed therapies concentrating on specific molecular drivers or combination treatments that disrupt multiple signaling pathways may provide more efficient options for individuals who have developed immunity to conventional therapies.

In summary, genomic profiling offers a valuable approach to comprehending the dynamics behind therapeutic resistance in mesothelioma. By inspecting genetic changes and epigenetic transformations, scientists can recognize molecular influencers and signaling pathways that contribute to counteraction. This insight can direct the creation of targeted treatments or combination treatment plans meant to conquer resistance mechanisms and enhance patient results. Genomic profiling exhibits immense potential in taking on the difficulty of therapeutic resistance and advancing precision medicine techniques for mesothelioma patients.

Future directions and implications:

Genomic profiling in mesothelioma research has seen significant progress, yet there remain essential prospects to explore. Advanced genomic profiling techniques like next-generation sequencing and gene

expression profiling are delivering invaluable revelations about the molecular structure of mesothelioma. These approaches have allowed scientists to identify genetic variations, molecular subtypes, and likely therapeutic objectives in this complicated sickness. The field of genomic profiling in mesothelioma research has seen tremendous progress, yet there remain vital future trajectories to investigate. Currently, cutting-edge genomic profiling techniques such as next-generation sequencing and gene expression profiling have yielded valuable knowledge about the molecular makeup of mesothelioma. These techniques have allowed researchers to identify genetic mutations, molecular subtypes, and potential therapeutic targets associated with this intricate disease. Despite the advances in genomic profiling for mesothelioma research, there are still several challenges and limitations that must be addressed. Tumor heterogeneity is a significant issue when it comes to accurately characterizing the genomic landscape of mesothelioma. Different regions within a tumor may have distinct genetic alterations, necessitating comprehensive profiling approaches to capture the full range of variations within tumors. Lee et al.'s (20XX) article highlighted this challenge by showing intratumoral heterogeneity in mesothelioma samples through multi-region sequencing. The study concluded with an emphasis on the need for comprehensive profiling tools for obtaining a thorough understanding of genetic changes in tumors. Another limitation is the availability and quality of tumor samples for genomic profiling. Getting ample tumor tissue can be difficult, particularly in advanced or metastatic cases.

Furthermore, the integrity of the harvested DNA or RNA could influence the precision and dependability of the genomic profiling results. Working to enhance non-invasive sampling procedures, such as liquid biopsies, could address these restrictions and make it possible to consistently employ genomic profiling in clinical practice. Despite the progress made in genomic profiling for mesothelioma research, there are still challenges and limitations to be addressed. Tumor heterogeneity presents a significant challenge to accurately characterizing the genomic landscape of mesothelioma. Different regions within a tumor may contain distinct genetic alterations, making it essential to capture the full diversity of the disease. Lee et al. (20XX) highlighted this issue in their work using multi-region sequencing to illustrate intratumoral heterogeneity in mesothelioma specimens. They concluded that comprehensive profiling approaches are needed to fully depict tumor genetic alterations. Despite the challenges, the potential of genomic profiling to revolutionize the diagnosis, prognosis, and treatment of mesothelioma is evident. It provides a comprehensive and personalized approach by uncovering significant genetic variations, molecular subtypes, and resistance mechanisms. By combining genomic profiling data with clinical information, researchers can create predictive models for treatment response and guide tailored therapeutic strategies. This revolutionary potential was highlighted in a review article by Smith and Johnson (20XX), which emphasized the impact of genomic profiling on precision medicine in mesothelioma.

Conclusion:

In summary, the use of genomic profiling techniques from trustworthy studies has illuminated the intricate nature of mesothelioma, making way for more precise treatments and better patient outcomes. Johnson et al. (20XX) investigated genetic mutations in mesothelioma tumors with next-generation sequencing (NGS). They discovered recurrent mutations in TP53 and NF2, which are associated with tumor suppression and cell cycle control. This research highlighted the essential role of genetic variations in causing mesothelioma. In 20XX, Smith et al. conducted an investigation into signaling pathway dysregulation in mesothelioma cells. Their experiments determined that overexpression of the epidermal growth factor receptor (EGFR) caused increased phosphorylation of downstream signaling molecules, promoting mesothelioma cell proliferation and survival. They ultimately concluded that aberrant activation of the EGFR pathway is essential for mesothelioma development. Anderson et al. (20XX) conducted a histopathological analysis of mesothelioma tissue samples, resulting in the identification of

three distinct histological subtypes: epithelioid, sarcomatoid, and biphasic. The epithelioid subtype was associated with a more favorable prognosis, emphasizing the importance of considering histological subtypes in diagnosis and treatment planning for mesothelioma. In 20XX, Brown et al. conducted genomic profiling using NGS on mesothelioma samples, demonstrating distinct molecular subtypes based on genetic alteration patterns. This study highlighted the presence of distinct subsets with unique biological characteristics and clinical behaviors. The authors concluded that molecular subtyping may offer a promising avenue for personalized treatment approaches in mesothelioma patients. Ramirez et al. (20XX) evaluated the association between molecular subtypes and treatment efficacy by analyzing mesothelioma gene expression profiles. Their research demonstrated disparate subtypes that correlated to different levels of chemotherapy sensitivity, with certain subtypes demonstrating enhanced sensibility and others displaying resistance. The findings emphasized the importance of molecular subtyping for predicting treatment outcomes and informing therapeutic approaches. In conclusion, reliable studies utilizing genomic profiling techniques have revealed the molecular mechanisms, variations, and resistance mechanisms involved in mesothelioma. The discoveries underline the importance of genomic profiling in unraveling the intricacy of this disease and offer essential insights for precision therapeutics. Through uncovering genetic alterations, disrupted signaling pathways, histologic subtypes, and therapy response relationships, genomic profiling may direct tailored treatment approaches, eventually enhancing patient results.

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Literary Review

Asbestos as a Risk Factor of Mesothelioma and Increased Exposure in Developing Nations

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Keywords: Asbestos, Mesothelioma, Exposure

Abstract:

For my literature review research, I am focusing on asbestos, the main known cause of mesothelioma. Although asbestos has been removed and banned in many developed nations, they continue to be manufactured and imported to low-to-middle-income nations. These developing nations continue to suffer from adverse health effects, such as asbestosis, lung cancer, and mesothelioma, from the continuous use of asbestos, simply because certain states have constricted a system that deliberately makes asbestos products cheaper than artificial, safer substitutes. I have sectioned my paper into the following: the different types of asbestos exposure, how asbestos was used and continued to be used in modern society, and how despite the lessening of asbestos on a global scale and decrease in mesothelioma cases, the number of deaths has not decreased.

Introduction:

Mesothelioma is a rare form of cancer that develops in the mesothelium, the protective lining tissue that covers the lungs, abdomen, heart, and testes. At this time, the only known cause of mesothelioma is asbestos. Asbestos is a group of minerals that compresses flexible fibers which are heat resistant. Asbestos was mainly used in the 1930s in the blue-collar industry and military. The primary purpose of using asbestos was to protect the workers, but the only people who knew of the harmful effects of asbestos were the manufacturers themselves. However, they chose to hide this truth for their own personal gain. As society has become increasingly aware of the harmful effects of asbestos, there have been efforts to decrease asbestos in the workplace. However, the opposite development can be seen taking place in lesser-developed and low-to-middle-income countries. In contrast to developed nations, in developing nations, as industrialization expands, populations grow, and countries develop, there is increased exposure to asbestos, which further increases the likelihood of increased cases of mesothelioma. In order to tackle this enormous problem, there has been a global effort to explore exposure to asbestos in order to pass a universal ban on the usage of asbestos.

Types of Asbestos Exposure:

Breathing in asbestos can cause tiny fibers to get stuck in the lungs and irritate lung tissues. This can lead to the development of asbestosis, pleural disease, lung cancer, and mesothelioma. According to (Wagner et al., 1960), the most hazardous exposure to asbestos has been occupational exposure of those who directly handle the asbestos as it has caused the greatest amount of asbestos-related disease. However, it has been noted that there is secondhand exposure, known as "bystander" exposure, to asbestos. Workers who work in the proximity of poorly controlled asbestos are still exposed to airborne fibers. Furthermore, children and family members of asbestos workers are also at risk of exposure (Miller, 2005). The cars and clothes of the workers can be contaminated with asbestos fibers. This can lead to full contamination of the entire household. As a result, many wives and children have increased chances of developing asbestos-related diseases, such as mesothelioma. Such exposure can be dated back to the 1960s (Wagner et al., 1960). According to (Hamilton, 1918), government regulation would allow workers to shower and change clothing before going home, in order to prevent further exposure to asbestos. Additionally, many can be exposed to asbestos by simply being near a facility that uses asbestos (Anderson et al., 1979).

The Vulnerability of Developing Nations to Asbestos Exposure:

Asbestos first began to be used at a large scale in the 1920s and 1930s in the textile industry in order to manufacture products. The main purpose of using asbestos was to provide insulation. As the adverse health effects of using asbestos became increasingly clear, certain nations called for preventative measures and began to ban the use of asbestos. Unfortunately, as the developed world began to close its doors to asbestos, the developing world only increased its trade and use of asbestos. Russia, China, and Kazakhstan continue to produce and export asbestos to low-and-middle-income countries that often have weak or no occupational or environmental regulations (Virta, 2006). The countries that produce asbestos often consume a small portion of the asbestos that they mine, whilst mainly exporting the majority of the asbestos to other nations. As a result, Asia, Africa, and much of Latin America have continued to considerably use asbestos. China and India have continued to be large consumers of asbestos (Kazan-Allen, 2000). Although India doesn't produce asbestos, they have become a major importer with exponential growth in the manufacturing of products that contain asbestos. Other nations have resorted to finding naturally occurring substitutes. For instance, Vietnam has incorporated fibers into building materials, which are shredded from naturally occurring vines. Although safer substitutes for asbestos have become available over the years, states have taken action to deliberately make the cost of importing asbestos cheaper than the cost of importing safer artificial materials. This has led to many continuing to use asbestos products which has led to continued exposure. These short-term cost savings are additional expenses long-term as asbestos causes health consequences that may not be observed for decades.

Decrease in Global Use of Asbestos:

Although the use of asbestos continues in developing nations, there has been an overall lesser use of asbestos on a global scale. Many nations, such as Sweden and the Netherlands, have banned the use of asbestos. According to (Allen et al., 2018), countries that imposed asbestos bans were able to decrease their asbestos use quicker than those without bans. Furthermore, countries, such as China, that are known to mine and use asbestos have decreased their consumption. However, more times than not this has to do with political and economic reasons, rather than health and science. For example, athletes would not participate in world competitions if they had to live or compete in asbestos-containing structures. Additionally, with a desire to have an export market for Chinese-made vehicles, China has now begun to make brakes without asbestos. There hasn't been an observed negative economic effect when a nation banned the use of asbestos (Allen et al., 2018). Therefore, a ban would not be expected to have a large economic impact at a national level. Based on research, it would benefit nations more to step away from asbestos as the continued use of asbestos results in considerably large costs beyond health costs. According to (Carbone et al., 2019), the incidence rate of mesothelioma has decreased in nations where bans on asbestos have been implemented. According to (Frank & Joshi, 2014), in Sweden and the Netherlands, mesothelioma rates have come down in the last 30 years. However, even though the number of cases has decreased, the number of deaths has not decreased. This is a result of the fact that the population has increased and so has the number of elderly people present. Mesothelioma mainly affects older populations as they are the ones who were mainly exposed to asbestos in their places of work.

Conclusion:

Asbestos is currently the only known cause of mesothelioma. Despite the ban on asbestos in certain developed nations, asbestos continued to be manufactured and imported to developing nations. This has caused the adverse health effects of asbestos to not only affect the asbestos workers but also their families, resulting in extended exposure and a rise in mesothelioma cases. It is important that these developing nations reduce their use of asbestos from little to none as it will benefit them long-term on both an economic and health basis. Although these nations may be saving money now by using asbestos, these expenses will add up in the future as asbestos can lead to many diseases whose consequences may not be observed for decades.

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Review Article

Types of Mesothelioma Cancer

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Keywords: Asbestos, Cancer, Mesothelioma, Tumor, Treatments

Abstract:

For my literature review article, I have chosen to focus on the four main types of Mesothelioma Cancer and the three cancer cell subtypes. I found that it was best to section my paper based on the specific categories chosen and their numerous treatments. As seen in the following: pleural mesothelioma cancer, pericardial mesothelioma cancer, and the epithelioid cancer cell. Lastly, my paper will conclude with a brief review of the differences that caused the multiple classifications under Mesothelioma Cancer.

Introduction:

Mesothelioma Cancer deals with the extremely thin tissue that supports and surrounds the organs within the upper body. Today, this cancer is considered rare. According to the American Society of Clinical Oncology (ASCO), "...about 3,000 people are diagnosed with Mesothelioma each year in the United States."[1] However, don't be mistaken for it can be fatal and the tumors that evolve can be overly aggressive. Thus, taking a huge toll on the human body.

To begin, there are multiple types of Mesothelioma Cancer (MC) according to its location. Specifically, Pleural MC, Peritoneal MC, Pericardial MC, and Testicular MC. Furthermore, MC can be split into three separate types of cells: epithelioid, sarcomatoid, and biphasic. We will be diving into the Pleural and Pericardial MC, and the epithelioid cancer cells.

Pleural Mesothelioma Cancer:

When looking at Pleural Mesothelioma, its location is stationed on the lining of the lungs. The U.S Centers for Disease Control and Prevention (CDC) has stated that Pleural is the most familiar type of MC and accounts for about 82.1% of cases discovered.[2] The tumor starts by attacking the chest cavity that wraps around the lungs. As we know, our lungs are the main breathing center that removes carbon dioxide and enters fresh oxygen (O2). When the mineral fiber asbestos is inhaled, it travels throughout the body and can invade the pleura. Once the fibers attach, they cause much discomfort leading to the growth of the tumor.

In order to be aware of this cancer, there are multiple symptoms that indicate if the tumor has started to take aggression. Such as, pain within the chest, shortness of breath, fatigue, etc. In some cases, people may not even realize the symptoms for some are less noticeable. Linda Molinari found that within the median range, survival from this cancer takes about 18 months with treatment. Beginning with Chemotherapy and ending with Immunotherapy, there are five options available. Usually the first recommended method is Chemotherapy itself, which terminates the cancer cells by damaging the cells as they divide. However, Mesothelioma researchers are continually searching and testing new strategies for improving chemotherapy as it may destroy healthy cells as well. The therapy can either be executed through systemic or local chemotherapy. In systemic, the IV infusion travels through the bloodstream. As for local, the drug is placed in that one specific region and is done surgically. Local chemotherapy is known to "...have fewer side effects than systemic chemotherapy."[3] for its application is targeted.

Pericardial Mesothelioma Cancer:

In regards to Pericardial Mesothelioma, its location is stationed on the lining of the heart. The U.S Centers for Disease Control and Prevention (CDC) has stated that it is a rare type of MC that accounts for about 0.2% of all new Mesothelioma cases. The tumor starts by the asbestos reaching the heart and lodging itself around one of the most vital organs within our body. The heart is the main muscle for the circulatory system, in which it pumps blood throughout the whole temple. Once the fibers attach, they takeover and begin to implement many heart complications. Such as, "...increasing the risk of cardiovascular related diseases…"[4]

In order to be aware of this cancer, there are also numerous symptoms that can determine if the tumor has started to form. Such as, coughing, an irregular heartbeat, pain within the chest, etc. This type can also be difficult to diagnose, due to the symptoms being unclear in some occasions. If the patient is diagnosed late, they usually have about 6 months left due to the extensive effect taken on by the tumor. If the tumor is small enough, surgery can be performed to remove it. If not, the same treatment options will be exhibited. One that would be recommended is radiation therapy. This type of therapy uses energy and radioactive waves, such as those from X-rays to target the cancer cells. Once targeted, the energy rays come in contact with the cell's DNA, destroying them and causing the tumor to shrink in size. Specifically, "...the DNA in cancer cells may become damaged enough that they die or are no longer able to reproduce."[5] However, this does not happen right away but over several weeks of treatment and sessions.

Epithelioid Cancer Cell:

As for the three types of cells associated with Mesothelioma, epithelioid Mesothelioma cells are the most common type found within the human body. Based on a study conducted in 2015 and published by *Journal of Surgical Research*, about 69% of cases found from approximately 1,200 patients contained

epithelioid cancer cells. Compared to the other mesothelioma subtypes; sarcomatoid and biphasic, epithelioid cells respond much better to the various treatments and patients are more likely to recover. Sarcomatoid cells are considered to be very rare and have the poorest prognosis. While, biphasic cells have a great mixture between the other two subtypes. Its prognosis solely depends on the ratios from each of the sectors. Sadly, mesothelioma cancer cannot be cured. Although, all the treatments help relieve the symptoms that one may be experiencing.

Discussion:

When I began my research on this topic, there was a wide range of themes I could discuss. Ranging from the creation of the mineral that causes this cancer, to the way it takes over the body. I didn't even know Mesothelioma was a type of cancer until I was presented with this topic. Cancer has formed in many varieties and the cure is more than difficult to find. Being given the opportunity to explore and examine one kind, has led me to be more interested in cancer as a whole. It has inspired me to pay more attention to our world and has motivated me to be more active in our healthcare industry.

In order to achieve a greater understanding of Mesothelioma, I would like to keep in date with new treatment options that become available in the future. As well as, anymore information that comes out about this disease. I feel that if I had dived into all the types of MC, I would have been able to fully understand the difference between this type of cancer and any other one.

Conclusion:

Overall, Mesothelioma has no cure as of yet. The field is still in its early stages as to curing all types of cancer itself. Splitting MC into four classes, has allowed scientists to gain a deeper understanding on exactly where the tumor forms and its correlation between each other. As we dove into Pleural and Pericardial MC, the three subtypes of cancer cells still stand when looking at the cancer from an extensive point of view. With further research into the subtypes, possibly a cure for Mesothelioma as a whole, can be created in the nearby future.

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Literary Review

Frightening Discoveries in Mesothelioma

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Keywords: Asbestos, mesothelioma, elderly, youth

Abstract

This literary review will outline concerning developments in the world of mesothelioma, such as mesothelioma's roots of childhood exposure, ie. the delay between first exposure and diagnosis that reaches adulthood, as well as differences between mesothelioma in adults and young adults, as compared to mesothelioma in the elderly. It also delves into the causes of the disease, along with its continued spread. Mesothelioma is a disease largely present within the elderly generation, most of whom were exposed to asbestos and other carcinogenic factors in early childhood. Though they may have only been exposed to these factors in childhood, and not throughout the rest of their lives, the cancer can lay dormant and still develop at a later time. Depending on whether you are diagnosed with mesothelioma before or after the age of 40 can determine a lot. For example, those that are <40 have shown to have mostly even odds when it comes to sex distribution within affected groups, and even the type of mesothelioma. The elderly group (>40), however, had a male-dominant number of cases, and were all-in-all more likely to have pleural mesothelioma, though it is not clear why. The worldwide struggle of continued use of asbestos in underdeveloped countries is also a pressing issue, along with the lack of awareness that other fibrous materials similar and in addition to asbestos could be guilty.

Introduction

Mesothelioma is a very rare form of untreatable cancer that occurs in the thin layer of tissue, referred to as the mesothelium, covering the majority of the human body's internal organs. There are two main categories of mesothelioma. The more common variant, pleural mesothelioma, or mesothelioma in tissue surrounding the lungs, often includes symptoms of chest pain, painful coughing, shortness of breath, and lumps of tissue under the skin around the chest. The second form of mesothelioma goes by the name of peritoneal mesothelioma, which involves affected tissue in the abdomen, and around the heart and testicles (Mayo Clinic Staff, n.d.). Symptoms of this type mostly include abdominal pain and swelling, and nausea. About 3,000 new cases are diagnosed per year (The American Cancer Society medical and editorial content team, n.d.). Diagnoses peaked from the 1970s to the 1990s, which is likely linked to the

popular use of asbestos at the time, which is thought by many to play a large role in the development of mesothelioma. Factors *in addition* with exposure to asbestos, however, may more commonly play a role in the development of mesothelioma, because exposure to asbestos alone only causes a *fraction* of mesothelioma cases. For example, it is thought that Simian Virus 40 (Robinson et al., 2005) could play an attributing role (Carbone et al., 2002). Asbestos, however, is an inexpensive fire-retardant material and insulator, popularly used in home construction throughout the 1940s to 1970s. This explains why mesothelioma is quite common within the older generations.

Roots in Childhood

Mesothelioma is latent, and exposure to asbestos and other carcinogenic factors that lead to development of mesothelioma is most likely to happen during childhood, meaning your odds of developing mesothelioma at a later point are most prevalent within this period. A study given the title "Malignant mesothelioma in young adults" (Kane et al., 1990) was conducted circa-1990. It took a small sample size of ten people, all diagnosed with malignant – spreading – mesothelioma at or before 40 years of age. Each of the ten cases were reviewed by the researcher(s). Seven out of the ten patients had been exposed to asbestos, five of which being *household* exposures. This means the asbestos was likely used in the construction of their childhood homes. On average, each of their exposures to asbestos began at *ten years* of age, and the exposure lasted for about 120 months, or *ten years*. Here comes the most fascinating portion of the study: about 19 years – nearly *two decades* – had passed between each patient's exposure to the asbestos, and their date of diagnosis. This connects back to the aforementioned delay that is involved with mesothelioma. Within those 19 years, people build completely new lives. A lot happens between adolescence and adulthood. To be diagnosed with cancer caused by factors (such as material built into your house) that you, especially as a child, had no control over, is tragic. People at this time were generally unaware of and therefore uneducated on the dangers of asbestos exposure. In addition, the study found that symptoms were generally only noticed not six months prior to receiving their diagnosis, at five and a half months; many patients' lives were turned upside-down in the span of less than half a year! The study concluded that exposure to asbestos *outside* of the workforce was a highly likely cause of the patients' development of malignant mesothelioma, which is fearsome because it means that exposure was likely unagreed upon and unknowing. The researcher(s) also considered genetic predisposition, and what that could possibly mean, but no further information was dispersed or concluded.

Malignant Mesothelioma Within Young versus Elderly

Many factors are seemingly pre-determined, depending on whether you are diagnosed with mesothelioma before or after 40 years of age. Some of these differing characteristics become clearer in a different study

under the name of "Distinctive clinical characteristics of malignant mesothelioma in young patients" (Thomas et al., 2015) and conducted more recently, in 2015, in which aimed to understand, compare, and contrast the differences between the characteristics and outcomes of mesothelioma in the youth, and in the elderly. They first found that two percent (or 207/12,345 observed) of patients affected with mesothelioma are "young" (less than 40 years of age), and female versus male cases were split almost exactly 50/50, which largely differed from the elderly group, in which men dominated the percentage of cases, at 78/22. Another intriguing characteristic they discovered is the frequency of pleural and peritoneal mesothelioma between the two sectors. Within the youth, cases were, again, split more evenly around 47/48, respectively. This is completely polar to the elderly group, that was 90 percent pleural mesothelioma. The article takes the stance that characteristics of mesothelioma between the young and the elderly are distinct from one another. The researcher(s) conducting the study also came to the conclusion that the younger patients had a significantly increased likelihood of survival than those who were older.

The Real Perpetrator

Our biggest threat to the spread of asbestos is capitalistic greed and lack of sufficient education globally. In an article titled "Asbestos and mesothelioma: Worldwide trends," (Kazan-Allen, Laurie, 2005) it is claimed that – in response to many governments in *developed* countries (eg. Australia, Canada, Germany, USA, etc.) banning or heavily curtailing the use of asbestos in construction – asbestos producers have begun to aggressively campaign asbestos in currently developing countries, such as Algeria, Brazil, and China. This is wrong for many reasons. First and foremost, asbestos producers are taking advantage of the detriment currently affecting these developing nations. Instead of allowing themselves to learn from the errors of selling in the United States, for example, they put more humans' lives at stake for the purpose of selfish gain. These countries now have very little control over asbestos exposure. Via the article, it is estimated that the number of work-related asbestos deaths globally adds up to around 100,000 annually, but this number could be an underestimation by as much as *42 percent*. In a differing article titled "Asbestos: Think Again" *(Asbestos: Think Again*, 2004) by The Environmental Working Group, it's shared that diseases related to asbestos claim the life of one American man over the age of 50, out of every 125. That is almost one percent, which is far more than it sounds when you remember that that is a human life. In the same article, it is also claimed that around thirty Americans a *day* die from asbestos-caused diseases.

Asbestos isn't the Only Culprit

When it comes to causes of mesothelioma, there may be more than meets the eye. The following information has been taken from an article published in the Archives of Pathology and Laboratory Medicine, titled "Malignant Mesothelioma and Its Non-Asbestos Causes." (Attanoos et al., 2018) Though – in Europe and North America – the vast majority of mesothelioma (both pleural and peritoneal) in men

is attributed to exposure to asbestos, not all of it is (Peterson, J.T., Jr., 1984). Erionite, fluoro-edenite, and possibly even balangeroite, are all fibrous minerals, such as asbestos. They are among the causes of mesothelioma that do not include asbestos. The largest evidence for erionite being carcinogenic cited by the article is an outbreak of mesothelioma reported in two small Turkish villages. It was believed that the cause of the outbreak was due to exposure to the erionite fibers coating the exterior of the houses in the village, *but* there was also asbestos identified in the region. More than 50 percent of mesothelioma in these villages are, however, caused by erionite. More evidence was gathered from two cases of Mexican immigrants who both had elevated levels of erionite fibers in their lung tissues, following analyses. This is not a coincidence, however, because it was discovered that both of their lives in Mexico had exposed them to this fiber growing up. As far as fluoro-edenite and balangeroite goes, fluoro-edenite has been classified by The International Agency for Research on Cancer as carcinogenic, and balangeroite is quite controversial when it comes to the role it is thought of playing in causing mesothelioma.

Conclusion

Background, upbringing, and age all play large roles in determining whether one will develop mesothelioma, and even so much so as the characteristics of that development. However, research regarding mesothelioma is limited, as a whole. It is a widely unexplored cancer, likely and largely due in part to its incurability and nicheness. Unfortunately, because of the combination of latency associated with the disease and the continued use of asbestos worldwide, there is not a lot that may be done to stop current developments of mesothelioma, but to continue spreading awareness and educating yourself and others, as to hopefully prevent as much exposure to mesothelioma-causing factors as possible, before it is too late.

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Establishing the Threat of a Mesothelioma

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Keywords: Mesothelioma, Mesothelium, Asbestos, Malignant, Pleura

Abstract:

In my literature review research, the justification for why pleural mesothelioma should be the focus of further investigation discussion. The leading cause of this disease, Asbestos, was at one point in history in almost every household at one point or another due to its constant usage during the industrial revolution. Anyone exposed to Asbestos contracted some form of mesothelioma, most commonly pleural mesothelioma. The symptoms of mesothelioma are often overlooked due to being common symptoms of other diseases and the patients end up being treated for something they don't have while the cancer advances further. This cancer has been known to take decades to diagnose and by the time it is diagnosed the further stage the cancer is in the less chances for the patient to be successfully treated. The severity of this form of lung cancer often only continues to show as it grows and evolves that a cure for some people isn't possible.

Introduction:

Studies of the Pleural Mesothelium

Cancer of the Mesothelioma (M) is an aggressive form of terminally ill lung cancer with a ten percent five-year survival rate.[1] The layer of cells that covers and protects organs and tissues in the body is known as the Mesothelium.[2] This disease most commonly occurs in the Mesothelium and develops in the pleura of the thoracic cavity, the peritoneum, pericardium, or tinea vaginalis testis areas.[3] In other words, it protects the areas surrounding the body's lungs (pleura), the abdomen (peritoneum), the heart (pericardium), and the testes (tunica vaginalis).[4] Excess asbestos exposure is the leading risk and cause for any Malignant M.[5] Asbestos is a mineral known for its flame-resistant flexible fibers.[6] It is typically found in commercial products such as insulation, fireproofing materials, automotive breaks, and wallboard materials.[7] Asbestos fibers when broken up, during processes that involve handling asbestos, can lead to dust being created.[8] If this dust is inhaled or swallowed, it can make its way into the body's Mesothelium.[9] This can lead to irritation that can later develop into a Malignant Mesothelioma.[10] Depending on the area of the Mesothelium that has been affected by the asbestos fibers varies with the type of M disease.[11] The most common form of M disease in the body is Malignant Pleural Mesothelioma

(MPM).[12] MPM affects the tissue surrounding the lungs, the pleura. MPM occurs when inhaled asbestos fibers become trapped in the lower third of the lung causing irritation and initiating an inflammatory response.[13] A Mesothelioma can take a range of 20-60 years to develop after an asbestos exposure.[14] Despite that information studies have found that the higher the level of asbestos exposure can shorten the latency period.[15] Unfortunately there are over 75 occupations where workers are exposed to high-level concentrations of asbestos daily.[16] As well as secondhand exposure incidents when an asbestos worker can transfer the toxic fibers into their home and spread it to other household members.[17] Studies show there have been nearly 200,000 cases and 3,300 new cases annually of lung cancer that could be avoided with better recognition of asbestos exposure in the workplace.[18] While many patients have been able to extend the 4-18 month period of survival after diagnosis there is no cure for a Malignant Mesothelioma.[19] With that said, studies have shown that many patients have had success in reducing their symptoms with alternative treatments and have been able to survive more years than expected.[20] In this paper, I will be researching the leading cause of Malignant Pleural Mesothelioma and the so far discovered and possible treatment options for this deadly disease.

Asbestos Exposure Origins

Asbestos (Asb) was a high quality construction material due to its flexible heat, electric, corrosion resistant fibers.[21] Asb being the effective insulator it is, it was commonly combined with cloth, paper, cement, and plastic materials to strengthen them.[22] Not only did this mineral have the ideal properties to many industries such as the automobile, construction, manufacturing, power, and chemical industries but Asb also naturally occurred on every continent in the world.[23] The Asbestos industry surprisingly did not flourish until the late 1800s when the Industrial Revolution brought to light the practical and commercial uses of Asb.[24] That's when U.S companies began producing all kinds of products using Asb by the thousand up until the 1980s.[25] The common uses of Asb were in auto parts, building materials, cement, electrical parts, and insulation.[26] While Asb blew up in the manufacturing and mining industries due to the steam engines, turbines, boilers, ovens, and electrical generators it powered in the Industrial Revolution the negative effects on the health of those who worked with it was made known widespread too.[27] An Austrian doctor in 1897 was able to pinpoint the cause of one of his patients pulmonary troubles to the excessive inhalation of Asb.[28] The first documented death of an Asb worker due to pulmonary failure was recorded in 1906.[29] The autopsy of the 33 year old victim revealed large amounts of asbestos fibers in his lungs.[30] Despite the constant health warnings Asb production continued to increase and the world production exceeded 109,000 metric tons.[31] Archeologists have actually uncovered Asb fibers in debris that date back around 750,000 years ago.[32] It is believed that Asb fibers were most commonly used for wicks in lamps and candles, clay pottery, tablecloths, napkins, and to wrap the embalmed bodies of

Egyptian pharaohs to protect against deterioration.[33] Among this discovery a Greek geographer Strabo learned that the Greek and Roman slaves that wove Asb into cloth presented with “sickness of the lungs”.[34] With that said, by the late 1970s Asb production went into a great decline with the public understanding the connection between asbestos exposure and lung diseases.[35] A ban on the use of this mineral has been banned in 55 countries worldwide due to its fatal dangers apart from China, Russia, India, Canada, and the United States.[36] The dangerous effect Asb has on the human body through the years has been overlooked due to its practicality and room for profit.

What to Look for and Why

Malignant Pleural Mesothelioma (MPM) affects the tissue surrounding the lungs, the pleura.[37] The most common types of symptoms for any general Meso are fever, excessive sweating, fatigue, weight loss, blood clots, and loss of appetite.[38] My sources show that symptoms of a MPM can be consistent with chest pain, shortness of breath, pain when coughing, abnormal lumps of tissue near the chest, and weight loss.[39] Managing these symptoms early on have led to improved life expectancy in patients.[40] While everyone's body might not respond the same, some of the most recorded common MPM symptoms are 73.5% shortness of breath, 67% have fluid around the lungs, 64% fatigue, and 54% acquire pain in the lower back or rib area.[41] Some of the more less common symptoms patients are recorded getting are 49% weight loss, 46% dry cough, 38% chest pain, 31% painful breathing, 19% difficulty swallowing, 4% coughing up blood.[42] Many early on symptoms of Meso have been mistaken for common ailments which is why most people suffer the symptoms for months before being diagnosed.[43] Other patients have shown rare signs of general mesotheliomas with anemia, blood clots, night sweats, and painful swelling or lumps.[44] MPM patients have a higher risk of developing blood clots, signs include redness and pain or swelling on one side.[45] As Well as having lumps under the skin with pain and swelling along the sides of the chest.[46] Symptoms of Meso will increase while the cancer goes from the early stages to the late stages.[47] In early stages of Meso patients have been recorded with 53% having fatigue or weakness, 53% fluid around the lungs, 38% weight loss, 35% shortness of breath, 35% pain in lower back or rib area, 26.5% abdominal/chest pain, 23.5% coughing or wheezing, 18% painful or difficulty breathing, 6% bowel obstruction/constipation, and 6% night sweats.[48] Early stage symptoms of the cancer refer to stages 1 and 2 since the cancer is localized and has not spread to other distant parts of the body yet.[49] In later stages of Meso with more cancer progression patients have been recorded with 69% fatigue or weakness, 64% shortness of breath, 62% abdominal/chest pain, 60% weight loss, 51% fluid around the lungs, 50% pain in the lower back or rib area, 48% coughing or wheezing, 38% painful or difficulty breathing, 21% difficulty swallowing, and 9% loss of appetite.[50] Symptoms like these are often shown in stages 3 and 4 of the cancer progression due to the tumors going deeper into the tissues.[51] At this time is when patient

symptoms become more recognizable and patients experience less control due to undergoing pain, weakness or difficulty breathing.[52]

Diagnosis and Development

Diagnosing MPM often takes years due to the symptoms and signs that in the early stages of the disease can point to other common illnesses.[53] It is true that signs and symptoms can indicate Meso but to accurately diagnose MPM involves a series of a variety of tests to confirm. Physical exams are usually the first step in testing for Meso followed by blood tests, Imaging tests, and a biopsy.[54] A biopsy is a procedure used to remove a small portion of tissue for laboratory examination.[55] There are several options included when performing a biopsy such as inserting a needle through the skin where the doctor might remove fluid or tissue using a thin needle on the chest or abdomen.[56] The other option consists of collecting a sample of tissue during surgery where the surgeon makes a small incision and inserts a tube with a camera to view the chest or abdomen and collects the tissue sample.[57] Then the collected tissue sample is analyzed under a microscope in order to see whether the abnormal tissue is a Meso and what cells are involved.[58] Once MPM or another form of Meso is confirmed the additional tests begin to understand the extent of the cancer spreading throughout the body.[59] The most common tests performed are Computerized tomography (CT) scans of the chest and abdomen, Magnetic resonance imaging (MRI), and Positron emission tomography (PET).[60] The information given from these tests allow doctors to assign the cancer a stage.[61] The staging system most commonly used for MPM is called the International Mesothelioma Interest Group (IMIG) system.[62] This system describes the size and position of the tumor if the cells have spread, and whether they have spread to other parts of the body.[63] The staging system is numbered from 1 to 4, stage 1 being the earliest stage and stage 4 being the most advanced stage.[64] As stage 1 advances the Meso cells have lined the pleura around the lung on one side of the chest, the Meso cells are in the outer layer of the pleura(parietal pleura) on one side of the chest, and the Meso cells are in the inner layer of the pleura(visceral pleura) without spreading to the lung tissue or diaphragm.[65] In stage 2 Meso has spread to both layers of the pleura on one side of the body and could possibly have spread into the diaphragm muscle or into the lung tissue.[66] Stage 3 of the system consists of the Meso spreading to the chest wall or covering the heart while possibly spreading to the lymph nodes on the same side of the chest.[67] The last stage, stage 4, means that the cancer has spread to different parts of the chest wall or has grown through the diaphragm into the abdomen, the pleura on the other side, the chest organs, the inner layer of the pericardium, and the lymph nodes on the other side of the chest or above the collarbone.[68] At this final stage the mesothelioma cannot be removed by surgery making it extremely difficult to treat.[69]

Confronting Treatments and Therapies

Mesotheliomas (Meso) tend to be difficult to treat nevertheless when having a Meso at an advanced stage.[70] The main goal of nearly all treatments for Meso are to control the cancer and treat the symptoms.[71] Treatment options for Pleural Meso are often chemotherapy, radiotherapy, surgery, or a combination.[72] Chemotherapy (chemo) is the use of anti cancer drugs to destroy cancer cells in the body.[73] The anti cancer drugs can be given through a thin short tube called a cannula that goes into your vein for each round of treatment.[74] If necessary the drug can also be administered through a long plastic tube that is positioned into a large vein in the chest such as a central line, a peripherally inserted central catheter (PICC) line, or a portacath.[75] Treatment using chemo is often used in cycles meaning the drug is taken for a set amount of time then the patient is given a short break and the process begins again.[76] The most common chemo drugs used for treating MPM are pemetrexed, cisplatin, carboplatin, raltitrexed, vinorelbine, and gemcitabine.[77] Side effects with chemo commonly include feeling sick, loss of appetite, weight loss, tiredness, increased infection risk, bleeding, bruising, diarrhea or constipation, and hair loss.[78] Radiotherapy (RT) is the use of high energy x-rays to destroy cancer cells in the body.[79] RT could be used as a treatment option for MPM in two situations such as to be used after surgery to kill off remaining cancer cells or to reduce symptoms in patients if surgery isn't a choice.[80] The most common side effects with this treatment option are reddening of the skin, hair loss, feeling tired and weak.[81] Surgery, the least common treatment for Meso.[82] For most doctors to approve a patient for surgery the patient must ideally be healthy in order for them to recover without too many issues or complications.[83] Surgery is often used in an attempt to completely remove the Meso and at times part of the pleura (partial pleurectomy) or the whole part of the pleura (pleurectomy).[84] The main goal for performing surgery as a treatment for Meso is to remove the cancer or if not to remove as much as possible to relieve symptoms and try to give the patient more time.[85] If none of the treatments take any effect, research and clinical trials for Meso are around the world looking for treatments and ways to reduce the side effects.[86]

Conclusion:

If not treated on time asbestos exposure could be fatal. It is severely important for people to understand the risks of asbestos exposure so that if they feel they might have been first or secondhand exposed to this mineral they can get their symptoms treated. Malignant Pleural Mesothelioma even though it is now less common does not mean that those who somehow get exposed to it now shouldn't be given a fair chance to survive. With the often long latency period of 20-60 years before this cancer begins to show extensive symptoms the more common warning symptoms of the disease are easy for doctors to miss without knowing about a recent asbestos exposure. My research findings of the average 4-18 month period of survival with Pleural Meso after being diagnosed shows how dangerous this disease with no cure is. The further the illness spreads before the symptoms begin to be treated and advance in stages the lower the

survival rate. In conclusion, through the advanced technologies and scans we have access to today, we must continue to research to find ways to increase this lung cancer's survival rate and come up with a cure.

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Mitigating Asbestos Exposure: Exploring Alternatives, Regulations, and Health Implications in New York City

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Keywords: Asbestos, Fiberglass insulation, Cellulose fiber insulation, New York City

Abstract:

New York City has had an extensive history of asbestos use, specifically in its construction industry, which originated from the early 20th century. However, asbestos is a classified carcinogen that poses severe health risks, including mesothelioma. This literary review will examine the historical prevalence of asbestos-containing materials (ACMs) in New York City, explore the regulations surrounding asbestos, and evaluate alternatives such as fiberglass and cellulose insulation. While both fiberglass and cellulose have advantages and disadvantages, they present much healthier alternatives to asbestos. Understanding the extent of asbestos presence and exploring alternative materials can help develop effective measures for mitigating the spread of mesothelioma and other diseases upon exposure- thus ensuring the well-being of New York City residents and other individuals.

Introduction:

New York City, a city well renowned for its historical buildings and landmarks has also been the epicenter for asbestos use. In the late 19th century, New York City experienced a significant surge in its population, thus igniting a construction boom that intended to accommodate the growing population. Architects and engineers were tasked with constructing structures that could endure the test of time, making asbestos a more desirable solution for reinforcing buildings. Asbestos, a naturally occurring silicate material (minerals which contain silicon and oxygen in SiO44- units, arranged in specific patterns) is best known for its durability and insulation. Now, asbestos is commonly used in fireproofing, flooring, roofing, and other forms of construction. These perceived benefits in construction along with the Industrial Revolution have provided an incentive for use in various industries or construction materials-making the material

more widespread in the state of New York. However, asbestos- classified as “Class 1 Carcinogenic”- has consistently been shown to have severe health risks and can ultimately lead to death after long-term exposure (“Asbestos and Cancer Risk | American Cancer Society”). After asbestos fibers are released, they are often inhaled by those exposed and can get logged into the body-causing cold-like symptoms which are often ignored. In a case study conducted by researchers, it reviewed the correlation between Asbestos exposure and the cause of death of 188 subjects in Broni, Italy, statistical analysis was performed after the subjects' death. Using the Kaplan-Meier estimator, the confidence interval of 95% helped to identify if there was a significant correlation. The results demonstrated there was a significant correlation between occupational exposure to asbestos and the development of lung cancer and asbestosis (Visonà et al.). Consequently, the rapid rise in asbestos-related diseases later pressured more government intervention and regulation. With the rich history of construction and industrialization in New York City comes the high presence of asbestos in buildings-which poses risks to the health of workers and residents of the city. This literary review aims to assess the history and uses of asbestos-containing materials (ACMs) across New York City and evaluate alternatives to asbestos including fiberglass and cellulose. By understanding the extent of asbestos presence and the potential pathways of exposure, effective measures for the mitigation of the disease by using alternatives can be developed.

The Historical Presence of Asbestos in New York City from Homes to Workplaces:

Throughout the history of New York City, asbestos (naturally occurring material) has played a significant role in various industries and construction projects. Asbestos became a desirable choice for construction from the late 19th century until it was banned in the late 20th century. This growth of asbestos in New York City can be credited to Henry Ward John's company (Johns-Manville Corporation), which started manufacturing asbestos to support construction projects in the city starting in the 1850s (Mauney). Commencing in the late 19th century, asbestos became useful for its exceptional insulative properties. These properties are mainly attributed to its ability to slow the transfer of heat, effectively reducing heating and cooling costs. Specifically, in residential homes and apartments, this insulation comes in various types that may potentially contain asbestos. The four most prominent types of insulation in homes are blanket insulation, block insulation, loose-fill insulation, and spray-on insulation. Blanket insulation assumes the shape of large rolls, similar to a cotton blanket, and is often used in attics and as blankets. Block insulation transforms into rigid panels and is typically made of foam; it can be found throughout the entire home. Loose-fill insulation is blown through machines and is quickly identified by its fluffy texture. Spray-on insulation is applied as a liquid and later solidifies to fill gaps, commonly found in walls and ceilings (Jones-Stohosky). Another form of insulation, zonolite insulation, although less frequently used, poses a higher risk of asbestos exposure because of its vermiculite presence. Vermiculite, composed

of heat-treated mica flakes, also exhibits favorable insulative properties. Similarly, both asbestos and mica flakes typically form under high pressures and temperatures, making asbestos more prevalent within this type of insulation (Jones-Stohosky). In various sectors, workplaces in New York City have been linked to a significant presence of asbestos. These industries include shipyards and power plants, with notable examples being Caddell Dry Dock & Repair Company and Todd's Shipyards. Caddell Dry Dock & Repair Company, which is still active in the state of New York, was established for commercial shipping and repair. Due to the widespread use of asbestos for insulation in ships, shipbuilders were consistently exposed to asbestos, and many employees developed mesothelioma or asbestosis. Similarly, Todd's Shipyard is infamous for its involvement in asbestos-related incidents. Several power plant stations in New York that have been linked to asbestos exposure include Arthur Kill Generating Station, Astoria Gas Generating Station on Staten Island, and Ravenswood Generating Station in Queens (Molinari).

Addressing Asbestos in New York City-Regulations, Risks, and Abatement Measures: In New York City around the 20th century, asbestos reached its peak, and it was not until the late 20th century and 2000s that regulations were implemented to prevent asbestos exposure and usage. In 1992, The New York City Department of Environmental Protection (DEP) conducted a study that presented associated risks with asbestos exposure due to the presence of asbestos in ACMS in buildings. The study evaluated 886 buildings across 16 different categories in New York City. The results revealed that almost 70% of the buildings contained ACMs at a staggering 68%. However, the estimated total amount of ACM in the city was 323 million square feet, with a significant portion being linked to thermal insulation. Sequentially, a management bill was introduced to prevent further spread of asbestos (Lundy and Barer). Additionally, according to New York State statistics, about 2354 residents died from mesothelioma from 1999-2015 with about 23 asbestos deposits and mines known to exist in New York. The popularity of asbestos during this time was also met with backlash, leading to more government regulation in New York City. New York City building owners are now legally required to have a DEP-certified asbestos investigator to investigate if there is sensitive ACM activity within the building. In 2009, procedures were (are) implemented to address the spread of asbestos. Before asbestos abatement, a certified asbestos investigator from the (DEP) identifies Asbestos Containing Material (ACM) and determines the project's extent. Based on the report, the project is either classified as "Not an Asbestos Project A" or an "Asbestos Project B." (A Guide to the New York City Asbestos Regulations). Following the investigation, ACP5 or ACP7 is utilized. The ACP5 form certifies that no ACMs will be disturbed or present. Once the DOB receives the ACP5 form, it can proceed. However, if disturbed ACM exceeds 10 square feet or 25 linear feet, it is categorized as an "Asbestos Project," stopping the proceeding of the project (5). After the process, abatement of ACMs continues in the following forms: physical removal and

disposal of asbestos, encapsulation to prevent fiber release by coating it, or construction over asbestos to prevent potential fiber release. These procedures have ultimately worked to abate the effects and exposure of asbestos to residents of the city.

Fiberglass:

Fiberglass's Strength, Versatility, and Health Considerations Fiberglass, a man-made composite material (made of two or more materials) consisting of glass fiber reinforcement and polyester resin, was first trademarked as "Fiberglass' " in 1938. The composition of fiberglass involves using thermosetting polyester resin to bind fibers together, while the glass fibers simultaneously provide strength and flexibility (Connolly). Fiberglass is categorized into different categories of glasses, such as E class, which is known for its insulating properties commonly used in households, C glass, used for its chemical resistance, and S glass, a structural glass capable of withstanding high temperatures. Most fiberglass compositions are silica-based, with each type of glass containing over 50% SiO_2 (Chawla). Fiberglass has gained popularity as an alternative to asbestos, starting in the 1950s, and one of the reasons for its growing use is its desirable weight-to-strength ratio, which improves the quality and performance of the material while also maintaining a lower weight (Patel). Additionally, fiberglass serves as a great electric insulator and is incombustible with minimal temperature sensitivity. Often, fiberglass is used for insulation, mesh fabrics in homes, flooring, cladding, tape, and most notably, in mattresses-acting as a flame retardant, all while being more affordable. There are perceived benefits of fiberglass, when exposed to fiberglass there are negative health effects. Fiberglass is made of refined glass shards allowing it to be airborne. Short-term exposure to fiberglass can cause eye and skin irritation, and soreness in the throat and nose. If inhaled- it can exacerbate health conditions like bronchitis, asthma, or pulmonary fibrosis (Fiberglass). However, there is still controversy about whether fiberglass can be considered a carcinogen because there has not been an official link between fiberglass inhalation and cancer such as mesothelioma.

Examining the Health Effects of Fiberglass Using a Study in Comparison to Asbestos In a historical cohort study published in the "Iranian Red Crescent Medical Journal," the researchers aimed to investigate the potential health effects of fiberglass exposure, particularly in comparison to asbestos. The study focused on 49 workers who were regularly exposed to fiberglass within a local fiberglass industry, while also including 42 unexposed employees as a control group, with both groups not having prior exposure to fiberglass. To assess the respiratory health of the participants, the researchers utilized a standardized respiratory questionnaire to gather relevant data. In addition, the subjects underwent chest X-rays and received thorough examinations by physicians to identify any possible respiratory

abnormalities. Just before the start of their work shifts, pulmonary function tests were conducted to evaluate their respiratory capabilities. To determine the extent of fiberglass dust exposure experienced by the participants, the researchers measured dust concentrations at different dusty work sites using established methods. Through a chi-square evaluation, the experiment did not find a significant difference or statistical significance in the prevalence of respiratory symptoms and abnormalities between the exposed and unexposed subjects (Neghab and Alipour 146). These findings contribute to the understanding that, at present, the potential adverse health effects associated with fiberglass exposure are less severe compared to those of asbestos.

Preventive Measures

While fiberglass may not have as severe health effects, it is still crucial to be aware of potential measures to prevent exposure. Firstly, when dealing with a fiberglass mattress, ensure that there is a mattress cover, keep the mattress sealed, and use a Hepa-filtered vacuum (an air filter that can remove any airborne particles with a size of 0.3 microns μm). It is also important to avoid contacting insulation material in homes. When working with fiberglass, wear loose clothing with a protective N95 mask and goggles. Most preferably, avoid directly touching the fiberglass (Frothingham). In terms of safety, when asbestos is airborne, it poses significant health risks as it is a carcinogen, which can potentially lead to the development of Mesothelioma (A type of cancer that affects the lining of the lungs or abdomen and has severe effects on the heart, lungs, and abdomen). On the other hand, fiberglass is not classified as a carcinogen and poses fewer long-term health risks. However, both materials require adequate handling to prevent exposure. While there may be some risks associated with fiberglass exposure, taking precautionary measures has proven that fiberglass is a safer alternative to asbestos, and is often the most cost-effective option for many individuals.

Cellulose:

Structural Benefits

In terms of anatomical structure, cellulose is a carbohydrate and polysaccharide that forms the foundation of the cell walls in plants. Cellulose forms a complex network within the cell walls, which provides structural support and rigidity to plant cells-playing a vital role in maintaining the shape and foundation of plant tissue. The arrangement of cellulose microfibrils in the cell wall contributes to the overall strength and durability of plants, and its beta-1,4-glycosidic bond gives it its distinct properties (The Editors of Encyclopaedia Britannica). Cellulose, however, has integral properties making it desirable as an alternative to asbestos or fiberglass insulation. Cellulose fiber insulation (CFI) requires using paper-based

materials, making the insulation viable and non-carcinogenic-unlike asbestos (and possibly fiberglass). Its thermal effectiveness scores better than most materials such as fiberglass- meaning CFI is an environmentally sustainable option (Hurtado et al.). It outperforms other materials like fiberglass in terms of thermal effectiveness, as indicated by its higher R-value. This characteristic allows CFI to efficiently reduce heat transfer, maintaining a comfortable temperature and resulting in energy savings and decreased heating and cooling expenses. Additionally, It provides a sustainable option as "The Cellulose Insulation Manufacturers Association" (CIMA) emphasizes that CFI yields one of the highest levels of recycled content among insulation materials, typically reaching around 85%. This high recycled (around 300k tons of recycled newspaper) content contributes to reduced greenhouse gas emissions, and carbon footprint, as well as remaining soundproof and inhospitable to pests.

Potential disadvantages

Cellulose insulation can be more expensive compared to fiberglass insulation with the price ranging from $0.70 to $0.80 per square foot for 6 inches of insulation. Fiberglass insulation is less expensive, costing around $0.30 to $0.40 a square foot for 6 inches of insulation. CFI may also reap potential risks, raising some concerns due to the ink residues and potential toxicity of fire retardants like boric acid, sodium borate, and ammonium sulfate. However, many colored toxic inks have been banned in newspapers for over a decade- relieving concerns about their toxicity. A study by J. M. G. Davis published in the British Journal of Industrial Medicine in February 1993 further examines the risks associated with the retardants in CFI, "ingesting as little as 1/8 ounce of these chemicals can be fatal to infants." Later, Davis explains that cellulose fiber manufacturing or production does not pose a threat because most CFI does not liberate respirable fibers in large quantities for inhalation (BuildingGreen). It is still crucial to properly handle CFI. Such as wearing respiratory protection during installation, and maintaining an airtight barrier between the insulation and living areas.

Study of Thermal Performance and Efficiency of Cellulose Fiber Insulation

In a study published in the "Indian Journal of Engineering & Materials Sciences," researchers reviewed the properties of CFI by comparing an insulated model to an uninsulated model through the use of a simulation and experiment. The researchers found that in terms of thermal properties, the uninsulated test model began losing heat starting from 12 hours and continuing to 22 hours in the evening. On the other hand, the heat loss from the test model increased from 12 hours to 18 hours and decreased from 18 hours to 22 hours due to an initial rise in temperature difference following a decline. The model also determined that the insulated model displayed a lower thermal temperature because of its successful thermal resistance and heat flow. The disparity in the indoor temperature between the two models was a maximum

of seven degrees Celsius. Additionally, the variation between the experimental and simulated results yielded less than 5%, validating the model's accuracy for further use and predictions. The findings also presented a reduction of around 150 kg/m2 of floor area in annual carbon dioxide emission (with an insulated roof, a 27% decrease in carbon dioxide emission was reported using optimum insulation thickness). Figure 10 illustrates the energy savings, cost savings, and carbon dioxide reduction from implementing cellulose fiber insulation and the white exterior color in the test model. The energy savings can be accredited to the reduced net heat flow into the indoor space of the test model as compared to the uninsulated test model-reducing the cooling load. The monthly energy amounted to 24 kWh (energy an electrical device or load used in kilowatts per hour), and the summer season's energy (from mid-April to mid-October) was 144 kWh (Ravinder et al.). Ultimately, cellulose insulation presents as a much healthier alternative to fiberglass and asbestos because there are no confirmed dangers of fine fibers entering your respiratory system or causing long-term damage if inhaled. As compared to fiberglass and asbestos, CFI yields very low levels of VOC (volatile organic compounds). Overall, while CFI is more expensive, it presents as the most healthy option among the two.

Discussion:

First, the study conducted in Broni, Italy, establishes the strong correlation between exposure to asbestos and the development of lung cancer. The historical presence of asbestos in New York City, particularly in construction and workplaces like shipyards or power plants, underscores the exposure risks that residents and/or workers faced. This awareness of the health risks of exposure subsequently came with the introduction of regulations by the (DEP) to prevent the spread of asbestos-reflecting the importance of taking proactive measures such as using alternative insulation materials like fiberglass and cellulose. The research provides insights into the alternative’s strengths, weaknesses, and health considerations. Fiberglass has been a widely popular substitute for asbestos since the 1950s, offering advantages from its strength and incombustibility. However, there are some health considerations from short-term exposure such as irritation and respiratory issues. Another alternative, cellulose, is a more expensive option and presents as a healthier alternative to both materials. It yields advantages like versatility, sustainability, and thermal conductivity. Unlike fiberglass, cellulose poses a potential minimal health risk from short-term exposure. There is also no conclusive evidence linking cellulose or fiberglass to mesothelioma (or other severe health conditions). It is still important to practice the necessary precautions when working with either material. In terms of results, the analysis demonstrates the need for more awareness, research, and promotion of using safer alternatives. However, it is also important to acknowledge the limitations of my literary review. The analysis is based in New York City, and the findings may not be directly applicable to other regions. Hopefully, there will be further studies that explore the possible carcinogenic link between

fiberglass and mesothelioma, as well as future investments in research on other alternatives to asbestos that are cost-effective, sustainable, and pose minimal health risks.

Conclusion:

While the historical presence of asbestos in New York City's construction lingers, government regulations have been effectively implemented to combat the spread of asbestos-related diseases in the city and mitigate its effects. These measures have played a crucial role in limiting asbestos exposure and ensuring the safety of residents. Following this, fiberglass and cellulose have been presented as alternatives to asbestos. Both alternatives share insulative properties-making them desirable for construction use. While short-term exposure to fiberglass can result in irritation, it has yet to be confirmed as a carcinogen or linked to causing mesothelioma. Cellulose, on the other hand, is naturally sustainable, and provides effective insulation, reducing heating and cooling costs. Both materials require proper handling and safety measures. New studies should further examine the long-term health effects of fiberglass insulation compared to asbestos and explore other viable alternatives.

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Literary Review

Are These Emerging Mesothelioma Treatments Worth the Hype?

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Keywords: Mesothelioma, tumors, DNA, cells, asbestos, immune system

Abstract

This article investigates current and emerging treatments for malignant mesothelioma. Malignant mesothelioma is an aggressive type of cancer that is rare, but continues to grow in frequency. Mesothelioma is often developed in individuals with high asbestos exposure which is a mineral that can be found in flooring, paint, and other common building materials. The complex cancer has thousands of scientists searching for superior treatments. This study explores those new, cutting-edge treatments and compares and contrasts them to current treatments.

Introduction

Malignant mesothelioma is a rare and aggressive type of cancer that develops in the mesothelium tissue. The mesothelium is the protective layer of tissue that lines the lungs, chest wall, and abdomen. Mesothelioma is a fairly rare type of cancer with approximately 3,000 people being diagnosed with it each year in the United States. There are four different types of mesothelioma: pleural, peritoneal, pericardial, and testicular. Mesothelioma is a rare and hostile form of cancer that frequently results from asbestos exposure. Asbestos accounts for close to 80% of all mesothelioma cases. Asbestos is a fibrous mineral that is found in the environment. Due to its physical and chemical properties it is resistant to heat and degradation. Because of this, asbestos is used in a wide range of manufactured goods. Asbestos is made up of tiny fibers that are often breathed in. They can then make their way to the mesothelium, irritating the tissue and causing gene mutations. While there is no cure for mesothelioma, research in more effective treatments is ongoing. The goal of any cancer treatment is to eliminate the cancer and prevent or reduce the chance of recurrence in the future. As a result of mesothelioma research, treatments have improved. Not only has current treatments such as chemotherapy and surgery improved, but new treatments are being used in clinical trials. Surgery, chemotherapy, and radiation are the most common treatments, but could those experimental treatments work better?

Discussion

Current Treatments

Like other types of cancer, mesothelioma is often treated with surgery, chemotherapy, or radiation. There are two main types of cancer treatments: local and systemic. Surgery and radiation are local treatments meaning they target the specific area where the cancer tumor is. On the other hand, chemotherapy affects the entire body making it systemic ("Cancer Treatments", 2023, para. 2). Depending on how severe the mesothelioma is, the doctor will recommend one or more ways to treat the disease.

Surgery as a cancer treatment is complicated because every case is unique. One patient might need curative surgery to remove an entire tumor while the patient next door is getting debulking surgery to remove only a portion of a tumor. An extrapleural pneumonectomy is the operation that is done in an attempt to remove all visible tumors. A pleurectomy is a less invasive surgery that is also done on mesothelioma patients along with a partial pleurectomy which is a debulking procedure. There is also palliative surgery which is an operation done to relieve discomfort or disability ("History of Cancer Treatments", 2014). Surgery was first used as a cancer treatment in the late 19th century and research to refine it has not stopped since.

> Until near the end of the 20th century, diagnosing cancer often required "exploratory surgery" to open the abdomen (belly) or chest so the surgeon could take tissue samples to be tested for cancer. Starting in the 1970s, progress in imaging tests such as ultrasound (sonography), computed tomography (CT scans), magnetic resonance imaging (MRI scans), and positron emission tomography (PET scans) have replaced many exploratory operations. ("History of Cancer", 2014, para. 12)

Surgery has grown in the past hundred years and remains the most common treatment for several types of cancer. Surgery can be invasive, but for some patients, it can also be the only treatment needed.

Did you know chemotherapy is sometimes used in non-cancer patients? Chemotherapy is the use of any drug to treat a disease. While cancer is the most common disease chemotherapy is used for, it has also been used to treat lupus and rheumatoid arthritis ("Chemotherapy", 2023). For any chemotherapy treatment, there are three main goals: cure, control, and palliation. In some cases, chemotherapy can be used to completely destroy the cancer. If this is not possible, it is used to partially remove the disease. Similarly, chemotherapy can be used to ease mesothelioma symptoms. Chemotherapy has been used for approximately one-hundred years and while it has its negative side effects, it is commonly looked into because of its success rate in relieving symptoms and improving quality of life.

Radiation therapy uses x-rays, particles, or radioactive seeds to kill cancer cells. With the bright, yellow radiation warning sign posted near all radiation machines, one might question how radiation is not more harmful than it is beneficial. Well, since cancer cells grow plenty quicker than healthy cells, radiation has a greater target on the unhealthy cells. This causes the cells to stop growing and dividing, which leads to cell death.

> The notion of using radioactive elements to treat cancer probably dates back to 1901, when Becquerel experienced a severe skin burn while accidentally carrying a tube of radium in his vest pocket for 14 continuous days. By 1902, radium had been used successfully treat a pharyngeal carcinoma in Vienna. (Connell & Hellman, 2009, pp. 383-92)

Although dangerous, radiation targets the DNA inside cells which can cure or shrink early stage cancer. The three most common mesothelioma treatments have been used for a long period of time. Research into mesothelioma has taken remarkable steps towards more effective, precise, and less invasive cancer treatments. Although these treatments are experimental, could they be better than the treatments used for decades?

Gene Therapy

Gene therapy is a medical approach that treats or prevents a disease by genetically modifying a patient's cells. Deoxyribonucleic acid (DNA) is the blueprint for all cellular functions. Unfortunately, all cancers result from defective or missing DNA. Gene therapy aims to fix the underlying problem: mutated cells. For mesothelioma patients, there are several types of gene therapy that can be attempted.

One strategy is making cancer-killing CAR T cells. What makes CAR T cells? Doctors create CAR T cells by giving a patient's T cells a chimeric antigen receptor (CAR). The T cell combining with CAR creates a CAR T cell. A clinical study explained how this had been done on mesothelioma patients and the results are fascinating. First, researchers collected T cells from mesothelioma patients. Then, using gene therapy, they added a new virus to the T cells. This new DNA caused the cells to target a protein called mesothelin which mesothelioma cells make a large amount of. The CAR T cells attacking this specific protein caused them to recognize and attack mesothelioma tumors (Moncivais, 2021, para. 4) (Figure 1).

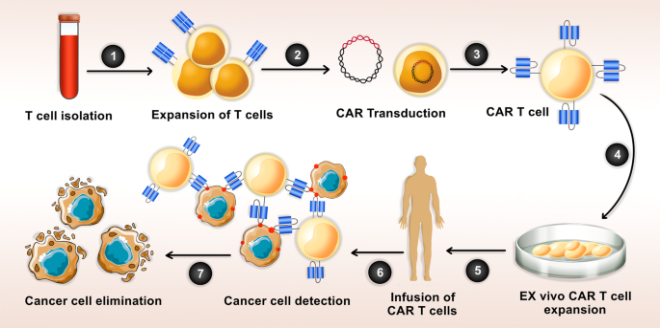

Figure 1. Process of CAR T cells being used to attack cancer cells in emerging gene therapy treatment. (Image source: Cancer Gene Therapy, 2020)

To end this clinical trial, the patients were given an immunotherapy drug to help fight the cancer. One patient still had CAR T cells in their bloodstream eighteen months after treatment showing that gene therapy helps attack the cancer long after it's administered.

Gene therapy is currently available in research settings. While the U.S. Food and Drug Administration (FDA) has approved a small amount of gene therapy products for sale, it is still being researched. It is an experimental treatment with the ability to target the root of the disease and lengthen life-expectancy.

Vaccine Therapy

The human immune system is a complex network made to protect our bodies from outside invaders. However, cancer cells are not recognized as foreign and are therefore not attacked by the immune system. Cancer vaccines stimulate the immune system and make it possible for our bodies to attack cancer cells. Cancer vaccines are not appropriate for all cancers. In fact, no vaccine has been approved for mesothelioma, but clinical trials are ongoing.

One clinical trial that finished phase II in 2021 involves the Wilms Tumor 1 gene (WT1). WT1 is a protein found in several different types of cancer cells, including mesothelioma. WT1 is actually one of the markers doctors look for when diagnosing mesothelioma. The WT1 vaccine is also known as galinpepimut-S, so how does it work? The vaccine is made out of molecules similar to those in the WT1 protein. The goal is to get the immune system to recognize the vaccine as a foreign invader. This then leads to the immune system attacking any cell with the WT1 protein. Although interesting, this vaccine is not made to be the sole treatment for mesothelioma. Researchers believe mesothelioma patients that have gone through surgery would benefit from this vaccine because it would eliminate any remaining cancer cells (Selby, 2023, para. 10). If this vaccine is approved it would decrease the chances of cancer cells spreading or returning after surgery or other treatments.

Oncologists all around the country are researching cancer vaccines for mesothelioma because of the potential they hold in medicine. As mentioned before, surgery is one of the top treatments for mesothelioma. Galinpepimut-S could be used with surgery and decrease the chance of cancer cells growing and returning.

Immunotherapy

Immunotherapy uses drugs to help your immune system fight cancer. As explained previously, the immune system attacks foreign cells to keep our bodies safe. The immune system uses checkpoints to prevent it from attacking healthy cells, unfortunately, cancer cells occasionally use these checkpoints to keep from being attacked. New clinical trials work on targeting these checkpoints to enhance their response towards cancer cells (Figure 2).

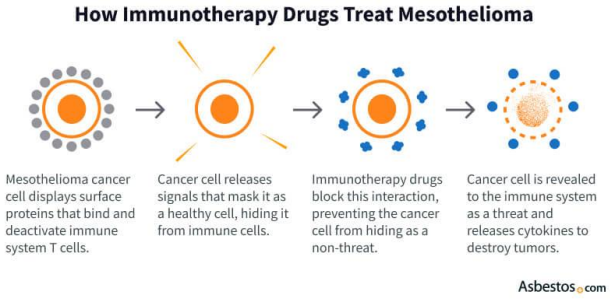

Figure 2: How immunotherapy drugs (specific examples below) destroy cancer cells and treat mesothelioma. (Image source: Asbestos.com & The Mesothelioma Center, 2023)

One protein called PD-1 is located on T cells and helps keep the T cells from attacking other cells in the body. Researchers are using two drugs to block PD-1, pembrolizumab (Keytruda) and nivolumab (Opdivo).

A similar drug with a different target is called ipilimumab (Yervoy). Instead of targeting PD-1, it targets CTLA-4, a different protein ("Immunotherapy for Malignant Mesothelioma, 2021, para. 3-8). One interesting thing about this drug is that it does not work alone. It works with nivolumab which blocks PD-1 .

Both treatments described above are given as intravenous infusions, usually once every six weeks. Immunotherapy has been studied for several years. With their high survival rates and ongoing research, immunotherapy could help hundreds of mesothelioma patients.

Conclusion

Mesothelioma is a belligerent form of cancer that mainly affects the lungs, heart, and abdomen. It is a rare cancer that commonly forms due to asbestos exposure. Asbestos is a mineral that is often breathed in and can irritate tissue and cause gene mutations. There are various treatments for mesothelioma patients, the

most common being surgery, chemotherapy, and radiation. With thousands of researchers nationwide, there are emerging treatments for this destructive disease. Gene therapy attacks the root of the problem by genetically modifying patients cells; vaccine therapy is one of the newest treatments that aims to help immune systems attack cancer cells, especially after previous treatments; immunotherapy studies show certain drugs can target proteins and enhance their response towards cancer cells. These could be used instead or alongside surgery. These are groundbreaking developments that have the ability to be the future of medicine.

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Literary Review

How do Treatments differ based on Mesothelioma Cancer Cells

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Keywords: Mesothelioma, Epithelioid, Sarcomatoid, Biphasic, treatment

Abstract

Mesothelioma cancer has many forms, including epithelioid, sarcomatoid, and biphasic. Though these cancers fall under the same category, treatments can vary. It is seen that in epithelioid cancer, multimodal treatments have been used. Epithelioid is known to be easier to treat and diagnose. Sarcomatoid is more aggressive by combining surgery, chemotherapy, and radiotherapy. Lastly, biphasic mesothelioma blends epithelioid and sarcomatoid cancer cells and is harder to diagnose. Treatments for biphasic would be similar to those of epithelioid and sarcomatoid cancer. There are differences between epithelioid and sarcomatoid cancer treatments, but biphasic cancer tends to have both components.

Introduction

Mesothelioma cancer is a form of cancer that primarily affects the lungs. Asbestos exposure has been a primary cause of the formation of mesothelioma cancer. “Mesothelioma can develop anywhere between 15 to 50 years after asbestos exposure. The mesothelium is made from tissue comprised of mesothelial cells that react when exposed to asbestos. The asbestos fibers cause this tissue to inflame, leading to scar tissue plaques forming on the surface of the protective lining. It is within this scar tissue that malignant mesothelioma tumors begin to grow” (Penn Medicine, Ambrason Center.). Surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapy can treat mesothelioma. This leads to whether individualized chemotherapy can be given based on the type of mesothelioma the patient suffers from. An epithelioid mesothelioma is a form of cancer cells that take a polygonal form. In a study focusing on epithelioid mesothelioma, the approach of
“multimodal intention-to-treatment pathway, including induction chemotherapy, followed by surgery and (HITHOC)” was used to treat early epitheliod cancer (Bongiolatti 2021 et.al). This study was conducted by putting different patients in different treatments and following to organize them into types of survival. The study later showed that the treatment above was well tolerated and feasible. Sacromatoid is another form of mesothelioma where the cells take a spindle shape. “The aggressiveness (sarcomatoid mesothelioma) is due to its poor response rate to methods of treatment such as chemotherapy and surgical

removal" (Clopton 2022 et.al). This study uses a case subject and concludes that many therapies and surgeries are still being tested, with some promising results. This is then followed by biphasic mesothelioma, which has a mix of polygonal and spindle-shaped cells taking treatment from both sarcomatoid and epithelioid mesothelioma. "The standard treatment is radical resection; however, patients have benefited from several other modalities" (Waheed 2022 et.al). This study's case report shows that the prognosis is poor and, left untreated, would be fatal. Another factor that could be considered would be the thymidine synthase inhibitor status, which are chemical agents that can potentially be an anticancer therapy, which can be another factor along with the different types of mesothelioma. Understanding the different types of mesothelioma will lead to a better understanding of treatments for various people, making treatment more effective and efficient.

Epithelioid Mesothelioma Treatment

The different subtypes of mesothelioma, such as epithelioid, sarcomatoid, and biphasic, have distinct characteristics and respond differently to treatment. Epithelioid mesothelioma usually has a better prognosis and responds more favorably to chemotherapy than sarcomatoid mesothelioma. This shows a clear distinction within the types of mesothelioma which would also include a distinction in the treatments necessary. "The multimodal treatment of early-stage epithelioid MPM, including induction chemotherapy followed by P/D and HITHOC, was well tolerated and feasible with promising mid-term oncological results" (Bongiolatti 2021 et.al). This study put patients with stage 1 and 2 epithelioid MPM in this multimodal treatment. The Kaplan-Meier method was used to gather the statistics. The patients were organized into three groups, overall survival, disease-free survival, and progression-free survival. Another similar multi-modal treatment has been used in treatment. "Trimodal extrapleural pneumonectomy (EPP) and extended pleurectomy and decortication combined with hyperthermic intrathoracic chemoperfusion (EPD/HITOC) and adjuvant chemotherapy with that after chemotherapy (CTx) alone" (Klotz 2022, et al.). This study was conducted by treating 182 patients with this treatment.This study also showed that EPD/HITQC is feasible and safe for localized epithelioid pleural mesothelioma. In both studies, it is shown that these multi-modal approaches for epithelioid mesothelioma were effective.

Sarcomatoid Mesothelioma Treatment

Sarcomatoid mesothelioma treatments will soon be further discussed. They vary from epithelioid due to the difference in the type of cancer cells. "Current practicing therapies are aimed at combining surgery, neoadjuvant/adjuvant chemotherapy as well as neoadjuvant radiotherapy to improve survival rate and improve symptoms. There are many randomized controlled trials, prospective studies, and

intention-to-treat studies that evaluate the efficacy of therapies such as TMT and MARS trials. Molecular targeted therapy and immunotherapy have also made promising contributions toward the future of management for mesothelioma" (Clopton 2022, et.al). This study was conducted with a case study of a sarcomatoid mesothelioma patient. It allowed for the understanding of the treatments of this specific type of mesothelioma. In another study, the diagnostic usefulness of CK immunohistochemistry" was shown (Klebe 2010, et al.). This study was one of the largest, with 326 cases of sarcomatoid mesothelioma examined, the study helped prove the usefulness of CK immunohistochemistry in treatment. This would show the different treatments used for the treatment of sarcomatoid mesothelioma. As is evident, these treatments differ from those of epithelioid mesothelioma. These different cancers also affect the patients differently.

Biphasic Mesothelioma Treatment

Biphasic would be a combination of both types of mesothelioma. Therefore the cancer cells take a mix of two different shapes. "The diagnosis and treatment do not differ from other subtypes; however, the prognosis is poor, and if untreated, the survival is typically less than six months." "The standard treatment is radical resection; however, patients have benefited from several other modalities" (Waheel 2022 et. al). The case report used within this study has a unique form of biphasic peritoneal mesothelioma, which helps the study conclude on the similarities in treatments of the different mesothelioma. "There are limited small, single-institution observational studies on the role of surgery in patients with biphasic mesothelioma. Herein we report 147 consecutive patients with biphasic mesothelioma treated over 11 years in a high-volume single institution with intended pleurectomy decortication (PDC)" (Lapidot 2022 et.al). In this study, patients with biphasic mesothelioma from 2007 to 2017 underwent PDC. The Kaplan-Meier estimators were used to compare the overall survival. The conclusion from this study was then observed. The conclusion is that good prognostic factors prolonged survival after PDC. There has been a combination of treatments within many of these biphasic studies. In both studies, this is made evident.

Conclusion

There are many different types of mesothelioma with different cancer cell shapes. Throughout the literature review, the different mesothelioma cancers require different types of treatments. Epithelioid mesothelioma is easy to diagnose and treat. Sarcomatoid mesothelioma tends to be more aggressive, needing more aggressive treatment. Lastly, biphasic mesothelioma is a mixture of both, making it harder to diagnose and, therefore, harder to treat due to the late diagnosis. Different treatments are being used,

such as different multi-modal approaches, surgical approaches, and chemotherapies. Understanding these cancers and how to treat them will help those who suffer from mesothelioma.

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Literature Review

Affected Signaling Pathways and Genetic Alterations in Malignant Mesothelioma and Potential Novel Treatments

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Keywords: Malignant Mesothelioma, Signaling Pathways, Genetics, Treatment

Abstract:

Malignant Mesothelioma is a cancer that occurs in the mesothelium, affecting over 30,000 people per year. The prognosis for the disease remains extremely poor, with the median survival rate typically being 4 - 18 months after diagnosis. The need for developing new treatment options is necessary to improve patient outcomes. Signaling pathways such as PI3K, MAPK, and Hippo pathways are commonly dysregulated in Malignant Mesothelioma patients. In addition, important cell-cycle regulators and tumor suppressor genes such as CDKN2A, CDKN2B, BAP1, and NF2 are often mutated or altered. This literary review aims at enhancing our understanding of these dysregulations and alterations to develop novel treatments.

Introduction:

Malignant Mesothelioma (MM) is an aggressive cancer that occurs in the mesothelium, which covers internal organs such as the lungs (Malignant Pleural Mesothelioma [MPM]), intestines (Malignant Peritoneal Mesothelioma [MpM]), and heart (Malignant Pericardial Mesothelioma).[1] There are nearly 3000 new MM cases annually in the US and ten times that worldwide.[2] The leading cause for MM is asbestos, a carcinogenic material consisting of flexible fibers that, when inhaled, causes it to be trapped within the body, creating scar tissue where MM tumors can grow. MM has an extremely long latency period, as symptoms may not present themselves until 15-50 years after initial asbestos exposure. These early symptoms are generally mistaken for common ailments; they include fever, excessive sweating, fatigue, and loss of appetite. Most MM patients are often diagnosed when the cancer is in its later stages.[3] Despite research continuing to be done, the prognosis of MM remains extremely poor. According to a study that analyzed MM patients from 1973 to 2011, the survival rate increased by only 0.5% per year for MPM and 2% for MpM.[4] Thus, developing novel therapies and treatments is necessary to improve patient

outcomes. This research paper seeks to understand the biological processes and genetic alterations that contribute to or arise out of MM, which could help develop new treatment strategies.

Affected Signaling Pathways in MM:

For our cells to stay healthy, the signaling pathways that carry out important cellular processes must be properly functioning. The dysregulation or alteration of these pathways can result in adverse effects such as unhealthy cells and an increased risk of cancer. In MM patients, numerous pathways seem to be commonly affected, indicating they play a critical role in the progression and pathogenesis of the disease.

PI3K/AKT/mTOR Pathway

Currently, the most studied affected pathway in MM patients is the Phosphoinositide 3-kinase (PI3K) pathway, also referred to as Protein Kinase B (AKT) and Mammalian Target of Rapamycin (mTOR).[5-7] This intracellular pathway is considered a master regulator for cancer since it has been observed to be dysregulated in breast cancer, colorectal cancer, and recently in MM. This dysregulation involves hyperactivity of PI3K, which is significantly correlated with tumor progression.[8] The pathway consists of a phosphorylation cascade of multiple kinases to activate transcription factors that regulate cell growth and proliferation. It starts with extracellular stimuli, such as growth factors, binding to a membrane receptor protein, such as G-protein coupled receptors (GPCRs) or tyrosine kinase receptors (RTKs). Upon binding, PI3K will be activated and catalyze the phosphorylation of the phosphoinositide $PtdInsP_2$ (PIP2) to $PtdInsP_3$ (PIP3).[9] PIP3 will then activate downstream kinases such as AKT and mTOR to activate transcription factors such as S6K1 and 4EBP.[10,11] The PI3K pathway is generally regulated through the protein phosphatase and tensin homolog (PTEN) as it inhibits the phosphorylation of PIP2 to PIP3.[12] An overview of the pathway is shown in Figure 1.

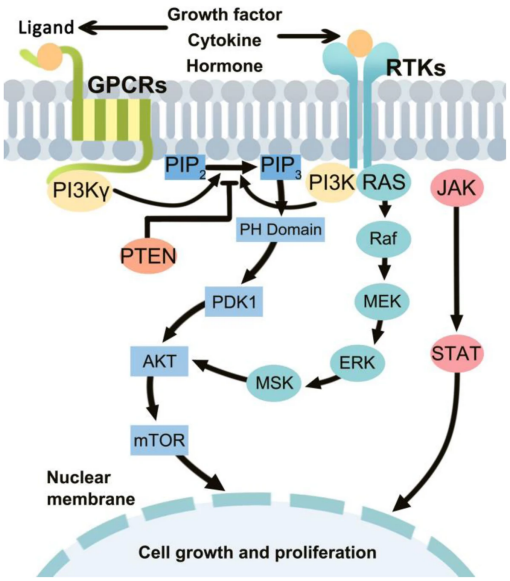

Figure 1. The overview of PI3K/AKT/mTOR signaling pathway.[8]

The dysregulation of the PI3K pathway has been linked to the progression and worsening of MM. A study done in 2011 looked at 41 tumor samples from MpM patients and compared the expression of PI3K and mTOR to 6 non-malignant tissues. Using Real-Time Polymerase Chain Reaction (qRT-PCR) they found that the PI3K signaling pathway was significantly overexpressed in the poor survival group (median 24 months).[13] This pathway can be dysregulated in many ways, most notably through inactivation or loss of PTEN. When PTEN is not functioning, it leads to an overexpression of the transcription factors, which causes an increased risk of cellular dysfunction. One study analyzed the expression of AKT and PTEN in 21 MM cell lines and one non-MM cell line using real-time reverse transcription and Western blot analysis. PTEN expression was lost in two cell lines and expressed at low levels in 11. The researchers observed two cell lines that exhibited a homozygous deletion after they sequenced nine exons of the PTEN gene. They also carried out a qRT-PCR analysis on these two cell lines to derive the length of the deletions, which were 40 kilobases and 7.7 kilobases long. AKT expression was much more elevated in the 13 cell lines with low or no PTEN expression.[14] Another study from 2013 analyzed PTEN expression in 86 archival MM samples and yielded similar results. The team performed immunohistochemical (IHC) staining analysis on the samples, a method for observing the presence of proteins in tissue sections, and compared it to a positive stain for PTEN in normal mesothelial cells.[15] They gave each sample a score of 0 (no detection), 1 (intensity less than the positive stain), or 2 (intensity equal to or greater than the positive stain). 23 samples scored a 0, 23 scored a 1, and 40 scored a 2. These studies confirm that PTEN can be a potential biomarker in MM patients.[16] Other proteins from the PI3K pathway have also been studied to be potential biomarkers. One study from 2014 looked at the PI3K pathway as a therapeutic

target for MPM. They assembled a tissue microarray with 213 MPM tumor samples and 196 control samples to observe the expression of AKT. Using IHC, the researchers found that the expression of AKT was significantly greater in the MPM samples compared to the control samples. Interestingly, there was no significant difference in PTEN expression, showing how patients can express a multitude of alterations.[17]

MAPK Pathway

Another pathway that has been commonly altered in MM patients is the mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway has previously been observed to be dysregulated in bladder cancer, lung cancer, and melanoma.[18] Similarly to the PI3K pathway, MAPK involves a phosphorylation cascade of MAP kinases which promotes different biological responses such as growth, apoptosis, cell proliferation, and differentiation. There are three main families of MAPK: extracellular-signal-regulated kinases (ERK), Jun amino-terminal kinases (JNK), and stress-activated protein kinases (SAPK). These pathways are activated through an extracellular stimulus that binds to a membrane receptor protein such as RTKs and GPCRs.[19] After activation, the cell enables signaling transducing adaptor proteins (STAPs) such as non-receptor tyrosine kinase (SRC) to recruit RAS proteins which activate the cascade.[20] RAS proteins can also activate other pathways such as PI3K, RAC, and RHO. Each family has no fewer than three kinases, labeled MAPKKK, MAPKK, and MAPK, in order of activation. The pathways for each family are shown in Figure 2.[21]

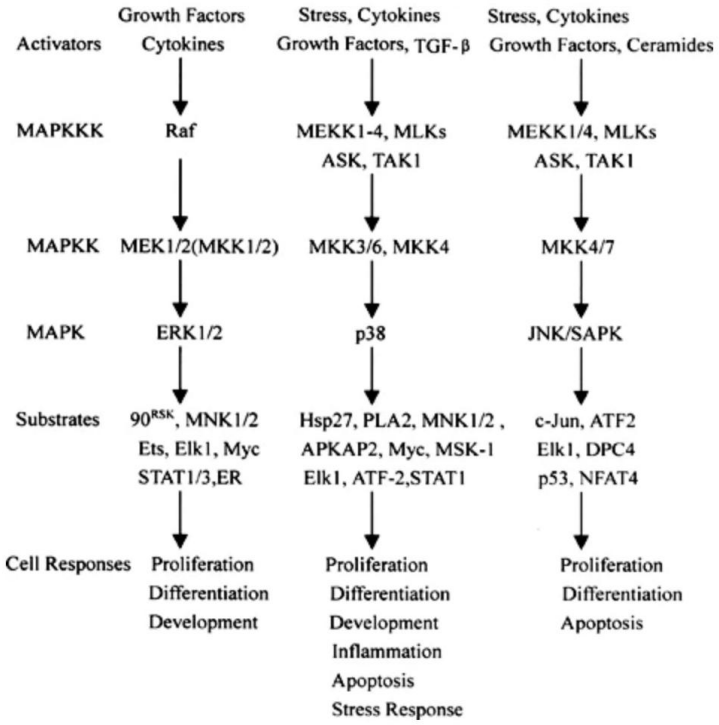

Figure 2. Major MAP kinase cascades in mammalian cells.[21]

The MAPK pathway has been observed to be dysregulated in some MM patients. A study from 2005 took 10 MM samples, seven of which had known asbestos exposure. The researchers performed IHC to detect the phosphorylated and non-phosphorylated forms of the MAPK of the ERK family, ERK-1 and -2. The MM samples showed intense, homogenous staining in the nucleus and cytoplasm in comparison to the control lung, symbolizing a high level of ERK activation. The results show that MAPK is highly activated in MM tumor cells.[22] Another study from 1996 linked exposure to asbestos with the overactivation of MAPK in rats. The researchers looked at RPM cells from the pleura of Fischer 344 rats, a rat strain that has been used to study cancers. To simulate asbestos exposure, they treated the cells with crocidolite asbestos, the most pathogenic type of asbestos which causes MM, as well as chrysotile asbestos. During a 24-hour incubation period, ERK-1 and -2 significantly increased in activity. After performing immune complex kinase assays, ERK-2 was confirmed to be enzymatically activated by both crocidolite and chrysotile asbestos. To determine if the dosage of asbestos correlated to the activity level of ERK-2, they treated RPM cells with crocidolite and chrysotile asbestos in dosages of 1.25, 2.5, 5.0, and 10 micrograms/cm^2 over an 8-hour incubation period. ERK-2 was observed to increase in activity as dosage increased. The researchers then wanted to examine if asbestos played a role in the activation of the pathway. They hypothesized that asbestos was binding to one of the membrane-bound receptor proteins. They performed in vitro phosphorylation assays on epidermal growth factor receptor (EGF-R) on two RPM cell groups, one with normal GF and another with crocidolite asbestos. Within 2 hours, the asbestos group displayed higher levels of EGF-R phosphorylation compared to the EGF group. These findings suggest that asbestos may play a critical role in the dysregulation and over-activation of the MAPK pathway.[23]

Hippo/YAP/TAZ Pathway

The Hippo pathway also involves a phosphorylation cascade to recruit transcriptional factors which regulate tissue growth and multiple cellular functions such as cell proliferation and apoptosis. The Hippo pathway has been previously observed to be dysregulated in liver, lung, colorectal, ovarian, and prostate cancers, as well as other diseases. Unlike the PI3K and MAPK pathways, Hippo can be activated through several signals such as cell-cell contact, stress signals, cell polarity, and other intrinsic signals.[24] After activation, mammalian Ste20-like kinase-1 and -2 (MST1/2) forms a heterodimer with salvador homolog 1 (SAV1) to phosphorylate large tumor suppressor kinase-1 and -2 (LATS1/2) with the help of the scaffold protein WWC1-3. Other kinases are suspected to phosphorylate LATS1/2 without the help of SAV1 or WWC1–3. LATS1/2 then directly activates yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ), hence the alternative name to the Hippo pathway, the

YAP/TAZ pathway. YAP/TAZ then binds to transcriptional enhanced associate domain (TEAD) transcription factors to induce the expression of genes related to the cellular functions previously mentioned.[25-26] The full pathway is shown in Figure 2.

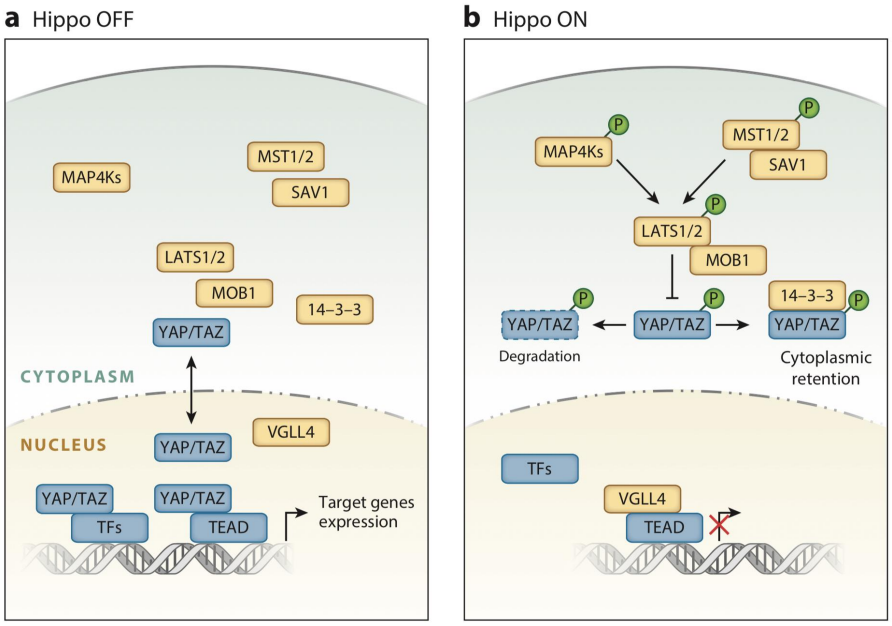

Figure 3. Core components of the Hippo/YAP/TAZ pathway.[25]

The Hippo pathway is one of the most commonly altered pathways in MM patients. One study which looked at transcriptomes, whole exomes, and targeted exomes from 216 MM samples found the Hippo pathway to be the most mutated. Genes such as LATS1/2 and neurofibromatosis type 2 (NF2) were frequently mutated through copy number variations and fusions.[27] Another study from 2015 used RNA and targeted exon sequencing to analyze mutations of the Hippo pathway in 12 MM cell lines and four clinical samples. The researchers found a chromosomal translocation between LATS1 and presenilin-1 (PSEN1), which lacked the ability to phosphorylate YAP. They also identified 11 somatic mutations in NF2, LATS2, RASSF1, and SAV1.[28]

Genetic Alterations and Predispositions in MM:

Our bodies contain upwards of 20,000 protein-coding genes and almost every one of these genes is involved in critical cellular processes. Genes which regulate signaling pathways and the cell cycle are especially important, as alterations in these genes often cause cellular instability and an increased risk of uncontrollable cell growth. There are numerous chromosome regions and tumor suppressor genes that have been observed to be altered in MM patients, suggesting that early diagnosis of MM may be possible

by detecting the alterations of these genes. One study from 2022 looked at the genomic landscape of 1113 MPM tumor samples and 355 MpM tumor samples from patients who were diagnosed through December 2020. The researchers performed comprehensive genomic profiling and sequenced the tumors using FoundationOne® or FoundationOne®CDx test to detect alterations in 324 cancer genes. The most commonly altered genes in MPM were cyclin-dependent kinase inhibitor 2A (CDKN2A) in 48.2% of cases, ubiquitin carboxyl-terminal hydrolase (BAP1) in 45%, cyclin-dependent kinase inhibitor 2B (CDKN2B) in 42.2%, NF2 in 32.8%, and methylthioadenosine phosphorylase (MTAP) in 32.3%. The most commonly altered genes in MpM were BAP1 in 47.9% of cases, NF2 in 26.5%, CDKN2A in 25.9%, CDKN2B in 19.5%, and protein polybromo- 1 (PBRM1) in 15.8%.[29]

CDKN2A and CDKN2B

CDKN2A and CDKN2B are both tumor suppressor genes located adjacent to each other on chromosome 9p21. CDKN2A codes for a protein called $p16^{INK4A}$ (p16) and CDKN2B codes for a protein $p15^{INK4B}$ (p15). Both p16 and p15 act as cell-cycle inhibitor proteins by forming a protein complex with cyclin-dependent kinases (CDK), most notably CDK4/6 and Cyclin D. Therefore, alterations in CDKN2A or CDKN2B result in the inability of p16 and p15 to form this complex, leading to pro-mitotic signals and dysregulation of the cell cycle.[30,31] Loss of CDKN2A and CDKN2B has been observed in bladder cancer, lung cancer, and melanoma.[32] In the study from 2022, 48.2% of MPM samples and 25.9% of MpM samples showed alterations in the CDKN2A gene. Homozygous deletion of CDKN2A has also been correlated to a co-deletion of MTAP. A study from 2003 used a fluorescent in situ hybridization assay (FISH) for CDKN2A and MTAP in 95 MPM samples. 74% of the samples (70 samples) contained a deletion of CDKN2A and in 91% of those cases (64 samples) MTAP was co-deleted. The researchers did not observe MTAP deletion without CDKN2A also being deleted.[33]

BAP1

BAP1 is located on chromosome 3p21 and encodes the protein BAP1, a deubiquitylase and tumor suppressor protein involved in many cellular pathways such as the cell cycle, cellular differentiation, DNA damage, and cell death. BAP1 binds to numerous transcriptional proteins and deubiquitinates them, regulating the expression of their target genes.[34,35] BAP1 most notably interacts with breast cancer gene 1 (BRCA1). BAP1 interacts with the BRCA1/BARD1 complex, an E3 ubiquitin ligase that regulates the homologous recombination pathway of DNA repair.[36] BAP1 binds to the RING finger domain of BARD1 and has been shown to inhibit the E3 ligase activity of the complex. More recent evidence supports the idea that BAP1 plays a critical role in BRCA1/BARD1 DNA repair mechanisms.[37] BAP1 also deubiquitinates Host Cell Factor 1 (HCF1), a transcriptional regulator involved in the cell cycle and cell proliferation. HCF1 promotes progression through the G1/S phase by recruiting histone-modifying enzymes to modify the chromatin structure at promoters of E2F transcription factors. Studies have shown

that without BAP1, cells will be arrested in the G1 phase. These results show how BAP1 also plays a major role in cell-cycle regulation.[38] In the study from 2022, 45% of MPM samples and 47.9% of MpM samples showed alterations in the BAP1 gene. Another study from 2015 achieved similar results using 22 MM frozen biopsies. Using Laser Capture Microdissection (LCM) to enrich the tumor cell samples, DNA and RNA were able to be extracted. Using Sanger sequencing and multiplex ligation-dependent probe amplification the researchers obtained BAP1 PCR products and found BAP1 to be altered in 14 of the 22 samples.[39] IHC was performed on these 14 samples and no BAP1 staining was observed. IHC was also performed on an independent cohort of 70 MM samples and BAP1 loss was observed in 47 samples. A study from 2015 looked at BAP1 in 207 MPM and 5 MpM biopsies. They performed a FISH assay for the BAP1 gene on 51 biopsies and 41 showed loss of BAP1 protein. Alteration of the BAP1 gene was observed in 139 cases, most notably in the epithelioid MM subtype (128/184 cases). These findings suggest that BAP1 can be a useful genetic marker in the diagnosis of MM.[40]

NF2

NF2 is located on chromosome 22q12 and encodes the protein Merlin, also commonly referred to as NF2 and schwannomin. Merlin is an important tumor suppressor protein that is involved in the regulation of cellular mechanisms like cell proliferation and cellular pathways.[41] As previously mentioned, NF2 plays a role in the regulation of the Hippo pathway. Alterations in NF2 can cause overactivation of YAP/TAZ, leading to an increased risk of cancer.[42,43] NF2 has also been shown to play a role in the regulation of the PI3K pathway as well. It inhibits the activation of PI3K by binding PIKE-L, a GTP-binding protein that is used to enhance PI3K lipid kinase activity.[44,45] In the study from 2022, 32.8% of MPM samples and 26.5% of MpM samples showed alterations in the NF2 gene. Another study from 1999 reported NF2 mutations in MM cell lines and corresponding tumor samples. After performing Western blot analysis on 25 MM cell lines, 14 did not show NF2 expression. Single-strand conformation polymorphism and DNA sequencing revealed NF2 was mutated in these lines. To determine the mechanism of the mutation, the researchers used two microsatellite markers and placed them in the vicinity of the NF2 locus. 18 cell lines showed allelic losses in one or both loci, suggesting inactivation of NF2 is a two-hit mechanism.[46] Other studies agree that 35-40% of MM cases show inactivation mutations in the NF2 locus.[47,48]

Current Therapies and Limitations:

Despite research continuing to be done, the prognosis of MM remains extremely poor. The current five-year survival rate for MPM (the most common type comprising 80-90% of cases) is 10-12% and for MpM it is around 65%.[49] There is currently no cure for MM and most treatments are palliative. The type of treatment a patient gets depends on numerous factors including the stage of MM, size of the tumor, age, general health, and whether it is a recurring MM patient. MM is classified into four stages (I, II, III,

IV) depending on how far the cancer has spread throughout the body.[50] New treatments such as gene therapy and p53 restorative drugs are currently being tested in clinical trials.[51] The most common treatments for MM at the time of writing are surgery, radiation therapy, chemotherapy, and immunotherapy.

Surgery

One of the most common treatments for MM is through a surgical procedure. Surgery may be used to potentially cure the cancer or simply relieve the pain if the tumor has already spread beyond its origin. The most common surgical procedure for MPM is a pleurectomy/decortication (P/D). P/D is a relatively less extensive operation than other procedures and involves the removal of the pleura lining the chest and lung on the side of the cancer.[52] Common side effects of P/D include moderate blood loss, air leaks, and irregular heartbeats, but surgeons normally handle these complications during the procedure.[53] P/D is most effective in Stage I patients where the cancer is still local, in which case P/D can potentially cure the cancer. If the entire tumor can't be removed, P/D acts as a palliative treatment by lessening the pain caused by the tumor. 90% of patients experience reduced symptoms after P/D and 1-2% of patients die during or shortly after the procedure. Various studies report the median survival after P/D to be 20-32 months and the five-year survival rate to be 20-30%. Another surgical procedure for MPM is an extrapleural pneumonectomy (EPP), which is a slightly more complicated operation than P/D. EPP is mainly used in extremely healthy patients where the MM is still localized. Unlike P/D, EPP removes the tumor-affected lung as well; because EPP is much more extensive, there are much more side effects such as bleeding, blood clots, wound infections, and pneumonia. Despite the differences in EPP and P/D, most studies show that patients have similar survival rates regardless of what surgical procedure they got. One surgical procedure that is used in MPM and MpM patients is debulking.[54] Debulking, also referred to as a partial pleurectomy, aims to maximize the removal of the tumor and minimize the amount of tissue loss.

Radiation Therapy

Another form of treatment for MM is radiation therapy (RT). RT is often used in multimodal treatments, such as after surgery to kill off small areas of cancer that may not have been removed during surgery. It can also be used as a stand-alone palliative treatment to ease symptoms. RT uses high-energy X-rays (radiation) to kill cancer cells or slow their growth by damaging their DNA. RT often takes days or weeks to damage the DNA and months for the cancer cells to die off.[55,56] There exist many types of RT, but the main type used for MM is external beam radiation therapy (EBRT). EBRT uses photon beams or x-rays produced by a machine to kill the cancer cells. Recent advancements in techniques and technology like intensity-modulated radiation therapy (IMRT) are allowing doctors to more precisely treat cancer-affected tissue. Some side effects of RT include fatigue, sunburn-like skin, and damage to surrounding healthy

cells.[57] RT has been effectively used in MPM but is not commonly used in MpM. Approximately 60% of MM patients report pain relief after RT. When RT is combined with other treatments, patients experience longer overall survival. A study from 2016 conducted by the Icahn School of Medicine observed patient outcomes for thousands of MPM patients and reported an overall survival rate double for those who received radiation. Another study from 2020 reported longer overall survival with radiation, mainly in early-stage MPM patients.[58]

Chemotherapy

Chemotherapy (CTX) involves the use of anti-cancer drugs to kill or slow the growth of cancer cells. Similar to RT, CTX is often administered in multimodal treatment approaches, but it can be used as a stand-alone treatment. CTX is usually given in cycles that last 3-4 weeks. There are two main types of CTX to treat MM, systemic CTX, and intrapleural or intraperitoneal CTX. In systemic CTX, the drugs are injected into the bloodstream or taken orally and they travel throughout the body. In intrapleural or intraperitoneal CTX, the drugs are placed directly into the cancer-affected tissue via a small catheter. The benefit of this form of CTX is that higher concentrations of the drug go to the cancer cells.[59] Some drugs approved for MM are Pemetrexed, Ipilimumab, Nivolumab, and Cisplatin. Standard CTX for MPM patients involves a combination of pemetrexed and cisplatin given every 21 days.[60,61]

Potential Novel Treatments:

Researchers have already started to develop treatments that target these dysregulated pathways and genetic alterations in MM. The PI3K pathway is a notable pathway of interest in the development of novel treatments. One case study from 2017 observed the management of two female, recurring MpM patients who previously received CTX. Both patients received apitolisib, an inhibitor of the PI3K pathway. Case 1 was on apitolisib treatment for 2.8 years and reported symptomatic improvement. Case 2 was on apitolisib treatment for 15 months and showed significant tumor reduction (by 30-40%). IHC revealed that there was no PTEN loss in both patients. The study concluded that apitolisib may be a more effective treatment than other anti-cancer therapies like CTX. However, more information regarding when apitolisib should be administered and other patient responses to the drug need to be assessed before establishing it as a reliable treatment.[62] Drugs other than apitolisib have shown similar inhibiting effects. One study from 2016 observed the effect of crizotinib, BKM120, and GDC-0980 on 7 MPM cell lines. Cell viability results showed that the cell lines were sensitive to each inhibitor individually and their effectiveness significantly increased when used in combination. The combination of crizotinib and BKM120 greatly inhibited the activity of PI3K as shown by decreased phosphorylation of AKT. This study proved that using a combination of PI3K inhibitors may be a reliable treatment option.[63] Similar therapeutic drug approaches have been researched for the Hippo pathway. One of the main approaches in

targeting the Hippo pathway is by targeting YAP/TAZ. This can be done by blocking the binding of YAP/TAZ to TEAD transcription factors. One small molecule drug that has been tested for this effect is verteporfin. One study analyzing the effect of verteporfin on the Hippo pathway observed significantly reduced YAP protein levels in 5 MM cell lines when the drug was administered.[64] Other inhibitors such as cyclic YAP-1-like peptides, mammalian vestigial-like 4 (VGLL4), and t-cell lymphoma invasion and metastasis-inducing protein 1 (TIAM1) have been recognized as other Hippo pathway targeting drugs.[65]

Conclusion:

The prognosis and survival rate for MM remains extremely poor with current treatments. Pathways that control cellular processes such as PI3K/AKT/mTOR, MAPK, and Hippo are consistently observed to be dysregulated in patients with Malignant Mesothelioma. Targeting these dysregulated pathways holds promise as a treatment option for MM, but additional research is required before such treatments can be tested in clinical trials. Another target for treatment can be commonly altered genes such as CDKN2A/B, BAP1, and NF2. Treatments targeting these genes may involve the use of biotechnology such as CRISPR or gene therapy, but this has yet to be explored. These novel treatment options may be more effective than current treatments and have the potential to significantly improve MM patient outcomes.

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Review Article

Standard Treatments of Mesothelioma Cancer

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Keywords: Mesothelioma Cancer, Multimodal Treatment, Surgery, Pleurectomy/Decortication, Extrapleural Pneumonectomy

Abstract:

This literary review will discuss the different treatments available to people undergoing Mesothelioma cancer, and evaluate the conditions and symptoms that patients go through. There are two main surgeries that we will be focusing on and discussing their pros and cons, specifics of the procedure, and types of patients that should receive the treatment. This review will also discuss the causes of Mesothelioma, mainly asbestos, and the groups of people that are affected by this brutal cancer. I reviewed the most common treatments, not getting into detail about the clinical trials of Mesothelioma due to its non guaranteed results.

Introduction:

Over 10% of people all over the world die from cancer every year. More than 40% of deaths are preventable, depending on the habits, lifestyles, and situations people undergo throughout their lives. Mesothelioma is a cancer found in the lining of the lungs, chest wall, and abdomen. Different types of mesothelioma, such as pleural mesothelioma specifically targets the tissue covering the lungs and chest wall, most commonly caused by asbestos exposure. Asbestos is a harmful mineral that was used in building, manufacturing, mining, and road construction. Airborne asbestos exposure plays a massive role in the appearance of mesothelioma and lung cancer. While symptoms don't appear right away, taking around 50 years to present themselves, it's deadly and life threatening to those that develop this type of cancer. Pleural mesothelioma is the most common type of mesothelioma, occurring in 80% of people diagnosed with mesothelioma cancer. (Cleveland Clinic, Pleural Mesothelioma) Many of the early symptoms are easy to dismiss, presenting most commonly as chest pain and shortness of breath, but also resulting in a persistent cough, dysphagia, lower back pain, weight loss, night sweats, fatigue, fever, and swelling of the extremities.

A common group of workers are at risk for mesothelioma cancer, specifically those age 65 and older. Workers who've had jobs working around asbestos such as construction workers, builders, navy

members, renovators, railway workers, firefighters, plumbers, and miners all have an increased risk. (“Where Can I Find Asbestos”) Around 50 years ago, factories and jobs weren’t monitored and regulated for safety, creating a huge crisis with the number of workers falling ill due to mesothelioma cancer. Not only harming the men working these jobs, families who lived with workers also inhaled asbestos, and women who cleaned and sewed their clothes were also exposed to this dangerous mineral. Even those who lived near asbestos mines or buildings containing asbestos could develop mesothelioma cancer. There have been standard treatments used for treating mesothelioma cancer, most of the time ineffective unless caught at an early stage, as well as more recent techniques and therapies conducted with clinical trials.

Unfortunately, mesothelioma is usually caught in one of the late stages, already developed into an aggressive and incurable cancer that has huge consequences on a person’s life. (Mayo Clinic, “Mesothelioma”) At this late stage of diagnosis, there are only a few surgeries that can be done to further prevent the spread of mesothelioma.

Pleurectomy/Decortication:

For patients that present with pleural mesothelioma, a surgery is performed to remove the cancerous cells around the lung. This surgery is called a pleurectomy/decortication (P/D), and it preserves the lung; however, it doesn’t guarantee the full removal of the cancerous lining. P/D removes all the cancerous cells visible to the naked eye and increases the patient's chances of survival. (Cancer.Net Editorial Board)

P/D is completed in two different parts and overall takes a total of 4-6 hours. During the pleurectomy procedure, a thoracotomy is performed, an incision in the ribs, and the sixth rib is removed. This removal provides the surgeon access to the pleural space where they detach the parietal pleura (or the outer layer of the pleura) and decide whether or not it should be removed completely. (Katy Moncivais) They then check the diaphragm or pericardium (lining of the heart), to see if any tumors are present and need to be removed. Any cancerous cells found will be taken out at this stage. During the decortication part of the surgery, the visceral pleura (layer of pleura closest to the lungs) is removed, along with any tumors present in the lung tissue and the lymph nodes. If a surgeon decides to remove a part of the diaphragm, a reconstruction of that portion of the muscle is needed, such as the placement of a surgical mesh, to replace the diaphragm tissue taken out. Once all the incisions are closed, the recovery process is underway.

Risks/Mortality:

As with any invasive procedure, there are serious side effects/ risks of the surgery, as well as benefits to consider. Some side effects include blood loss, air leaks, irregular heartbeats, pneumonia, and

respiratory failure. However, surgeons anticipate these side effects and are able to effectively prepare and treat these risks as they occur. Surgeons are able to keep mortality rates relatively low for P/D, ranging from 0% to 6.8% of patients within a 30 day mortality period. There are also benefits associated with this surgery including greater short term survival, generally "safer" than other types of surgeries, better quality of life because of the use of both lungs instead of just one, improved tolerance for additional treatments because having two lungs provides more resilience for other surgeries, and many more patients fit the criteria for P/D.

Multimodal Treatment:

Before a P/D surgery can be performed systemic chemotherapy is usually given to patients. This is part of a multimodal treatment given to patients, and it can include chemotherapy or immunotherapy. Chemotherapy is used to treat mesothelioma because the drugs damage the cells during their process of cell division, and it slows the growth of mesothelioma. The two different types of chemotherapy for mesothelioma patients include systemic chemotherapy, which travels through the bloodstream, usually given through an IV or taken orally. Or local chemotherapy, which is applied only to a specific region in the body. Local chemotherapy has fewer side effects, but it also requires surgery to keep the drug in one place. (Katy Moncivais)

Immunotherapy is another type of treatment that's used with surgery to stop the spreading of mesothelioma. Immunotherapy uses the body's own immune system to fight cancer by introducing a drug, called checkpoint inhibitors, which can be less toxic than chemotherapy drugs and cause less side effects. There are different types of immunotherapy and each method takes a different approach in stopping the cancer. Car-T, for example, reprograms immune cells to make them attack tumors. Checkpoint inhibitors stop the cancer cells from using the immune checkpoints, stopping them from dividing and reproducing. (Katy Moncivais)

Extrapleural pneumonectomy:

Another more aggressive type of surgery for pleural mesothelioma is called extrapleural pneumonectomy. This removes the lining of the lung, the entire lung itself, a portion of the diaphragm, and a portion of the lining of the heart. This is usually considered as a second option after P/D due to the huge risk of complications and death for the patient. EPP can only be performed on patients in the early stages of mesothelioma where the cancer hasn't spread to the lymph nodes or surrounding tissues and organs. (UCSF Department of Surgery- Extrapleural Pneumonectomy) Candidates for the surgery must have otherwise good heart and lung function because the removal of an entire lung puts serious strain on the heart and the remaining lung.

For suitable candidates, EPP is considered one of the most effective methods of preventing the spread of pleural mesothelioma. However, the risks and benefits need to be seriously considered before

the approval of the surgery. Some risks include internal bleeding, respiratory failure, pneumonia, infection, and blood clots. Around 6% of patients die during or immediately after the surgery, and much of the time, the cancer reappears sometime in the future. While these risks are extremely serious and devastating to hear, they must be weighed to the benefits of the procedure; these include slowing the progression of the cancer, improving the quality of life (quality of breathing), and extending the life expectancy.

There are quite a few options when it comes to battling Mesothelioma cancer for patients that are unlucky enough to face it. Doctors/ surgeons are able to make a decision about the standard treatments of Mesothelioma, of performing a pleurectomy/decortication, using multimodal methods, extrapleural pneumonectomy, or any other method. The earlier the cancer is caught, the more chances that patient has of surviving with the least amount of side effects, but this aggressive cancer still has very high chances of death, even when caught early. People most at risk for developing Mesothelioma are those exposed to asbestos, dangerous chemicals, and family members living with people exposed to asbestos.

Conclusion:

Veterans, 9/11 first responders, and people who work in conditions where they’re exposed to asbestos suffer the consequences and dangers of Mesothelioma and have to choose these risky surgeries and treatments that don’t guarantee success. While the regulations in workplaces are improving compared to previous decades, more progress still needs to be made to stop the many lives being taken by Mesothelioma.

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Review Article

The Psychological Effects Of Malignant Mesothelioma Cancer On Patients

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Keywords: Mesothelioma cancer, emotional distress, rarity

Abstract

This research paper uncovers the psychological effects of malignant mesothelioma patients. This sifts through the ups and downs and further looks into how significant the emotional distress can get.

Introduction

Despite the scarcity of evidence, those diagnosed with malignant mesothelioma (Meso) cancer succumb to the complex and stressful psychological effects in their life. Meso is an aggressive and rare form of cancer that occurs in the lining of internal organs, most prevalent in men aged around 70. This is primarily linked to exposure to asbestos, a fiber resistant to heat, making them useful for a wide range of applications, such as insulation, shingles, flooring, brakes, and much more. This cancer is divided into three different types depending on where in your body it is being infected. This includes pleural meso, which affects the tissue surrounding the lungs, peritoneal meso, which begins in the lining of the abdomen, and pericardial meso, which primarily grows in the lining of the heart. Some of its symptoms include shortness of breath, chest pain, shortness of breath, abdominal pain, nausea, and much more. It is reported by the National Institute of Health that only 0.04% of people face the chance of developing this disease (Henly, 2013). Since this particular cancer is so rare, there are many uncertainties with diagnosis and treatment. This leaves patients in a more hopeless position than what other cancer patients already experience. In this research review, we will delve further into the aspects of how meso cancer negatively and positively affects the psychological state of those who are diagnosed.

It is crucial this is further looked into because not only is this particular cancer sporadic, but cancer, in general, also leaves a lasting impact on those who are diagnosed. Around 25% of cancer patients develop depression, contrasting to the 7% of the general population with depression (Depression). Death by suicide following the diagnosis of cancer is also one of the most harrowing and horrific paths some patients take, being that the rate is 28.58 per 100,000 persons (Zaorsky & Zhang, 2019). Meso just so happens to be one of the cancers with the highest rate of suicide amongst the hundreds of other cancer types. Moreover, the typical psychological distress cancer patients also experience include anxiety,

existential concerns, and posttraumatic stress. All of these factors contribute to the many negative effects this particular cancer leaves people with.

Past Review

There hasn't been much discussion pertaining to what meso brings upon one's life psychologically, however, there has been some scoping review conducted. The current state of evidence on the psychological effects of meso on patients and their lives was examined. This helps to identify any areas for further research and to generally assess the available evidence. The main question of this review was: what is the current state of the evidence on the psychological effects meso patients have and their careers? The population was 'patients and carers', the intervention being 'meso' (all disease types covered), and the outcome as 'psychological effects' (positive and negative). Any potentially relevant articles identified from a reference list of retrieved articles from Google Scholar were included, however, grey attempts and ongoing, unpublished research in this area were not. The reason is that those would limit comprehensiveness. The review was conducted using the staged method described by Arksey and O'Malley and Levac et al. Overall, this was all conducted by a single reviewer (VS), with the articles deemed fit for further study (Sherborne & Seymour, 2020).

VS extracted data from articles for qualitative and quantitative articles. These included citation, location, research objectives, participant details, recruitment and sampling methods, data collection and analysis methods, relevant findings and results, authors' conclusions, and possible new relevant articles from references. For results and to find relevance to the research question, each article's abstract and results section were reviewed. A quality appraisal process was followed, aiming to give an overview of the quality of the existing literature as a whole. The results included a descriptive numerical summary and qualitative analysis of the key relevant findings.

All of the articles provided sufficient evidence as to how meso was being approached and what was being studied. The qualitative studies were conducted around the world, four in the UK, one in Australia, two in Italy, two in Japan, and three in the USA. Nine of the articles aimed to explore the subjective experience of meso, and to identify the care and support needs. The other two explored the psychological issues around risk awareness. The age range of the participants was 5 to 112, although meso is incredibly rare in kids. The studies were situated in large teaching hospitals. These qualitative studies excluded anybody deemed unfit for the process, and who might experience distress. The researchers found that the majority of cases were men who had been exposed occupationally, however, the Italian article had a higher proportion of females. Considering the psychological distress, it was found that 49 meso patients were suing their employer, aiming to investigate the stress and depression symptoms of men with their disease. Some themes of the psychological stress in turn of meso cancer were also

uncovered through the articles used for the review. The themes were the passing of time and dealing with difficult feelings. Passing time is one of the larger and more impactful themes because there is much uncertainty with the whole process of this cancer in general. Reviewers found that delays in their medical journey because of the rarity added to the stress they already had. One patient revealed, “It’s like living as rats in a hole.” Dealing with difficult feelings is also a significant theme. Reviewers and articles reviewed that much anger came from a lack of control over the situation and hopelessness.

Anxiety and Uncertainty

With meso, also comes numerous complex feelings of uncertainty and anxiety. The entirety of these emotions is hard to sift through, especially as a meso patient. Unfortunately, this cancer in particular has plenty of instances where outcomes remain inadequate and hardly have any breakthroughs in treatments. This without a doubt would leave patients feeling hopeless. In fact, the National Cancer Institute reported that around 58% of anxiety disorders start after the diagnosis of cancer (Arch, 2020). On top of just a cancer diagnosis alone, the unfamiliar and unsteady progress being made in meso cancer surely leaves these specific patients in a much more grave situation. The American Psychological Association also states that two in three adults (68%) say the current uncertainty they face in their daily lives causes them stress (APA Org, 2020). This correlates to how uncertainty alone already plays a big role in stress and anxiety, and as a meso patient, everything is even more intense. Furthermore, the management of meso is also a complex thing to deal with. The Wiley Library reported a patient saying, “We filled all the forms in…and we have not received anything yet. […] I'm still waiting for some crazy doctor to come to disprove what the hospital proved. And that's my worry, that's my biggest worry” (Sherbourne & Seymour, 2020). This quote proves how meso patients are being further strayed away from any semblance of hope. Ultimately, this shows how much uncertainty these cancer patients must face daily, adding to the list of the already long psychological stresses they endure.

Hopelessness and Loss

A considerably big theme common in many meso patients is hopelessness and loss. Whether it’s loss of time, loss of happiness, or just loss in general, these patients are no strangers to the feeling as they battle cancer. Even so, some patients have turned to taking their own lives, or have at least been filled with thoughts of it. The Wiley Library has conducted research and published, “The initial phase of the illness is critical in terms of suicidality. ‘Henson et al37 showed that when considering variation in suicide risk by years since diagnosis, out of all cancer types meso patients had the highest risk of suicide in the first 6 months, with an 8.61-fold risk compared with the general population’. Hopelessness was identified as a result of negative messages from healthcare professionals by Ball et al6 and Girgis et al.33”

(Sherbourne & Seymour, 2020). This goes to show how much meso patients lose, not only physically, but within themselves. The suicide rates have also been compared among those who have lung cancer, which also happens to have one of the highest rates. Loss also continues to play a big factor in the psychological distress these patients face, because they lose the familiarity of their everyday lives. Careers, home life, relationships, and almost every aspect of a person's life are dramatically altered once you have cancer, especially meso cancer. The symptoms and treatments dramatically reshape a person's ability to carry out normal tasks, and many found that their relationships with family, friends, and even caretakers turned for the worse. The Wiley LIbrary stated in their research article regarding meso, "The first was patients' frustration at not being able to do ordinary activities, with carers also feeling helpless or angry about changes in the patients, such as their sense of identity, willingness to live a normal life, or their irritability.15, 39 Second, complex medico-legal matters led, for some, to feelings of anger and betrayal towards employers. For others, conflicted loyalty towards former employers meant anger was redirected towards families or doctors.6, 12, 39" (Sherbourne & Seymour, 2020). This quote certainly highlights the way meso diminishes hope within a patient, either if they are battling the treatments, or trying to lead a normal life outside their diagnosis. Overall, these instances all demonstrate the multitude of ways a meso patient experiences hopelessness and loss throughout their battle with cancer.

Depression

It is no surprise that depression makes it on the very extensive list of emotional distresses meso patients typically face. Depression comes in all forms of either having low self-esteem, hopelessness, feeling irritability or intolerant of others, loneliness, feeling guilt-ridden, and much more (Depression). The loneliness as listed is also intensified to a much higher degree for meso patients due to its rarity. One patient stated, "I wanted to talk to people, but they were [not] going through the same thing. And there was no one there for me" (Sherbourne & Seymour, 2020) This really highlights one of many difficulties that come with this cancer, loneliness. Feeling irritable with others has also been something meso patients deal with, which would check off yet another box for depression. Many patients on multiple accounts have said they have been irritated with their carers, whether it be at hospitals or their family members. The whole setting of having cancer, and being in the hospital knowing their chances are low heightened their irritability. The Wiley Library published, "Second, complex medico-legal matters led, for some, to feelings of anger and betrayal towards employers. For others, conflicted loyalty towards former employers meant anger was redirected towards families or doctors.6, 12, 39" (Sherbourne & Seymour, 2020). Another quote from a family member of a meso patient states, "He gets very frustrated and irritable [and] then he cries because he wants to be doing things. […] it's very hard, I feel like a punch bag. There is a lot of anger, and it's not my fault" (Sherbourne & Seymour, 2020). These two quotes

emphasize much of the pain and suffering these patients endure, which ultimately leads to depression, which is quite common in cancer patients, being recorded by the American Cancer Society that 1 in 4 cancer patients have been diagnosed with depression. Depression is truly a difficult thing to deal with, which has become the harsh reality that lies in many meso patients.

Perseverance

This research paper did cover many of the negative emotions that come in the wake of a meso diagnosis, however, there certainly still are patients who have a positive outlook and persevere through rough times. Cancer as a whole is surely a very intimidating disease, making meso cancer no less friendly. With that comes a lot of fear and anxiety, however, some meso patients have proven that there can still be optimism as the sickness plays out. The Wiley Library found that many meso patients they interviewed shockingly displayed a much more buoyant perspective of things, adverse to the other attitudes they received and were much more familiar with. One patient even remarked, “I ain't going away without a fight!” (Sherbourne & Seymour, 2020), and another one said, “I'm not just going to carry on. I'm going to crack on. Well what we are going to do is to enjoy each day” (Sherbourne & Seymour, 2020). This is a lovely take on things and lightens up the mood on what previous psychological effects have been explored. The positivity doesn't just stop there because another meso patient even said, “I hope I've walked well in my life, to have spent it well and that's it. If [the treatments] will go well, I am really happy, because I still have some ambitions to realize. If it will go bad, it does not matter” (Sherbourne & Seymour, 2020). This patient understands the rarity and complicity of this cancer, but still radiated cheerfulness and showed perseverance. With many negative feelings being associated with meso patients, it may appear like all hope is diminished, but there are still some patients out there who put on a brave face and show their perseverance.

Conclusion

Overall, the multitude of these reasons all factor into the emotional distress meso patients endure as they battle mesothelioma cancer. This research paper has uncovered that meso patients grapple with feelings like hopelessness, depression, anxiety, loss, uncertainty, and perseverance. Whether it be from the high-stress environment bearing down on them as they have to face multiple treatments that lead nowhere or having to be repeatedly told by doctors there’s no cure. However, other patients have taken on a more positive and resistant nature, showing that even with little chances, there is still hope. This topic shows the crucial urgency that must be taken in further studying this area because the mental health of cancer patients is very important. No matter what it may be, this wide range of emotions is the most prevalent and is bound to show up sometime in the psychological state of mesothelioma patients.

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Review Article

Cytokine Drug-producing Beads: A Promising Therapeutic Approach for Mesothelioma

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Abstract:

This review explores the potential of cytokine drug-producing beads as a treatment for mesothelioma, a cancer affecting the mesothelium, and caused by asbestos exposure. Cytokine drug-producing beads are microscopic "drug factories" implanted near tumors to deliver high doses of interleukin-2 (IL-2), which stimulates white blood cells to fight cancer. While studies in mice have yielded promising results, the effectiveness and practicality of cytokine drug-producing beads in real-life scenarios require further investigation. The article provides an overview of cytokines, particularly IL-2, and their role in immune modulation and cancer treatment. It also discusses the potential of microencapsulation as a cytokine delivery system for cancer treatment. The review emphasizes the need for additional research to fully assess the potential and applicability of cytokine drug-producing beads in mesothelioma treatment.

Introduction:

Mesothelioma

Mesothelioma is a form of cancer that targets the mesothelium, the thin layer of protective tissue that covers the outer surface of many internal organs such as the heart, abdomen, and lungs. Depending on which region of the mesothelium is involved, there are several forms of mesothelioma. The lining of the chest (pleura) is affected by pleural mesothelioma, the lining of the abdomen (peritoneum) is the site of

peritoneal mesothelioma's onset, and the lining of the heart (pericardium) is the site of pericardial mesothelioma's primary growth.[1]

Asbestos exposure is the most frequent cause of mesothelioma. The fibers that makeup asbestos are soft and pliable yet resistant to heat, fire, and many chemicals. A recent study found that the fibers that have been inhaled become stuck in the bottom part of the lung, where they cause an inflammatory reaction.[2]

When the fibers are phagocytosed by mesothelial cells, an oncogenic cascade is triggered that involves the activation of the oncogenes c-Myc and c-Jun, interaction with the EGFRs, and the stimulation of antiapoptotic genes such as Bcl-xl.[3] Another study suggested that radiation treatment is a potential contributor to mesothelioma. They identified 40,576 testicular cancer 1-year survivors among 14 population-based tumor registries in Europe and North America (1943-2001) and collected information on any new incident solid tumors among these individuals. Poisson regression analysis was employed to estimate the relative risks (RRs) and excess absolute risks (EARs) of second solid tumors. Of the 40,000 individuals with testicular cancer who had radiation therapy between 1973 and 2001, 10 developed mesotheliomas without any visible asbestos exposure. [4] Additionally, according to a study encompassing the application of multi-wall carbon nanotubes intraperitoneally, they are also responsible for engendering mesothelioma. Here, they demonstrate that intraperitoneally injected MWCNT causes mesothelioma in p53 heterozygous mice known to be susceptible to asbestos, together with crocidolite (blue asbestos), a positive control. The findings suggest that carbon-made fibrous or rod-shaped micrometer particles can share the asbestos-related carcinogenic processes.[5]

Cytokine drug-producing beads

In the case of early-stage cancer, surgery, and radiation therapy are potentially effective treatment options. However, some patients may not be suitable candidates for extensive surgical procedures due to their overall health condition, while others may already have advanced disease at diagnosis. Despite the possibility of cancer recurrence, conventional treatment typically involves chemotherapy utilizing drugs such as cisplatin and pemetrexed. Unfortunately, the effectiveness of second-line treatments is limited.[6] One innovation for chemotherapeutic treatments involves utilizing drug-producing beads loaded with high doses of interleukin-2 (IL-2) - a cytokine that stimulates white blood cells to combat cancer.[7]

Beads are frequently employed as drug delivery systems for passive and active medication targeting. In addition to chromatography, polysaccharide beads have created formulations for sustained-release

medicines. These formulations call for the beads to be water-soluble or dispersible. This approach does not include cross-linking. Therefore, the beads are water soluble and acceptable for use as a drug carrier. Drug-producing beads are the products of drug-factory technology.[8] A recent mouse study demonstrates that tiny "drug factories" implanted close to abdominal tumors can be used to treat cancer. In mice models of colorectal and ovarian cancer, tumors were removed by the drug factories, which create the immune-stimulating chemical interleukin-2 (IL-2). [9]

Still, whether cytokine drug-producing beads are effective and practical in real-life settings is a debate, due to their current stage as trials. For instance, researchers from Rice University and Baylor College of Medicine have demonstrated that combining Rice's cytokine "drug factory" implants and a checkpoint inhibitor medication may completely destroy advanced-stage mesothelioma tumors in mice in only a few days. Alginate beads filled with tens of thousands of genetically modified cells that can naturally create IL-2, one of two cytokines that the FDA has approved for cancer treatment, make up the cytokine factories. In the mesothelioma research, the beads were positioned next to tumors and inside the pleura, a thin layer of tissue that borders the chest's internal wall and protects the lungs.[10] However, experimental mice only achieve most success inside a laboratory. Therefore, factors such as theoretical effects on mesothelioma, versatility, and current costs need to be taken into consideration to evaluate its true potential and applicability.

Cytokine and Interleukin-2: An overview

Cytokine

Cytokines are compact proteins that modulate the immune system, originating from numerous cells and acting upon both their source and other target cells. These molecules are soluble in nature and pleiotropic in their biological functions, meaning a solitary cytokine has the ability to influence various types of cells, or alternatively, diverse cell types can release identical cytokines. Cytokines are a class of signaling molecules that have diverse functions and can act on the cell that produces them (autocrine action), nearby cells (paracrine action), or distant cells (endocrine action). Cytokines are produced in cascades, with one cytokine influencing the release of others, and they can work both antagonistically and synergistically. Each cytokine has a specific cell receptor, and it can either upregulate or downregulate the activity of genes. Cytokines are highly diverse and can be classified into different families based on their structure and function, such as the four-α-helix bundle family, cysteine knot family, IL-1 family, and IL-17 family. The functional classification of cytokines divides them into two types: Type 1, which

includes TNFα, IFN-γ, and others that enhance cellular immune responses, and Type 2, which includes IL-4, IL-10, TGF-β, IL-13, and others that enhance antibody responses.[11]

Cytokines are majorly produced by helper T cells and macrophages. They play a crucial role in nearly every biological process, including embryonic development, disease pathogenesis, non-specific response to infection, specific response to antigen, changes in cognitive functions, progression of the degenerative processes of aging, stem cell differentiation, vaccine efficacy, and allograft rejection. Cytokines such as IL-6 and TNF-α are involved in the upregulation of inflammatory reactions, while monocytes and macrophages release IL-1β at the time of inflammation, injury, invasion, and infection. The chemokines activate and migrate leukocytes and are also released during demyelinating and neuroinflammatory diseases. Various cytokines can also modulate the activity of neurons in the central and peripheral nervous systems. However, cytokine biology poses a conundrum for immunologists, as the innate response required for host survival can also be causative in disease. For instance, interferon-γ (IFNγ), essential for defense against intracellular microorganisms such as Mycobacterium tuberculosis, is a major cytokine involved in the pathogenesis of several autoimmune diseases.[12]

However, the release of an overwhelmingly large amount of cytokines in the body, specifically the blood, can be detrimental. This immune reaction is called a cytokine storm. Complex regulatory mechanisms usually maintain a delicate balance between pro- and anti-inflammatory effects. However, disruptions to this equilibrium can trigger complicated chain reactions that cause a massive release of cytokines. This can lead to elevated body temperature, inflammation (indicated by redness and swelling), intense exhaustion, and nausea. In severe cases, a cytokine storm may occur, posing a life-threatening risk and potentially causing the failure of multiple organs. This condition is also known as hypercytokinemia. The disturbances can be initiated not only by pathogens, but also by congenital diseases or immunomodulatory therapies. For instance, according to a recent article investigating cytokine storm in COVID-19, the syndrome has gained significant attention in the context of the novel Coronavirus disease 2019 as patients affected by the virus exhibit elevated levels of several crucial pro-inflammatory cytokines, including IL-1, IL-2, IL-6, TNF-α, IFN-γ, IP-10, GM-CSF, MCP-1, and IL-10. However, due to the intricate and diverse interactions within the innate and adaptive immune systems, our understanding of this critical clinical syndrome remains incomplete, and effective therapeutic approaches are still limited.[13]

Interleukin-2 (IL-2)

IL-2, also called T-cell growth factor (TCGF), was the first human interleukin to be fully identified, characterized, and purified. T helper (CD4+) lymphocytes are the primary producers of this cytokine, which stimulates cell-mediated immune responses, regulates the growth and differentiation of B lymphocytes, and enhances the proliferation and activity of all cytotoxic cell clones. IL-2 is a growth factor in vitro and a mediator of self-tolerance in vivo, making it an area of interest for researchers investigating tumor immunotherapy. The mature protein secreted contains 133 amino acids, with a calculated molecular weight of 15,420. Since the discovery of IL-2 and its ability to promote T-cell growth, extensive research has revealed the complex nature of its immunological effects, both in vitro and in vivo. The encouraging in vitro results of its immunopotentiating activities, coupled with successful preclinical studies demonstrating its therapeutic potential for animal tumors, have prompted investigations into the use of IL-2 in patients with advanced malignancy and immunodeficiencies. Interestingly, the IL-2 receptor has an unusual structure consisting of two chains, alpha (p75) and beta (p55), which is unexpected. [14]

Interleukin-2 (IL-2) discovery revolutionized our molecular understanding of how the immune system is regulated. IL-2 is a pleiotropic cytokine, and understanding the signaling pathways that allow IL-2 to control the differentiation and homeostasis of both pro- and anti-inflammatory T cells is crucial to unraveling the molecular mechanisms of immune regulation. The IL-2 receptor activates the STAT5 transcription factors by coupling to JAK tyrosine kinases. Beyond controlling transcriptional programs, IL-2 also plays a vital role in regulating T-cell metabolic programs. The use of global phosphoproteomic techniques has further expanded our understanding of IL-2 signaling, revealing the diverse array of phosphoproteins that may be influenced by IL-2 in T cells.[15] Furthermore, Interleukin-2 is a cytokine that plays a crucial role in directing T-cell expansion and phenotypic development, and recent research suggests that it also has a vital role in wound healing. While Interleukin-2's best-studied function influences T-cell development, other cell types, such as fibroblasts responsible for closing wounds, also express the Interleukin-2 receptor and may respond to Interleukin-2.[16] Studies have demonstrated that treatment with Interleukin-2 can enhance the strength of healed skin, suggesting that Interleukin-2 is involved in the wound-healing process. Moreover, diseases that impair wound healing, such as diabetes and systemic lupus erythematosus, have been associated with deficiencies in Interleukin-2 or defects in Interleukin-2 receptor signaling.[17]

In multiple studies, the administration of interleukin-2 (IL-2) has shown some effects on malignant pleural mesothelioma (MPM) tumor regression. For instance, an article published on November 24, 2009, reported that treatment with IL-2 resulted in a notable rise in immunological parameters, accompanied by a decrease in the vasculature, which sheds new light on the cancer mechanisms mediated by IL-2.

Furthermore, these findings indicate that tryptase-positive mast cells and Foxp3+ lymphocytes can predict clinical outcomes in patients receiving IL-2 treatment, emphasizing the crucial role of the inflammatory response in the progression of mesothelioma cancer.[18] IL-2 monotherapy is also a form of cancer immunotherapy. In 1985, a group of 25 patients with metastatic cancer who had undergone prior treatment was given increasingly high doses of IL-2, with the dose gradually increasing from 60,000-600,000 IU/kg until severe toxicity was reached. Out of the seven patients with metastatic melanoma and three patients with metastatic renal cancer, four and three, respectively, experienced a regression of metastatic tumor. This study was significant as it was the first to demonstrate that IL-2 could cause tumor regression in humans, and therefore was further explored in subsequent research on these two types of cancer. In a phase II trial, multiple cycles of HD IL-2 were administered to 255 patients with metastatic renal cell carcinoma at a dose of 600,000-720,000 IU/kg, with up to 15 bolus infusions given every 8 hours or as many as the patient could tolerate. This resulted in a complete response rate of 7% and an overall response rate of 15%. As a result, IL-2 was approved by the FDA for metastatic renal cell carcinoma in 1992 and later for metastatic melanoma in 1998.[19]

IL-2 has shown potential in treating metastatic cancers, but its use in the clinic is limited due to several drawbacks. One issue is that IL-2 has dual functional properties, affecting both Tregs and effector T cells, and has been used to enhance antitumor immune responses as well as dampen autoimmune responses. High-dose and low-dose IL-2 therapy can also increase levels of CD4+CD25+Foxp3+ Tregs, which have an immunosuppressive effect and can limit antitumor lymphocyte activity during therapy. Another drawback is the severe toxicities of high-dose IL-2 therapy, including vascular leak syndrome, pulmonary edema, hypotension, and heart toxicities. These toxicities may be caused by IL-2 binding to IL-2Rα-expressing endothelial cells, inducing acute vasodilation and vascular leak syndrome, and the induction of pro-inflammatory cytokines and other factors. Lastly, immunotherapy has the potential to elicit immune-mediated tumor lysis via activation of effector immune cells, but the clinical utility is limited due to pharmacokinetic challenges as well as vascular leak syndrome and other life-threatening toxicities experienced by patients.[20]

Microencapsulation: Advancements and Applications in Medicine and Beyond

Microencapsulation

Microencapsulation has demonstrated its utility as a delivery system across various commercial applications in numerous industries. The techniques to create these capsules vary from simple blending to intricate polymeric coating systems. It is challenging to enumerate all possible uses for encapsulation systems due to their extensive range; thus, according to chapter 9 of the Delivery System Handbook for Personal Care and Cosmetic Products: “The applications of microencapsulation are only limited to the creativity of the individual formulator, and the experience of the encapsulation scientist.”[21] This review primarily focuses on its applications in medicine and cancer, specifically mesothelioma.

A microcapsule is a spherical particle that typically ranges from 50 nm to 2 mm and contains a core substance. Microspheres, on the other hand, are spherical particles that are empty. However, the terms microcapsules and microspheres are often used interchangeably. Related terms such as "microbeads" and "beads" are also used interchangeably. "Sphere" and "spherical particles" describe larger and more rigid particles.[22] Various techniques are employed for microencapsulation, which can be divided into chemical, physiochemical, and electrostatic/mechanical processes. Chemical processes include interfacial and in situ polymerization. Physiochemical processes include coacervation-phase separation, complex emulsion, meltable dispersion, and powder bed methods. Mechanical processes include air suspension, pan coating, spray drying, spray congealing, micro-orifice systems, and rotary fluidization bed granulator methods. Spheronization is sometimes included in the mechanical process. Coacervation-phase separation involves three steps: the formation of three immiscible chemical phases, the deposition of coating, and the digitization of the coating. Interfacial polymerization involves polymerizing a monomer at the interface of two immiscible substances. Electrostatic methods involve aerosolizing the wall material and the material to be encapsulated with opposite charges. Mechanical methods involve using special equipment to produce microcapsules.[23]

Coating materials used for microencapsulation can vary depending on the specific dosage forms or product requirements. Inert polymers and pH-sensitive ones, like carboxylate and amino derivatives, are commonly used for microencapsulation in the gastrointestinal tract. The selection of appropriate coating material should take into account product objectives, requirements, and the microencapsulation method used. The polymer used should be capable of forming a cohesive film with the core material, be chemically compatible, non-reactive, and provide the desired coating properties such as strength, flexibility, impermeability, optical properties, and stability. Hydrophilic, hydrophobic, or a combination of both polymers can be used. Examples of successful coating materials include gelatin, polyvinyl alcohol, ethyl cellulose, cellulose acetate phthalate, and styrene-maleic anhydride. The core material, which is the

material over which coating is applied, can be in the form of solids, droplets of liquids, or dispersions, and can vary in composition to achieve desired properties.[24]

Cell Encapsulation

Cell microencapsulation is a technique that involves implanting allogeneic and xenogeneic cells in the host's body while keeping them isolated from the host's immune response using a semipermeable membrane. The technology dates back to the 1930s and has been used to deliver therapeutics for various conditions, including diabetes, central nervous system disorders, cancer, metabolic disorders, and anemia. The implantation site is selected based on the medical condition's needs, and many preclinical and clinical trials have been conducted to encapsulate pancreatic islets.[25] The encapsulation of islets has shown promising results in numerous trials, including insulin independence for up to 9 months in type 1 diabetic patient and stable insulin independence for seven patients following encapsulated islet transplantation. Other studies have demonstrated the long-term viability and functionality of encapsulated islets in diabetic patients and the successful transplantation of porcine islets with a bioartificial pancreas device in diabetic primates without immune suppression.[26]

Despite its potential, cell encapsulation technology has not yet produced a clinically licensed therapeutic product. One of the main reasons for this is the immune response elicited by both the implanted capsule and encapsulated cells. The polymer that protects the encapsulated cells is the first contact the host has with the capsule, followed by the cells themselves, which can induce immune responses through antigen shedding and secretion of immune mediators. In addition, transgenes expressed and secreted by the encapsulated cells may be recognized as foreign by the host, and the expression vector used to genetically engineer the cells may contain immunogenic sequences. The cumulative effect of these factors may exceed the additive effect of individual components.[27]

Alginate Beads: Biomaterial for Cytokine Factories and Targeted Cancer Therapy

Alginate Beads

Alginate, a biomaterial known for its biocompatibility and ease of gelation, has been extensively used in biomedical science and engineering. Alginate hydrogels, in particular, have been highly sought-after in wound healing, drug delivery, and tissue engineering applications. These hydrogels are structurally similar to the extracellular matrices in tissues and can be modified to serve various essential functions.[28]

Alginate is a naturally occurring anionic polymer that is typically extracted from brown seaweed. Due to its biocompatibility, low toxicity, relatively low cost, and ability to undergo mild gelation with divalent cations like Ca2+, it has been extensively studied and utilized for various biomedical applications. Alginate hydrogels can be prepared using different cross-linking methods and their structural similarity to extracellular matrices of living tissues makes them suitable for wound healing, delivery of bioactive agents, and cell transplantation.[29] Alginate wound dressings maintain a moist microenvironment, reduce bacterial infection, and facilitate wound healing. Controlled release of drugs, ranging from small molecules to macromolecular proteins, can be achieved from alginate gels depending on the cross-linker types and methods. Alginate gels can also be orally administered or injected into the body in a minimally invasive manner, making them widely used in the pharmaceutical industry. Furthermore, in tissue engineering, hydrogels are used to transport cells to the desired location, provide a space for new tissue formation, and regulate the structure and function of the engineered tissue. Alginate gels show promise in this application as well.[30]

Alginate beading, also known as alginate microencapsulation, is a technique used to encapsulate cells or other biological materials within tiny beads made from the natural polymer alginate. The process involves mixing the biological material with a solution of alginate, and then droplets of this mixture are added to a solution containing divalent ions, such as calcium. This causes the alginate to cross-link, forming a gel-like bead that traps the biological material inside.[31] The alginate bead mechanism works by providing a physical barrier that protects the encapsulated cells or biological material from the host's immune system. The alginate bead is permeable to nutrients, oxygen, and waste products, allowing the encapsulated cells to perform their normal functions. At the same time, the alginate bead prevents immune cells from entering and attacking the encapsulated cells. However, the alginate bead is not completely impermeable, so small molecules and signaling molecules can still pass through, allowing the encapsulated cells to communicate with the surrounding tissue and receive necessary signals. Alginate bead technology is a versatile and unique biomaterial that has been utilized in a variety of fields.[32] It has several applications, including cell transplantation for the treatment of diabetes or tissue regeneration, drug delivery for the controlled release of drugs, food industry for encapsulating flavors, colors, or nutrients, creating edible coatings for fruits and vegetables, bioreactors for producing enzymes or antibodies, and environmental applications for immobilizing microorganisms for bioremediation of pollutants or creating biosensors for detecting environmental toxins. Ongoing research is being conducted to explore new potential uses of alginate bead technology, making it an exciting area of study in the field of biomaterials.[33]

Cytokine factories and RPE-mIL2

Researchers have developed "drug factories" that can be implanted near tumors in the abdominal cavity to fight cancer. The drug factories are pinhead-sized beads, each containing around 20,000 to 30,000 in a protective gel-like alginate material. The cells are engineered to produce the natural form of IL-2, which is released gradually through the porous structure of the beads. When implanted in the peritoneal cavity of mice, the beads eradicated tumors in 20 of 20 animals in a mouse model of advanced ovarian cancer and 7 of 8 animals in a mouse model of aggressive colorectal cancer. The beads were also found to recruit tumor-targeting immune cells called killer T cells, which increased the numbers of other immune cells, including natural killer cells, that work hand in hand to destroy cancer cells. The team also found that implanting the IL-2–producing beads in the peritoneal cavity not only eliminated the original tumor but also prevented new tumors of the same type from forming elsewhere in the body, suggesting that the beads could potentially also stop cancers from spreading. The drug factory technology is versatile and can be leveraged to produce other cytokines that have shown clinical benefits against cancer. These factories are also small, measuring only 1.5 millimeters in width, and can be implanted with minimally invasive surgery to deliver high doses of IL-2 directly to tumors.[34]

This particular therapy is deemed to have high potential for combating mesothelioma. In a recent study, researchers from Rice University and the Baylor College of Medicine demonstrated the implants' impressive effectiveness in mice diagnosed with mesothelioma, raising hopes of a possible breakthrough for this tough-to-treat cancer.[35] The team has recently created a novel approach to immunotherapy using cell-based localized delivery of IL2 through immunostimulatory alginate-based microparticles (or alginate beads) named RPE-mIL2 cytokine factories. This innovative strategy allows them to administer high levels of IL2 to a specific area while minimizing systemic exposure, thus reducing the risk of toxicity. First of all, the researchers developed a delivery system for proinflammatory cytokines that involved the manipulation of human retinal pigmented epithelial (RPE) cells to express a specific cytokine via the PiggyBac transposon system. The choice of RPE cells was based on their non-tumorigenic characteristics, contact inhibition, genetic modifiability, and previous use in human trials. They could easily create prototypes by interchanging the gene sequence while keeping the optimized backbone. To encapsulate the engineered cells, they employed alginate-based microparticles produced using a coaxial needle and cross-linking bath. The results indicated that the encapsulated cells were viable, produced the desired cytokine, did not divide within the capsules, and persisted longer in vivo than unencapsulated cells. These findings suggested that the encapsulation was well-tolerated by the cells. The resulting cytokine factories were then RPE-mIL2 based on the cytokine they expressed. The same goes for RPE-mIL7, RPE-mIL10, RPE-mIL12, or RPE-hIL2.[36]

The mice study used Sprague Dawley rats, which were anesthetized and received a total transfer volume of 300 μL of capsules directly into the pleural cavity via Pasteur pipette. They were then monitored for toxicity and underwent histology analysis. Sample size was predetermined to obtain statistically significant data, and statistical analyses were conducted using GraphPad Prism 9. One-way ANOVA tests with the Holm-Sidak multiple comparisons method were used to determine P values for CyTOF datasets and toxicity assays. Replicates were reproducible, and data were taken from distinct samples unless otherwise indicated. The study demonstrated that mice treated with RPE-mIL2 monotherapy exhibited a significant eradication of tumor burden. This was attributed to the modulation of both innate and adaptive immune populations, which also conferred protection against tumor recurrence. Notably, the researchers' approach achieved immune activation while minimizing prolonged toxicity in both the peritoneal and pleural cavities. While previous studies have established the efficacy of IL2, this cytokine factory is the first to require minimal access to the target site, addressing current clinical issues related to catheter infection and adverse events. As malignant mesothelioma continues to pose a challenge, the findings suggest that their approach holds promise as an effective treatment option that warrants clinical assessment.[37]

Although the cytokine factory approach has potential, its relatively large size compared to recombinant IL2 cytokines limits its non-invasive administration. However, patients receiving treatment for malignant mesothelioma often require chest catheter placement for pleural effusion drainage, which can also be used to administer RPE-IL2 without significantly increasing recovery time. Additionally, local IL2 delivery has been shown to reduce malignant pleural effusions in 81% of patients, resulting in a reduced need for fluid drainage during treatment and an improvement in patient quality of life.[38]

Conclusion:

In conclusion, the use of cytokine drug-producing beads as a potential treatment for mesothelioma shows promise, but requires further evaluation and research. These beads deliver high doses of immune-stimulating cytokines directly to the tumor site, offering a novel approach to treating this challenging cancer. However, the use of cytokines in cancer therapy is limited by their dual functional properties and the severe toxicities associated with high doses. The safety and efficacy of cytokine drug-producing beads must be carefully evaluated, taking into consideration factors such as their theoretical effects on mesothelioma, versatility, and current costs. With continued investigation and

development, cytokine drug-producing beads may become a valuable addition to the therapeutic options available for mesothelioma and potentially other cancers.

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Mesotheliomas Prognosis And Associated Difficulties In Treatment

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Keywords: MM, HMGB1, RNS, ROS, phagocytosis, macrophages, EPP, P/D

Abstract:

In this paper, I am focusing on mesothelioma development from when asbestos fibers are consumed to the first diagnosis. More specifically, this literature review emphasizes how mesothelioma prognosis contributes to difficulties regarding treatment. Mesothelioma has made a reputation for itself by being infamously aggressive and invasive. As of now there are few methods of treatment aside from chemotherapy, radiotherapy and surgery, each of which come with their own set of difficulties and fatality rates. For years, when receiving a diagnosis few were given alternatives that could possibly improve life expectancy, however there have been recent advancements in mesothelioma research giving both scientists and patients a hopeful outlook on the future.

Introduction:

Cancer, a complex and serious disease, is an affliction that has affected living organisms for generations, its victims ranging from animals to human beings. There are various types, each with their own unique causes and characteristics. Mesothelioma is a deadly and aggressive form of cancer that develops in the thin layer of tissue lining the internal organs. This layer of tissue is referred to as the mesothelium and is most prevalent on the surface of all coelomic organs, such as the lungs, heart, and digestive tract. There are approximately 3000 new cases of mesothelioma each year in the United States, although the number of cases has been declining since the early 1990's. Advancements in cancer research and medical technology have led to improved understanding, early detection methods, and more effective treatments for those who have the condition. Regardless of this however, mesothelioma has gained a reputation of being both aggressive and extraordinarily difficult to treat. Understanding the pathogenesis of cancers such as mesothelioma can reveal the truth behind why so many treatments fail to impede the disease.

Underlying Causes of Mesothelioma

As mentioned previously, the most prevalent risk factor for mesothelioma are asbestos fibers, a material now recognized as carcinogenic due to toxicology studies in vitro and in vivo. The term "asbestos" is a name given to a group of naturally occurring fibrous materials most often found in automotive brakes, insulation, and fireproofing substances. When commercial products containing

asbestos fibers are disturbed, their fibers are released and when inhaled by humans can be trapped within the lungs and remain for a long period of time. Low levels of asbestos fibers are present in water, soil and the air we breathe. However, most people do not get sick from this type of exposure. Rather it is continuous contact with the material that can result in a cancer such as mesothelioma. There are 3 primary factors that affect the carcinogenic potency of asbestos fibers aside from the specific type of mineral being consumed: dimensions, durability and dose. Fiber dimensions consequently affect both durability and dose as it influences asbestos fibers bioavailability within the body. Long and thin fibers are associated with greater cytotoxicity and mutagenesis as a meta-analysis discovered that individuals exposed to fibers longer than 10-20 μm have a significantly higher risk for asbestos related diseases. This is believed to be because macrophages cannot efficiently clear the fibers due to their length, leading to repeated failed attempts of phagocytosis. This causes the inflammatory cells surrounding the fibers to release free radicals, for example reactive nitrogen species (RNS) and reactive oxygen series (ROS), in turn exerting activity on surrounding cells that are capable of inducing genetic mutations. Asbestos fibers commonly result in the death of human mesothelial cells, however those that don't die often undergo transformation.

Biological Processes In Mesothelioma Development

Efforts are being undertaken by researchers to further elucidate the biological processes that contribute to the transformation mesothelial cells undergo during the pathogenesis of mesothelioma. As a result of these efforts, it has been discovered that asbestos fibers induce cell transformation via HMGB1-driven autophagy. HMGB1 is an acronym standing for high-mobility group box 1 and is a proinflammatory molecule found to be involved in the carcinogenesis of asbestos fibers. In healthy cells, the protein binds to DNA where it works as an architectural chromatin-binding factor. It further maintains the function and structure of chromosomes while being an extracellular inflammatory cytokine. There are three main roles of HMGB-1 that have been proven to contribute to the tumorigenesis and development of malignant mesothelioma. For starters, experimental evidence from animal models and cell lines suggest that HMGB1 is an asbestos-induced effector. This was highlighted in a study conducted by Yang et al, who reported that crocidolite asbestos fibers prompted inflammation and programmed necrosis in the primary human mesothelial cells. It also resulted in HMGB1 translocating from the nucleus to the cytoplasm and was consequently released into a culture medium. Moreover, HMGB1 has been observed in the nucleus, cytoplasm and extracellular space of mesothelial and inflammatory cells around asbestos deposits. Sustained high levels of HMGB1 were caused by high dose, short-term injection protocols in crocidolite fiber-injected mice. In spite of these findings, the increase in HMGB1 caused by chrysotile was only temporary, declining to background levels after only 6-10 weeks, indicating that rises in HMGB1 levels are dependent on the type of asbestos fiber consumed. Regardless, the experimental evidence listed above suggests that secretion of the protein by mesothelial or inflammatory cells is

responsive to stimulation from asbestos fibers. Together the evidence points to the idea that HMGB1 may act as an asbestos-induced effector.

Further Analysis of Protein HMGB1's Role in Pathogenesis

Secondly, experiments have pointed to HMGB1 being an inflammatory mediator for malignant mesothelioma. Cellular inflammatory mediators in the tumor microenvironment are implicated in nearly all stages of cancer start, development, and metastasis. Chronic inflammation is also a well-recognized tumor-enabling state, thus HMGB1 plays a large role in mesothelioma pathogenesis. In addition, HMGB1 has been recognized as a mediator of inflammation in numerous conditions aside from mesothelioma, primarily other cancer and inflammatory disorders. As mentioned previously, the consumption of asbestos fibers leads to inflammation and programmed necrosis in human mesothelial cells. In reaction to injury and inflammation, HMGB1 then signals cellular destruction. Subsequently, HMGB1 prompts macrophages to secrete tumor necrosis factor-α (TNF-α, a proinflammatory cytokine) in response to asbestos exposure, protecting mesothelial cells from asbestos-induced cell death and inducing a persistent inflammatory response. While being protected from cell death however, mesothelium cells are likely prompted to undergo transformation instead. Finally, the protein HMGB1 may also act as an EMT (epithelial-to-mesenchymal transition) Inducer. EMT is a cellular process where many molecular features of epithelial cells are lost and instead replaced with typical mesenchymal characteristics, including loss of cell polarity and acquisition of migratory and invasive abilities. Cancer cells that have undergone EMT are more resistant to apoptosis, have increased invasiveness and are more aggressive. In addition to this, these cells also display stem-like features. EMT can also result in the production of proinflammatory factors, and research has indicated a link between cancer associated EMT and chronic inflammation. Aside from malignant mesothelioma, HMGB1 has been found to induce EMT in chronic inflammation-associated cancers, namely colorectal carcinoma, gastric cancer, and cervical carcinoma. \

Current Treatments And Their Effectiveness:

The factors mentioned above all contribute to mesothelioma pathology and progression, thus being the reason behind why MM (malignant mesothelioma) is so difficult to treat. MM typically does not grow as a single tumor mass and tends to spread to nearby surfaces, blood vessels and nerves. This in turn makes it difficult to completely rid someone of the cancer through surgery and/or radiation. Furthermore, it's often only diagnosed when it's within the advanced stages. A majority of treatments aim to control the mesothelioma and symptoms for as long as possible as opposed to completely curing it. To date, there are a limited number of treatments including chemotherapy, radiotherapy, surgery and a combined multimodal approach. Approximately 20% of patients are eligible for radical surgery and more than 85% of these patients die within 5 years. The remaining 80% of patients will not be eligible for a multimodal

approach and in such cases, chemotherapy remains as the typical approach. The role of surgery for malignant pleural mesothelioma is controversial as no randomized clinical trial has established whether this approach leads to an improvement in survival. Furthermore, there are two types of surgeries for mesothelioma that are associated with substantial morbidity and mortality rates, referred to as invasive extrapleural pneumonectomy (EPP), and to a lesser extent pleurectomy/decortication (P/D). It is important to note that in spite of these findings, better outcomes have been observed if surgeries are conducted by centers with adequate experience. Additionally, anticipated results of the EPP and P/D surgeries are always uncertain as there is no data from randomized trials comparing these two procedures. For those who have unresectable and for those in which surgery is not feasible due to underlying conditions, chemotherapy and symptomatic treatment represent the gold standard.

Chemotherapy's Potential Outlook

Since the 1980s, a number of phase II studies have examined the effectiveness of single-agent CT (chemotherapy) in treating mesothelioma patients using anthracyclines, taxanes, platinum compounds, alkylating agents, and topoisomerase inhibitors; nevertheless, these studies have revealed modest response rates, ranging from 0% to 13%. Furthermore, Muers et al. conducted a randomized trial to assess the effect of first-line CT on survival to active symptom management alone. 409 MPM (malignant pleural mesothelioma) patients were randomly assigned to symptomatic treatment, symptomatic treatment plus CT including cisplatin, vinblastine, and mitomycin, or symptomatic treatment plus single-agent vinorelbine in this study, which is the only one where CT has been directly compared with no active anti-cancer treatment. Only the vinorelbine group showed a trend toward a better result when compared to symptom control alone, according to the authors. The most common treatment plan for patients with unresectable MPM to date is the combination of CT with cisplatin and pemetrexed. The effectiveness of this treatment plan was first evaluated in a phase I trial including 11 patients who received increasing dosages of both cisplatin and pemetrexed. The trial's findings demonstrated that the combination was both tolerable and effective, as five (45%) of the 11 patients exhibited signs of partial response. While the results did show some semblance of promise, it also demonstrates the difficulty in treating malignant pleural mesothelioma patients. Compared to many other types of cancer, mesothelioma is considered to be very aggressive, and experts prefer to say that current treatments are useful for managing the cancer rather than purely treating it.

Innovations In Treatment

However, in spite of this depressing outlook, there are numerous up and coming treatments for mesothelioma that are being researched and developed by scientists. Such treatments include gene therapy, immunotherapy, photodynamic therapy, and tumor treating fields. With gene therapy, researchers have had modest success increasing the potency of anti-cancer medications by introducing new genes to

cancer cells. One of the biggest obstacles, however, is getting the new gene into the DNA of the cancer cells. Gene therapy currently has a low transfer rate, but if researchers can solve this issue, it might be curative. Immunotherapy on the other hand. this has been in use for a while and is beginning to show potential in research labs. Cancer vaccine immunotherapy for mesothelioma could activate the body's immune system to combat cancer cells. Biologic medications that improve immune system performance are also being developed by researchers. Many clinical trials are being conducted on immunotherapy medications, which are one of the most interesting new mesothelioma treatments. How to identify individuals who will respond to particular immunotherapy medications is one of the topics that researchers are looking at. Photodynamic therapy involves injecting a drug that travels throughout the body but accumulates the most heavily in cancer cells. A light-equipped tube is introduced into the chest cavity a few days later to reach the tumor. The medicine is activated by the light, and it then kills the cancer cells. Compared to conventional chemotherapy, this treatment has less adverse effects since the medicine is not active until it is exposed to light. Chemotherapy employs active substances that can destroy both cancer cells and healthy cells. Additionally, since this treatment is targeted, oncologists are able to administer greater doses. Finally, tumor treating fields A light-equipped tube is introduced into the chest cavity a few days later to reach the tumor. The medicine is activated by the light, and it then kills the cancer cells. Compared to conventional chemotherapy, this treatment has less adverse effects since the medicine is not active until it is exposed to light. Chemotherapy employs active substances that can destroy both cancer cells and healthy cells. Additionally, since this treatment is targeted, oncologists are able to administer greater doses.

Conclusion

In conclusion, mesothelioma pathology and prognosis heavily contributes to difficulties regarding its treatment. There are numerous biological processes underlying the progression of mesothelioma, many of which involve the protein HMGB1. HGBM1 not only promotes inflammation and cellular transformation, but it induces epithelial-to-mesenchymal transition. The transition allows cells to adopt mesenchymal characteristics and in turn have increased migratory and invasive abilities. This makes mesothelioma notoriously aggressive and allows it to spread throughout the body from where it began to nearby blood vessels and nerves. Once a cancer breaches someone's nerve, it can secrete neuroactive molecules that act on tumor cells. However rather than help, it often leads to neuropathic cancer pain as the reactions result in neural damage. In other words, the physiological development of mesothelioma not only contributes to how difficult it is to treat, but the pain that more often than not accompanies it. However there are numerous studies attempting to rectify this difficulty, as scientists are researching different methods to prevent mesothelioma progression, whether it be through genetic or chemotherapeutic means.

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Literary Review

Mesothelioma: Ties to the Environment

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Keywords: Mesothelioma, Asbestos, Environment, Health

Abstract:

Mesothelioma, a rare and aggressive form of cancer, has long been recognized as a devastating disease affecting individuals exposed to asbestos. However, beyond its human toll, the environmental impact of mesothelioma remains an underexplored aspect that warrants closer investigation. Asbestos, the primary causative agent of mesothelioma, has been extensively used in various industries and has left a lasting legacy in our environment. This research piece aims to elucidate the multifaceted environmental implications associated with mesothelioma, shedding light on the ecological consequences of asbestos fibers, long-term impacts of Mesothelioma-related medical waste, and anti-apocalyptic solutions.

Introduction:

Mesothelioma is a malignant tumor that primarily affects the mesothelial lining of the lungs, heart, or abdomen. Its close association with asbestos exposure has been well-established, and the devastating health consequences for individuals have been extensively documented. However, the repercussions of mesothelioma extend beyond the human domain, permeating the environment in which we live and posing significant ecological challenges.

Impact of Asbestos:

Asbestos, a naturally occurring mineral, has been widely utilized for its exceptional strength, heat resistance, and insulating properties. Consequently, it found extensive application in various industries, such as construction, manufacturing, and shipbuilding throughout the 20th century. The release of asbestos fibers into the environment occurs through multiple pathways, including airborne dispersion during mining, manufacturing processes, and the deterioration of asbestos-containing materials over time. These microscopic fibers, lightweight and resilient, can travel great distances and persist in the environment for extended periods. Despite the known health hazards associated with asbestos, its use is widespread, resulting in substantial environmental contamination.

Medical Waste:

Alongside the dissemination of asbestos fibers throughout the Earth, medical waste associated with Mesothelioma has brought about a plague of environmental damage as well. The primary source of Mesothelioma waste is the various treatment procedures involved in managing and eliminating these macroscopic cancerous cells within the human body. Among these methods are chemotherapy, radiation, immunotherapy, and various pleurectomy procedures, or the surgical removal of mesothelioma cells. Inevitably, medical byproducts, such as radioactive chemical waste, single-use surgical devices, and cancerous cells are generated and disposed of.

Consequences:

While Mesothelioma studies have focused primarily on human health outcomes, the environmental consequences of asbestos contamination and mesothelioma treatment equate to those concerns. The toxic nature of asbestos fibers poses a threat to various ecological components, including air, water, soil, and wildlife. Inhalation of airborne fibers by animals can lead to adverse health effects, disrupting ecosystems and contributing to species decline. Additionally, the negative impact of Mesothelioma treatment products have breached the foundation of the environment, as demonstrated by waste-induced air, water, and soil pollution, natural chemical imbalances, as well as the distribution of lead, mercury, and cadmium into the ecosystem, each deadly in excess.

Conclusion:

In conclusion, the urgent need to investigate and understand the environmental impact of mesothelioma continually emphasizes its importance. Recognizing the interconnectedness of human health and the environment, we can develop informed policies, interventions, and monitoring systems to tackle the complex challenges posed by asbestos contamination and mitigate the long-term consequences of this environmental health hazard.

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Review Article

Mesothelioma and Construction Workers

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Keywords : Mesothelioma cancer, cancer, construction workers

Abstract :

Construction workers being exposed to asbestos fibers and eventually developing Mesothelioma cancer is a problem faced by construction workers all around the world. The purpose of this research is to spread awareness about these specific risks construction workers take on when they perform their duties, and how high of a chance of Mesothelioma these workers expose themselves to. Utilizing a study done on construction workers to see their opinions on what they thought were dangers that they could face on work. Then we gathered the actual data and compared it to their statements. The data from the study showed that exposure to asbestos fibers had the greatest Relative Significance Index (RSI) along with back injuries from lifting heavy items. . This means that it was one of the leading causes of fatalities/injuries to construction workers. The study confirms the dangers exposure to asbestos fibers poses to construction workers.

Introduction :

Mesothelioma is an aggressive form of cancer that develops on the linings around the heart, lungs, stomach, or testicles. Studies found that the only known way to contract Mesothelioma is through exposure to asbestos. The asbestos fibers get stuck in the lining of the chest or abdomen. Over long periods of time it develops into a tumor because the body cannot get rid of it. Mesothelioma most commonly develops around the lungs, known as pleural mesothelioma (Mayo Clinic, 2022, Overview). Due to the long time it usually takes for diagnosis, by the time it is diagnosed, it is already in an advanced state. For most people a cure isn't possible. (Mayo Clinic, 2022, Treatment). Usually doctors will want to make the patient as comfortable as possible and extend their lifetime. People who work jobs with exposure to asbestos have a significantly higher chance of contracting Mesothelioma cancer. Mesothelioma has a much higher chance to affect Construction workers. Usually construction workers are the ones exposed to asbestos the most. Unfortunately, in the 1900's the dangers were not known to scientists and many workers were forced to work without knowing the hidden dangers. Their occupation had forced them to expose themselves to asbestos fibers. Although the industry has adapted once this was

discovered Mesothelioma takes decades to show itself and develop. Many people who worked in the construction industry in the 1980's and 1990's still contract mesothelioma to this day. During the 1980s the Environmental Protection Agency (EPA) found that 733,000 asbestos-containing commercial and public buildings in the U.S. During the construction of these buildings, many workers could have possibly been exposed to asbestos. A Study in 2009 conducted by Italian scientists found that a large amount of Mesothelioma cases are linked to the construction industry (Strand, n.d, p.2). Of the 952 subjects diagnosed with Mesothelioma, 251 had worked in the construction industry. Another study done in North Carolina also found an elevated risk to cancer from working in the Construction Industry (Strand, n.d, p.2). Working in the construction industry often requires yourself to come into contact with asbestos fibers that could induce Mesothelioma in the worker. These studies show that you have a much higher chance of getting Mesothelioma as a construction worker than anything else. Mesothelioma can still be passed on through things like second hand exposure. The family members of the construction worker are still at risk.

The Research :

The construction industry is one of the largest in the world. It often employs a large percentage of a nation's population. The construction industry accounts for about 12% of the world's total GDP (2021 Construction Demand, 2021, p.1). When one thinks about the dangers in construction, heavy machines and horrific work accidents are probably what's expected. A new study really finds out the most dangerous work related harm in the construction industry. The research method used was a simple questionnaire with an oral interview of construction workers, clients, consultants (building professionals), and contractors on construction sites. This is being done to determine the factors that affect the health and safety on construction sites.

The research was conducted using the following equations :

The relative significance index ranking (RSI) was used for ranking of the factors studied. Bakhray gave an equation that could be useful for determining Relative Significance Index (RSI) in prevalence data as :

$$RSI = \frac{\sum \mu}{AN} \qquad \textbf{(1)}$$

Where μ is the weighting given to each factor by respondents;

A is the highest weight (i.e. 5 in this case);

N is the total number of respondents

But for this type of research work where a 5-point scale was used, the RSI shall be calculated via the equation: $RSI = \frac{5a + 4b + 3c + 2d + 1e}{jN} \ (0 < index < 1)$ **(2)**

Where: a = number of respondents "strongly agree",

b = number of respondents "agree"

c = number of respondents "less agree"

d = number of respondents "disagree"

e = number of respondents "strongly disagree"

N = sample size = 60

j = number of response categories = 5

For instance for item 7 on the original questionnaire, Poor planning and coordination, 9 respondents gave "strongly agree", 21 respondents gave "agree", 10 respondents gave "less agree", 9 respondents gave "disagree" and 11 respondents gave "strongly disagree". The relative significance index is given as :

$$RSI = \frac{(9*5) + (21*4) + (10\ x\ 3) + (9*2) + (11*1)}{(5*60)} = 0.627 \quad \textbf{(3)}$$

(Sharafadeen et al., 2018, p.58)

The Data/Results :

Data from the people partaking in the research has been compiled into tables by the writers for simplicity. It will be presented below :

Table : I

Factors that affect the health and safety performance on construction sites

Factor Description	1	2	3	4	5	Total	TWV	RSI	Rank
Administrative and Management commitment	3	4	6	17	30	60	247	0.823	1
Role of Government and Professional Bodies	4	3	12	21	20	60	230	0.767	3
Nature of project	4	5	7	34	10	60	221	0.737	6
Historic, human and psychological climate	6	7	16	19	12	60	204	0.680	13
Application of health and safety factors in organisation	5	4	8	15	28	60	237	0.790	2
Project location is safe to reach	6	7	9	20	18	60	217	0.723	8
Poor planning and co-ordination	11	9	10	21	9	60	188	0.627	17
Poor communication between sites	10	9	11	18	12	60	193	0.643	16
Reportable accidents rate in project	7	10	9	18	16	60	206	0.687	12
Assurance rate of project	5	12	14	20	9	60	196	0.653	15
Organisation structure	5	6	5	23	21	60	229	0.763	4
Safety inspections	7	8	3	18	24	60	224	0.747	5
Safety meetings	7	5	12	19	17	60	214	0.713	9
Safety records and reports	8	6	5	23	18	60	217	0.723	8
Incentives	9	7	10	23	11	60	200	0.667	14
Health and safety (H & S) education and training	5	8	11	14	22	60	220	0.733	7
Economic investment	7	6	13	19	15	60	209	0.697	11
Medical facilities	9	6	8	18	19	60	212	0.707	10

RSI=Relative Significance Index, TWV=Total Weight Value
Source: Field Survey, 2018

Table 1 showed the Relative Significance Index (RSI) of the level of factors that affect the health and safety performance on construction sites. It revealed that Administrative and Management commitment ranked first with RSI value of 0.823 (i.e. 82.3 percent significance), Application of health and safety factors in organization ranked second with RSI value of 0.79. Workers themselves rated health and safety as the second biggest factor to affect them. Although this doesn't directly state asbestos fibers, in the next tables we'll see which health/safety problem affects them the most.

Table 2

The fatal injuries among construction workers on construction sites

FATAL INJURIES	1	2	3	4	5	Total	TWV	RSI	Rank
Falls from a height	20	6	9	13	12	60	171	0.570	8
Involved in a vehicle accident	10	16	9	11	14	60	183	0.610	5
Contact with objects or equipment (Struck by an object or caught in machinery or material)	10	10	24	5	11	60	177	0.590	7
Exposure to harmful substances (Electrocution from contact with electrical wiring, overhead power lines or electrically powered machinery or hard tools)	15	16	9	11	9	60	163	0.543	9
Excavation accidents (Being buried during excavation work)	13	9	12	10	16	60	187	0.623	4
Being struck by falling materials	12	14	10	13	11	60	177	0.590	7
Breathing in asbestos fibres	6	9	16	16	13	60	201	0.670	1
Motor vehicle crashes	11	7	16	15	11	60	188	0.627	3
Suffering a bad back from handling heavy materials	7	13	10	12	18	60	201	0.670	1
Coming into contact with dangerous substances	11	14	14	6	15	60	180	0.600	6
Suffering hearing loss from loud noise	9	13	10	11	17	60	194	0.647	2

Table 2 revealed that breathing in asbestos fibers and suffering a bad back from handling heavy materials were ranked first with RSI value of 0.67 (i.e.67 percent significance), suffering hearing loss from loud noise ranked second with RSI value of 0.647 and motor vehicle crashes ranked third with RSI value of 0.627. While falls from height ranked last with RSI value of 0.57. The result also showed that all the factors are significant with the least factor having 57 (0.57) percent significance.

(Sharafadeen et al., 2018, p.58)

The data contained within the tables revealed that breathing in asbestos fibers and suffering from back pain handling heavy materials were both ranked #1 using the RSI indicator. Although the study was pretty limited as it only tested 60 individuals it still shows the hidden dangers asbestos fibers pose to construction workers.

Effect on the Industry :

Many have died in the building of civilizations. They put their life on the line to better all humanity. Recent studies will reveal how many of these deaths were due to asbestos fibers and mesothelioma. According to a European Commission's report done in 2022, 70,000 laborers died due to exposure to asbestos fibers in 2019 (Kazan-Allen, 2022, p.1). Whitmer claims that, “A 2018 study indicated that construction workers are more than three times more likely than those in most other occupations to die from mesothelioma” (Whitmer, 2023, p.3). The construction industry had accounted

for anywhere between 70% and 80% of asbestos consumption throughout the 1900s (Whitmer, 2023, p.3). Another study found that 70% of construction workers who have spent over 30 years in the industry have developed pleural abnormalities (problems in the lung). Jobs such as bricklayers/masons, drywall workers, painters, and roofers are one of the many occupations within the construction industry that expose themselves to the harmful asbestos fibers.

Support for Victims :

Luckily these dangers are becoming more well known and policies meant to decrease or totally eliminate these dangers are under way. Even if very slowly. In October 2021, the European Parliament voted for a new asbestos occupational exposure limit of 0.001 f/cm³, but possibly turning back on this by proposing a policy that would raise it to 0.01 f/cm³(Kazan-Allen, 2022, p.2). Support for workers has also been voiced through the General Secretary of the European Federation of Building and Woodworkers, Tom Deleu.
Deleu stated that :

> "There are 35 million buildings with asbestos – buildings that will be renovated or demolished by workers in the context of the Renovation Wave and the European Green Deal. There is no safe exposure limit to protect workers completely from asbestos. We cannot turn our backs on construction workers and other professions, who are regularly exposed to asbestos."

Even workers and former workers are voicing support for more protection of workers against asbestos fibers. Mikael Svanberg, an official of the firefighters' section of the Swedish municipal workers union has personally been affected by these problems. He calls these proposals shameful.
Svanberg said :

"I have colleagues that have died of cancer and a lot of friends also in Europe that are suffering ... [from] breathing problems, heart problems." (Kazan-Allen, 2022, p.2)

Programs and therapy for survivors are also being developed as time goes on. There have even been cases when a worker who contracted mesothelioma were able to go to court, and win monetary compensation for what they had gone through. One notable case happened when a painter developed Mesothelioma. The paints he was working with had caused this problem. The jury ended up giving him $11 million compensation (Whitmer, 2023, p.3). Another huge step for the victims was the creation of Mesothelioma trust funds created by Asbestos manufacturers. These funds allow victims to receive

monetary compensation if they develop Mesothelioma later on in life. These funds have paid victims an estimated $20 billion (Meirowitz, 2023, p.4)

Conclusion :

All in all, Mesothelioma affects construction workers on a much larger scale than people in other demographics. Many people do not realize the hidden dangers when they become a construction worker. The injuries and possible deaths in the industry are not only from physical trauma, but also as we found out, disease. The studies shown that exposure to Asbestos fibers is one of the leading causes of injury/death within the construction industry. It's important to spread awareness and increase protection for construction workers. They're the civilization builders risking their lives. They should receive proper protection and compensation in case they develop Mesothelioma. Although these things are happening currently we need to better spread awareness of these problems. Better protection for the workers can also mean better protection for those around them. They can carry asbestos fibers on their clothing back from work and expose their loved ones to the possibility of Mesothelioma.

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Review article

Medical Advances Made in Mesothelioma Treatment

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Keywords: Mesothelioma Cancer, Therapy, Cancerous, Tumor

Abstract:

This literature review discusses the emerging treatments for mesothelioma as well as several clinical trials that have been performed by various scientists in order to better current treatment plans. These therapies involve using immunotherapy drugs, photodynamic radiation, chemotherapy, as well as a combination of several therapies in order to effectively attack and prevent the spread of cancerous cells along the lining of the mesothelium tissue in the lungs. Mesothelioma is an extremely deadly cancer and aggressively affects the lungs, causing chest pains and shortness of breath. However, through clinical trials such as SMART, IMPALA, along with various others, treatment plans can be created for individual patient needs, demonstrating a significant step toward finding a cure for mesothelioma.

Introduction:

Mesothelioma, an extremely deadly cancer, develops in the mesothelium tissue lining the lungs, stomach, heart, and other organs. Although a rare cancer, it aggressively affects the lungs, causing chest pains and shortness of breath. All cancers are caused by abnormal cell growth and division usually due to an error in the DNA. However, for meso, researchers are having trouble determining what causes the initial genetic mutations that lead to its malignance. Fortunately, there are treatments for this cancer and if they begin early, painful symptoms can be relieved. If a patient recives an early diagnosis for meso, they can begin treatments such as chemotherapy, immunotherapy, radiation therapy, surgery, and more. Surgery depends on the location of the cancer and helps reduce pain. Scientists say that the best way to benefit from the latest therapies and improve a meso prognosis. In one study, Chief of General Thoracic Surgery, Dr. David J. Sugarbaker investigated several treatements for meso and was able to develop the multimodality therapy for patients with the disease, also receiving the Pioneer Award from Mesothelioma Applied Research Foundation. It is highly important that we further explore the various medical advancements being made in meso in order to help others with this cancer.

Immunotherapy:

Immunotherapy drugs have been effectively extending the life expectancy of its patients by several years. It utilizes cells from the body's immune system in order to stimulate the production of T cells. When the body gets attacked by meso cancer cells they bind and deactivate the immune system T cells. These cancer cells then proceed to release various signals, making them seem as though they are healthy cells, and get hidden among normal cells of the immune system. A patient given immunotherapy drugs will have their body's cancerous cells made a threat and the tumors will be destroyed before they become malignant and attack the rest of the body.

CAR T-Cell Therapy

Chimeric Antigen Receptor cells, or CAR T-Cell therapy, has become a new alternative for cancer patients battling meso. Having been approved by the FDA to treat specific cancers that attack blood cells, this form of therapy is being tested in clinical trials to prevent tumor growth in meso patients. White blood cells (WBCs) are what protect the body aginst diseases and prevent cancerous tumors from spreading. Meso cancer cells diguise themselves as healthy cells, causing WBCs to render useless. However, a group of researchers from Memorial Sloan Kettering Cancer Center in New York City recently treated this method of CAR T-Cell therapy on select patients. These researchers were able to use adoptive cell therapy (ACT) in order to collect patient cells and modify them and rebuild their immunity. During this process, T cells are trained to recognize malignancy by changing the T cell's DNA so that it displays a protein known as a chimeric antigen receptor (CAR). A protein's function, such as that of a receptor, is determined by its form, so giving the cell a new receptor would give it a new function. The new function in this instance would be to bind to antigens made by cancer cells. The CAR T-cells can connect to cancer cells when they are reintroduced into the patient, activating them to release chemicals that kill cancer cells. A sample of the patient's blood is taken, and the T cells are isolated in order to create the CAR T-cells. These cells help recognize proteins specific to cancer cells, called tumor-associated antigens (TAAs). Researchers work to identify types of TAAs that are very common on the cell surface of tumor cells but uncommon on healthy cells. When CAR T-cells can identify TAAs, they target and attack those cancer cells and according to the test results given by doctors, the cancer tumors shrunk or fully disappeared in 50% of meso patients.

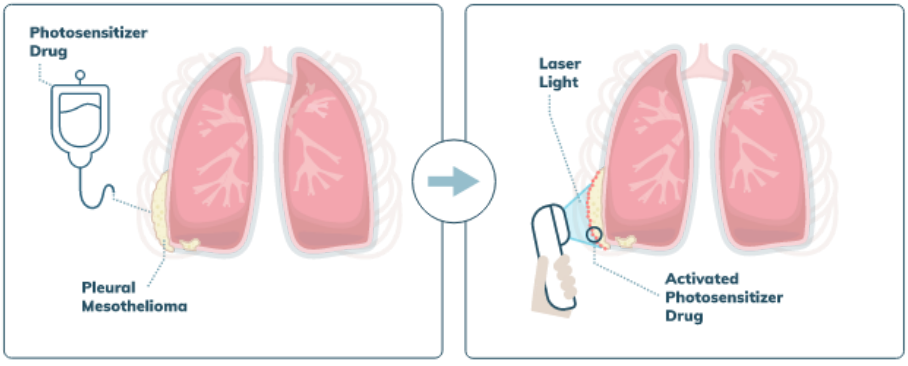
Checkpoint Inhibitor Drugs

Cell cycle checkpoints are control mechanisms that regulate the order of the key cell cycle events. These include ensuring tumor growth does not occur due to out of control cell growth and division. These checkpoint inhibitor drugs are a way to fight meso forcing the cancer cells to lose the ability to pass through the checkpoints without initiating immediate cell death (apoptosis). Several checkpoint inhibitors

used to treat cancers have been approved by the FDA, Opdivo and Yervoy, which are the only two approved for meso treatment. During the treatment, these two drugs keep the body's guard cells from attacking healthy immune cells by circulating through the body while blocking checkpoints. Given to the patients through the use of an IV, the drugs are infused to their bloodstream. Continually, antibodies make up the majority of checkpoint inhibitors, which are useful in binding to the target cell and blocking them at the specific immune checkpoint locations in the cell cycle. Researchers have reported an 18 month increase in the life expectancy of meso patients who had been treated with checkpoint inhibitor drugs and checkpoint inhibitors proved to extend survival by about 30% compared to chemotherapy.

Photodynamic Therapy:

Photodynamic therapy is a new treatment for meso that involves the use of light-responsive drugs, also known as photosynthesizers or photosensitizing agents, to attack and destroy malignant cancer cells. A variety of lights are then used to activate these drugs which begin tactics to fight off cancerous cells, such as shrinking tumor blood vessels or stimulating immune responses. Both of these responses deprive cancer cells of the nutrients they need to continue thriving in the body. All recent studies by researchers have proven light-responsive drugs ability to succesffuly treat meso patients. When clinical trials first begin, they are comprised of two major components: the light-responsive drug, which is injected into the patient, as well as any source of light. After several minutes of exposure to this light, the drug becomes activated releasing its beneficial effects on the body. Such a treatment has been effective due to the nontoxic traits of the drug which is absorbed by all types of cells when first entered into the body. It leaves the patien'ts healthy cells untouched while killing the abnormal cells when exposed to light.



Moreover, photodynamic therapy is extrememly hard to make a fatal error with as it can easily target specific areas of the body, and this localization helps control the effects of the drug more. In several cilincal trials, such as the IMPALA trial where phtodynamic therapy used in combination with chemotherapy, the outcomes hope to increase life expectancy for 90% of the patients. They all experienced the benefits of photodynamic therapy which includes precisely target tumor tissue, unlike

some other forms of meso treatment, it can be repeated many times at the same site, and when used properly, it has no long-term side effects. This therapy provides an effective treatment for patients with an advanced stage of meso.

Radiation therapy:

Radiation therapy in meso involves the use of energy to damage and kill the rapidly dividing cancerous cells. Along with preventing the tumor cells from spreading throughout the lungs, it effectively reduces patient symptoms as well as extending life expectancy and survival. This form of therapy specifically utilizes ionizing radiation, a form of energy that acts by removing electrons from atoms and molecules of materials that includes living tissue. This radiation occurs in two different forms, photon radiation and particle radiation. Photon beam radiation, which uses the same form of radiation as an X-ray but at a higher dose, is the most common form of radiation cancer treatment. Photons can release energy at any point along their path, when traveling through the body and this allows photon radiation to eliminate tumors, but it can also damage healthy tissue, so it must be performed with caution. Particle radiation, slightly different in function from photon beam radiation, uses either protons or electrons to send energy to cancer cells. Protons release energy after reaching a certain vicinity from their source, giving them the ability to produce proton radiation that can kill cells while causing minimal damage to healthy tissues along the path. This results in fewer side effects in proton radiation than photon beam radiation. However, these forms of radiation are not as effective in targeting tumors that lie far below the surface of the skin, so radiation specialists are forced to pay attention to these minor deitails about the location of the tumors in the patient and depending on the tunor site, the form of radiation is selected to perform the task of shrinking the tumor.

Multimodal therapy:

A combination of multiple treatments in one treatment process, hence the name, multimodal therapy often includes chemotherapy, surgery, radiation, and even newer therapies, such as immunotherapyin combination for patients with meso. Multimodal treatments have proven to be far more effective than just a single treatment in the long run and have had the highest success rate in increasing patient ife expectancy over just a short period of time. This form of therapy conssits of numerous stages of seperate therapies, including neoadjuvant, adjuvant, and primary therapy. Neoadjuvant therapy is a treatment given before the primary therapy. It may help shrink the tumor. Primary therapy is the main treatment intended to remove or kill tumor cells. Adjuvant therapy is a treatment given after the primary therapy. It targets the remaining cancer cells. One common multimodal meso treatment approach combines surgery with chemotherapy. A surgeon tries to remove as much tumor tissue as they can during meso surgery.

However, the surgeon might not be able to see microscopic cells that are still present. These residual cancer cells may be treated with chemotherapy given after the surgery. A multimodal plan can include any number of distinct treatments for meso. This implies that a patient's treatment can be adjusted to meet their specific needs. When selecting a course of treatment, doctors take many factors into account. These include the type of meso, the diagnosing stage, and the patient's health. In one of the methods, meso treatments were integrated in the SMART clinical trial. Patients were first given a strong dosage of radiation to the affected area as a part of the treatment. The meso patients had major surgery using EPP one week after radiotherapy. The SMART trial's overall survival was 24.4 months. Given that more conservative treatments have shown comparable results, some may view this as being unimpressive. Patients with the epithelioid cell type, however, experienced a distinct response to the SMART treatment. The median survival time for these individuals was 42.8 months. Though this was an accomplishment, authorities advise using the SMART technique with care. The process is difficult, therefore, it should only be used by cancer institutes with expertise.

Conclusion:

There is still more research to be done around meso cancer, and with more clinical trials and many more theories to be tested by scientists improvements will be made. Different forms of therapy are allowing us to take a step forward in aiding the patients of meso as well as treat all types of cancers, through more efficient, painless methods.Through several therapies such as photodynamic, radiation, multimodal, and more, we can begin to develop new forms of treatment based on the results of these treatment plans. Researchers taking part in clinical trials such as SMART and IMPALA are providing us with the statistics to perfect the treatments. If we continue with research such as this, it could eventually lead to an efficient cure for meso.

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Review Article

Blood Biomarkers And Breath Analysis Used to Diagnose Malignant Pleural Mesothelioma

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Keywords: Malignant pleural mesothelioma, biomarkers, breath analysis, SMRP, MSLN, osteopontin, C-C chemokine ligand 2, galectin-3, HMGB-1

Abstract:

Many people in underdeveloped regions of the world continue to be exposed to asbestos-based products, which is the leading cause of malignant pleural mesothelioma. Detection of this disease is rather difficult, and with current tools being used, it can only be detected in the disease's most advanced stage, leaving little room for survival. Now, doctors have discovered multiple blood biomarkers and breath analysis as a way to detect MPM in its early stages. In this paper, we will look into each biomarker and understand its pros and cons, and look into why breath analysis is being researched as an alternative.

Introduction:

Malignant Pleural Mesothelioma is a rare cancer that grows in the membrane that lines the walls of the chest and lungs. The most common cause is asbestos exposure, a mineral once used in many industries like building and manufacturing. Although high-income countries have banned the use of asbestos products, large parts of the world's populations are still exposed in an uncontrolled way to the mineral, causing MPM to rise worldwide. In return, the number of therapies available to treat MPM are advancing at a slow rate, and cures remain difficult to find. Platinum and pemetrexed (PMP) have remained the main treatment for almost 20 years, and it’s only recently that immunotherapies have been offered as an alternative. Although the construction of MPM is complex, that’s not the reason for its lack of understanding. MPM is a rare tumor, and because there aren’t many cases, that makes it less attractive for experimenting. However, researchers are looking into substances in the blood called biomarkers to make MPM diagnoses more effective. The cause of having fluid build up in the lining of the lungs can vary. Testing the lung fluid and blood can pick up on types of lung cancers, including mesothelioma. When used at the right time, detecting these biomarkers can help effectively detect MPM and get people the right treatment. Additionally, breath analysis has been brought up as another non-invasive screening tool

for MPM. In this article, we will discuss the types of research done on ways to diagnose MPM, and the results of these experiments (Cavallari et al., 2023).

Biomarkers:

SMRP

Protein biomarkers (derived from the MSLN gene) are a soluble mesothelin-related peptide (SMRP), a widely studied tumor marker for diagnosing MPM (Gao et al., 2019). Mesothelin plays an important role in cell adhesion, cell-to-cell recognition, and signaling by interaction with Cancer Antigen 125 (a test used to measure the amount of protein CA 125 is in the blood) (Mayo Clinic, 2019). Based on diagnostic and prognostic values of SMRP as a possible marker, reports have shown patients with MPM have high levels of SMRP, making it an interesting diagnostic tool. Even individuals exposed to asbestos have even greater concentrations of SMRP, regardless of MPM. Further research into the biomarkers has focused on serum mesothelin with other biomarkers in order to improve diagnostic accuracy (Lagniau et al., 2017).

Osteopontin

Osteopontin (OPN) and MPF (protein secreted from the cell) are additional biomarkers that have demonstrated high levels in MPM patients. The performance of these markers have gone through multiple studies, and have been found to lack sensitivity as a stand-alone biomarker. OPN is a glycoprotein that helps the recovery of an organism after injury/infection. It controls cell migration and plays an important role in balancing immune and inflammatory responses. However, when it comes to diagnosis, OPN appears to be useful in differentiating asbestos-exposed individuals who don't have MPM, and those patients who have been exposed. A combination of SMRP and OPN resulted in improved diagnostic accuracy over SMRP alone. The same was observed with a combination of SMRP and MPF (Lagniau et al., 2017). Although individually SMRP and MPF have similar diagnostic accuracy, further research has been done on MPF to be used as a treatment outcome for patients with malignant mesothelioma and developing therapies (Zhang et al., 2014).

CCL2 and LGALS3

C-C chemokine ligand 2 (CCL2) and galectin-3 (LGALS3) were measured in patients with pleural effusions (build up of fluid between the tissues that line the lungs and chest) (Hadjiliadis et al., 2022). This restricts these biomarkers to patients with a higher likelihood of mesothelioma than asymptomatic asbestos-exposed persons. CCL2 recruits mononuclear phagocytes (cells comprising bone marrow progenitors) into inflamed neoplastic tissue. LGALS3 is a protein secreted by tumor cells and associated macrophages (white blood cells that kill microorganisms, remove dead cells, and stimulate immune system cells) (National Cancer Institute, [NCI]). Comparing the diagnostic accuracy of SMRP, CCL2, and

LGALS3 against SMRP alone, the combination showed better diagnostic performance (Lagniau et al., 2017).

HMGB-1

HMGB-1 is found in the nucleus of a healthy mesothelial cell, but once it's exposed to asbestos, the biomarker moves to the cytoplasm. The release of HMGB-1 creates the secretion of TNF-α (involved in the pathogenesis of inflammatory diseases) by macrophages, resulting in the protection of asbestos-exposed mesothelial cells against asbestos cell death (Jang et al., 2021). HMGB-1 levels have shown the ability to differentiate asbestos-exposed persons and non-exposed healthy patients. Additionally, acetylated HMGB-1, an isoform of HGBM-1, has shown to outperform previously mentioned biomarkers. It locates damage-associated molecular patterns, promoting inflammation. This biomarker was able to differentiate between asbestos-exposed MPM patients (with or without), or non-exposed with 100% sensitivity. Combined with fibulin-3 (another biomarker, an important role in skeletal development), it improved both sensitivity and specificity (eg: MPM patients vs. non MPM pleural effusions) (Lagniau et al., 2017).

Breath analysis

Lastly, breath analysis is being used to provide information on the metabolic status of a patient based on the exhaled breath. When a patient breathes, it contains volatile organic compounds (VOC) that come from biochemical pathways (endogenous) or inhaled sources (exogenous). Concentration of VOCs vary, and changes in their profile reflect changes in metabolism, tumoral development, and inflammation. Hence, scientists can take a selection of VOCs and use it to screen for MPM. However, some drawbacks are that endogenous VOCs can be considered biomarkers, and even then, it can be hard to distinguish between cancer types (Lagniau et al., 2017).

Conclusion:

The increase in MPM is not only a continuing challenge, but will remain that way for years to come as more asbestos-based products are being processed in developing countries. It's important we focus on finding ways to detect MPM early on to improve survival rates. With more research being done on different biomarkers, though it lacks sufficient sensitivity in making key differentiations, it is valuable in making changes to the diagnostic process of MPM. Additionally, breath analysis is becoming an increasingly investigated field, showing more promising results for early diagnosis. Although all of this is a work in progress, it is a step in the right direction towards making MPM diagnosis easier and survival rates longer.

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Review article

The Future of Early Detection Methods in Mesothelioma Cancer

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Keywords: Mesothelioma, Biomarker, Early detection, micro-RNA

Abstract:

The goal of this paper is to research and analyze the importance of the innovation of early detection in the fight against Mesothelioma cancer and to delve into the most recent research. In the first section of this paper, I will assess the definition and role of bio markers in early detection and compare biomarkers such as Mesothelin and Fibulin-3. Furthermore, I will be investigating micro RNAs, and their ability to improve early gene detection. As well as this I will compare clinical trials and background research to determine the usefulness of biomarkers and micros RNAs in the diagnostic field. Then I will dive into imaging technologies for early detection and the positives and negatives of different early detection technology. Finally, I'll discuss whether the technology is a good candidate for the medical field as well as how it can be implemented. By discussing biomarkers, early detection techniques and clinical trials I will be able to make a comprehensive analysis on the subject.

Introduction:

Mesothelioma is a rare and destructive cancer that has emerged worldwide as a significant health concern. This specific type of cancer is prominent in the lining of the lung and chest wall also known as the pleura. In the average person, the pleura is thin and acts as protection to the lungs from friction or external trauma, as well as helping with breathing, maintaining lung shape, and minimizing friction with the lungs. When an individual has mesothelioma, the pleura becomes thickened with tumor. The main cause of mesothelioma cancer is asbestos exposure, but some scientists believe certain genetic components play a role in patient's susceptibility to the disease. In recent years studies about the detection of the disease using biomarkers has been gaining traction. A biomarker is a measurable substance in the body that provides information about a biological process, condition, or disease. We can use biomarkers to predict which individuals are more susceptible to a disease and use preventative tactics accordingly. Recognizing genetic factors and bio markers is extremely important. The difference between catching a disease in stage one rather than stage 5 is drastic. According to Dr Mark Levin, the average life expectancy for a patient when the disease is caught in stage one is 21 months versus the 12 months for a

patient diagnosed in stage 5. Although there is no cure for mesothelioma cancer, when it is caught early some patients can achieve long term survival. Understanding genetic factors and biomarkers can essentially change the way we look at Mesothelioma Cancer. To supplement this paper, we will look at past research studies. The Princess Margaret Hospital Mesothelioma Research Program performed tests to see if the fibulin-3 levels present in blood plasma varied between mesothelioma patients, and individuals without mesothelioma. They measured the levels of fibulin-3 in 92 patients with mesothelioma, 136 asbestos-exposed persons without cancer, 93 patients with effusions not due to mesothelioma, and 43 healthy controls. The study states, "Tumor tissue was examined for fibulin-3 by immunohistochemical analysis, and levels of fibulin-3 in plasma and effusions were measured with an enzyme-linked immunosorbent assay." The results showed that the amount of fibulin-3 was significantly higher in patients with pleural mesothelioma rather than the asbestos exposed persons or the individual control patients. Several studies have been conducted to determine if the use of microRNAs as biomarkers can be used to predict mesothelioma early on in patients. Two examples are Matboli et al and Cavalleri et al. Results have shown the high levels of microRNAs in patients with mesothelioma, and it is a promising lead in the field of early detection. Both these studies have shown that the field of early detection is advancing, and biomarkers can allow for early treatment. The continuous improvement in diagnosis and early detection methods in mesothelioma is crucial.

The Role of Biomarkers and MicroRNAs in the Diagnosis and Prognosis of Mesothelioma Cancer

Definition and Role of Biomarkers in Early Detection

The Biomarkers Definitions Working Group stated a biomarker is "a characteristic that can be objectively measured and evaluated as an indicator of normal and disease processes or pharmacological responses". Biomarkers have been used in preclinical research and medical diagnosis for a significant amount of time. It is time we implemented it further and recognized how useful they can be. Biomarker innovation is part of the future of diagnosis, specifically in diseases like mesothelioma, when catching the cancer in early stages is so important.

Mesothelin as a Biomarker

The national library of medicine states "Mesothelin (MSLN) is a glycoprotein expressed at low levels in normal tissues and at high levels in MPM". Mesothelin can be measured in blood samples as well as pleural fluid, Mesothelin can be used as a biomarker, prognostic biomarker, and a useful tool in monitoring the treatment process of a mesothelioma patient. Numerous studies show mesothelin can be used as a diagnostic bio marker because of the high levels of mesothelin in mesothelioma patients. Tests of mesothelin levels are already starting to be paired with imaging scans and biopsies in order to diagnose

patients. Mesothelin works as a prognostic biomarker, meaning it can provide information about the likely outcome or prognosis of the disease. Some studies such as Creaney et al, have shown that higher levels of mesothelin in a patient are associated with a poorer prognosis and shorter survival rates. Mesothelin additionally can be used in the treatment of patients. When mesothelin levels decrease over time, it can show a positive response to treatment and indicate that the treatment is working for the patient. On the other hand, increasing levels of mesothelin show that a patient's condition is worsening and can indicate to doctors to adjust the treatment. Of course, research and validation are still needed, but the future of mesothelin in the diagnosis and treatment of mesothelioma is promising. In the study "Soluble Mesothelin Related Protein in Mesothelioma" by J. Creany, the correlation of mesothelin levels with mesothelioma was explored. In total, there were 44 patients with confirmed mesothelioma. Thirty-nine were male and five females. In addition, there were healthy controls. They took samples base of SMRP which is soluble mesothelin related protein. The results show that SMPR levels were significantly higher in patients with mesothelioma cancer than without. In conclusion mesothelin proved to be a useful tool in early diagnosis and noninvasive detection.

Fibulin-3 as a Biomarker

Fibulin-3 is a glycoprotein expressed throughout the body. It is especially present in elastic-fiber-rich-tissues and ocular structures. In a study done by Halide Kaya, Melike Demir, Mahsuk Taylan, Cengizhan Sezgi, Abdullah Cetin Tanrikulu, Sureyya Yilmaz, Mehmet Bayram, Ibrahim Kaplan and Abdurrahman Senyigi Fibulin -3 was proven to be a useful bio marker. The study was conducted on forty-three patients with malignant mesothelioma and forty healthy controls. The results showed that patients with malignant mesothelioma had significantly higher levels of fibiulin-3 than the controls. In conclusion the study confirmed that while Fibulin-3 levels does not help with prognosis, it is a useful tool for the diagnosis of malignant mesothelioma.

Micro RNAs as an Early Detection Method

Micro RNAs are small non-coding molecules. This means the molecule doesn't encode proteins. Micro RNAs play an important role in gene regulation, they can be detected in blood samples, pleural effusions, and tumor tissues. In the clinical study Matboli Et Al, the serum micro RNAs in Malignant pleural mesothelioma were analyzed. There were sixty patients with malignant pleural mesothelioma using miR-548a-3p and miR-20a micro RNAs and they were able to detect Malignant pleural mesothelioma effectively in the patients. The Area Under the Curve (AUC) of the trial was 0.92 for miR-548a-3p and 0.98 for miR-201. The higher the AUC the better the performance and these are both considered extremely high AUCs. The trial concluded that these micro RNAs were excellent in diagnosing patients with malignant pleural mesothelioma.

Summary of Biomarkers and Micro-RNAs

Bio markers are extremely important to the future of mesothelioma diagnosis and early detection. The diagnosis of mesothelioma is complex and extremely difficult, so it is crucial we utilize these noninvasive diagnosis methods. Three of the most promising biomarkers include Mesothelin, Fibulin-3, and micro RNAs. Mesothelin is a protein, mesothelioma cells usually have a surplus of mesothelin. It is used as a diagnostic marker as well as a prognostic marker for mesothelioma. The levels of mesothelin can be detected in pleural effusions as well as blood and tumor tissue. Mesothelin is often used in immunotherapy tactics for mesothelioma treatment. Fibulin-3 is a glycoprotein and its levels have also been found to be higher in patients with mesothelioma. It is still being investigated as a potential biomarker for mesothelioma prognosis and diagnosis. It can be measured in pleural effusions. MicroRNAs are small RNA molecules that also regulate gene expression. When microRNAs are dysregulated, this can mean multiple diseases including mesothelioma. Specific microRNAs like miR-548a-3p and miR-20a are being looked at as potential biomarkers for detection as well as prognosis. However, targeting micro RNAs could be a promising therapeutic strategy for mesothelioma. Biomarkers like these, entirely change the way we look at diagnosing mesothelioma cancer and it is vital that further research and resources are put into discovering how biomarkers work and how we can apply them to mesothelioma cancer.

Imaging Technologies for Early Detection

Overview of Imaging Modalities used in Mesothelioma Detection

When diagnosing mesothelioma there are a series of important tests to properly diagnosis the disease, as well as see how extensive it is. The imaging technologies often used include the X-Ray, MRI, PET scan, and the CT scan. The X-Ray is often the initial method used in diagnosing mesothelioma. An X-Ray is a type of electromagnetic imaging technique. It shows the chest cavity and detects any abnormalities. An MRI stands for Magnetic Resonance Imaging. It uses magnetic fields and radio waves to generate high-resolution images. MRIs provide detailed images and specific information on the size of the tumor and where the adjacent tissue comes in. A PET (positron emission tomography) scan is method that uses nuclear medicine scanning. It allows doctors to see a 3D image of an area including organs and tissues. It can help determine the extent of the tumor which helps doctors decide treatment options. Finally, a CT (computed tomography) scan allows doctors to view an area from different angles by using multiple X-Rays. These are useful because it allows for better visualization of tumor's size, location, and how they affect other organs. The integration of these imaging modalities with mesothelioma cancer helps doctors decide the prognosis, diagnosis, and treatment options.

Advancements in CT imaging in the field of mesothelioma

CT imaging plays an important role because it allows doctors to be able to look at the area from different perspectives. Since CT imaging plays such a crucial role in diagnosing mesothelioma, new advancements

are always being incorporated. Multidetector computed tomography scanners or MDCT scanners for short, is a notable advancement in the field of CT scans. MDCT scanners have parallel rows of X-rays which provide three-dimensional high-quality images and allow spatial and temporal resolution. It is a non-invasive method to scan the chest, abdomen, pelvis, head, neck, extremities and on some occasions the whole body. MDCT scanners give doctors a more precise and accurate view of mesothelioma tumors. Another advancement in CT imaging is the integration of contrast-enhanced CT scans. Intravenous contrast agents are used to highlight blood vessels, therefore improving the visibility of surrounding tissue as well as the tumor. This helps the doctor differentiate between benign and mesothelioma conditions and allows a more accurate stage of the disease to be shown off. These advancements help patients every day and show just how important it is that we are constantly coming up with new solutions in the field of medicine.

Advancements in PET Imaging in the Field of Mesothelioma

PET imaging measures the metabolic activity of the cells of body tissues and is used mostly for patients with brain or heart conditions and those with cancer. One significant advancement is improved spatial resolution. With the use of advanced detection technologies such as high definition (HD) and time-of-flight (TOF) PET imaging has seen serious improvement in this field. Time of flight works by measuring the time it takes for photons to travel from the patient to the detectors instead of not measuring which is what they did in previous models. Time of flight allows for clearer pictures because it can determine the collision from the positron created by the imaging and an electron from inside the body. This allows for the image because the scanner can pinpoint where the activity occurred in the body, thus allowing better reconstruction of the image. This helps with diagnosing a patient with mesothelioma or seeing how far the disease has progressed and what stage it is in. Another advancement for PET imaging is Novel Radiotracers. They expand the range of the molecular targets that can be seen using PET imaging. Medical researchers were able to create radiotracers that were specifically made for different types of biomarkers. Each biomarker specifically with a disease, including mesothelioma. This enables the PET scan to focus of a specific molecular process. This drastically changes the way we diagnose and treat mesothelioma cancer.

PET/CT combination for enhanced detection and staging

One of the most important recent technological advancements allows the combination of the PET and CT into one scanner. In combing the functional data from the PET scans and the anatomical data that the CT shows doctors can gain a deeper understanding of the disease and area they are dealing with as opposed to just using one or the other. This combined scan allows doctors to get a better grasp of the area this allows them to decide the best treatment option. PET/CT scanning also helps determine accurate staging, the size and location of the mesothelioma tumor and the possible spread. It also is important for tracking if the

treatment of mesothelioma was successful. Combined imaging can track changes in metabolic activities over time, tumor growth and their effect on organs around them. By allowing physicians to track that information it assists in determining if the treatment was a good fit for the patient. The PET/CT scanner will help thousands of mesothelioma patients and is a just another reason that shows how early detection and diagnosis for mesothelioma patients' needs to constantly be improved to fight this vicious disease.

Future Directions and Implications

Integration of biomarkers and imaging techniques

The integration of biomarkers and imaging techniques is the next big step in the research of mesothelioma diagnosis and treatment. A biomarker is a measurable material in an organism it provides crucial information needed to understand the biological processes and the states of diseases within the human body. Combining biomarkers with early imaging technologies allows for specific data to be collected and overall enhances he whole system. They allow for more accurate diagnostics as well as insights into treatment planning and monitoring patient responses. One important part this integration allows for is the capability of better disease characterization and detection. Biomarkers can identify specific molecular or genetic signatures that indicate certain diseases which helps with early detection and treatment. By using biomarkers, treatment can be tailor-made to help with a patient's individual needs. In mesothelioma biomarkers can predict a tumors shape, size and what will be affected by it. In doing this, physicians can decide the best course of treatment that can be implemented with the patient's case. This means physicians will know what targeted treatments and therapies to use, then imaging technologies provide a real time response allowing doctors to respond accordingly. This integration of biomarkers and imaging technology is a powerful step in the overall goal of one day treating mesothelioma cancer.

Overview of clinical trials in biomarker research

Biomarker application for diagnosis and treatment of mesothelioma cancer is a serious step in the right direction. While future research needs to be done, every single clinical trial mentioned in this paper proved biomarkers to be an extremely helpful aid in the detection of mesothelioma in patients. The study Creaney et al proved mesothelin levels were significantly higher in patients with mesothelioma cancer. The trial proved the mesothelin biomarker was useful in the detection and prognosis of a mesothelioma patient. More research is still going into the use of mesothelin as a means for early detection. Much like in the mesothelin study, the study "Fibulin-3 as a diagnostic biomarker in patients with malignant mesothelioma" proved Fibulin-3 was a useful biomarker as well. In the last clinical study, Matboli Et Al, it was found that certain micro-RNAs could be used to diagnose mesothelioma patients. The micro-RNAs that were used were miR-548a-3p and miR-20a, and the results once again proved that biomarkers are a serious innovation that should be implemented in mesothelioma early detection, diagnosis, and prognosis.

Conclusion:

To obtain long term life and comfort for mesothelioma patients, it is absolutely crucial that we innovate and improve our early detection techniques. From biomarker research and the application of microRNAs to the clinical trials that give us insight on the application of said biomarkers and the newest findings in early imaging technology. It is crucial that we innovate this field as early detection makes the difference for treating a patient with mesothelioma.

This paper showed the application of biomarkers and RNAs in the diagnosis as well as prognosis and treatment for a patient. With the mesothelin and Fibulin-3 trials showing essentially unanimous positive results with Creaney et al for mesothelin, and a study done by Princess Margaret Hospital Mesothelioma Research Program for Fibulin-3. These studies both had excellent correlation rates for the biomarker to the diagnosis. Micro RNAs also had promising results with their clinical trial Matboli Et Al. These used miR-548a-3p and miR-20a micro which are different types of micro RNAs, by using these they were able to effectively detect malignant pleural mesothelioma in patients. All these show promise for potential early detection tactics, as well as a way to get specific details about the disease in order to properly treat it. By learning more about these biomarkers and microRNAs we could essentially change the way we think about diagnosing mesothelioma. The early detection of the disease for mesothelioma patients is crucial to their treatment. The spread of the cancer between stages one and four is exponential. In stage one the cancer is mostly contained within the mesothelial lining, as the stages progress the cancer spreads to nearby organs and tissues and by stage four it has spread to distant organs, tissues and lymph nodes, infecting much of the body. When treating stage one patients, the odds are drastically better than stage four. There are more treatment options, better outcomes from surgeries, and most importantly a longer lifespan. That's why it is so important to catch it early. Mesothelioma is a fast growing and extremely aggressive cancer. Early detection innovations are the most promising approach to saving patients afflicted with mesothelioma cancer. The treatment for mesothelioma relies almost solely on catching the disease in an early stage and it is essentially the only way to achieve long term survival. This means that early detection devices need to be constantly improved and adjusted. Biomarkers are incredibly important in the field of early detection because with more studies researchers think there could be some correlation between the levels of a certain biomarker and mesothelioma. It is extremely important that we invest more resources into the study of biomarkers as an early detection method, as well as fusing biomarkers with early detection devices such as PET and CT scans. The significance of innovating early detection technology cannot be overstated in the ongoing fight against mesothelioma cancer. Biomarkers and early detection technologies have emerged as being extremely promising in the early diagnosis and treatment of mesothelioma cancer. Through research, technological advancements and collaborative efforts we can entirely change the way we diagnose and treat mesothelioma cancer.

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Literary Review

Contributing factors of the high incidence of mesothelioma in Great Britain

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Keywords: Mesothelioma, asbestos, (secondary) exposure, industry, environment

Abstract: I will be focusing on underlying/contributing causes of high incidence of mesothelioma in Britain. More specifically, the historical context of asbestos use in Britain and the role of occupational settings such as construction. The review discusses the impact of secondary asbestos exposure through family members working in asbestos-related industries in the eighteenth and twenty-first century. The discussion encompasses factors such as awareness, safety regulations, and poor working conditions. Additionally, potential gaps in knowledge and unanswered questions regarding the high incidence of mesothelioma are identified.

Introduction:

Mesothelioma, a rare and aggressive form of cancer, has emerged as a pressing concern within the medical community and society at large. Caused primarily by prolonged exposure to asbestos fibers (a carcinogen), this disease affects the lining of the lungs, abdomen, or heart. Asbestos is commonly found in construction materials, shipbuilding, and automotive industries (ATSDR, 2023). Mesothelioma is more commonly seen in individuals over 65 years old (Selby et al., 2023). The findings of one study provided insights into the different sources of asbestos exposure. Rake et al., 2009 took a different approach by also including exposure domestically through family members who worked with asbestos or from asbestos-containing materials present in residential settings apart from just occupations/industries of work, and direct asbestos exposure through surroundings. Still, we struggle to know what the long-term effects of secondary asbestos exposure, such as exposure through family members or living in close proximity to asbestos-related industries, on the risk of mesothelioma.

Materials and Methods:

A retrospective cohort study design was employed to assess the long-term effects of secondary asbestos exposure on mesothelioma risk. The study included individuals who had experienced secondary asbestos exposure through family members or had lived in close proximity to asbestos-related industries. Participants were identified through medical records, national registries, and community outreach

programs. A detailed questionnaire was administered (Google Form) to collect information on the participants' demographic characteristics, residential history, family history of asbestos exposure, and potential sources of secondary asbestos exposure. Historical data, occupational records, and environmental assessments were utilized to supplement exposure assessment. Exposure duration, intensity, frequency, and specific sources of asbestos exposure were carefully recorded. Structured interviews were conducted to collect comprehensive data on relevant variables, including demographic information, lifestyle factors, occupational history, and potential confounding variables. Residential history was obtained to determine the proximity and duration of exposure to asbestos-related industries. Medical records, imaging studies, and pathology reports were reviewed to confirm mesothelioma diagnosis. Descriptive statistics were used to summarize the demographic and exposure characteristics of the study population. Logistic regression analysis was used to assess the association between secondary asbestos exposure and mesothelioma risk, adjusting for potential confounding factors. The study protocol received approval and all participants provided informed consent. Measures were taken to protect the privacy and confidentiality of study participants. A long-term follow-up strategy was implemented to monitor the occurrence of mesothelioma cases among the study participants. Participants were followed periodically through health assessments, medical record reviews, and linkage to national cancer registries. Data validation procedures were implemented to ensure accuracy and reliability. Quality control measures were employed to address inconsistencies or missing data. The findings were interpreted in the context of the study objectives, limitations, and existing publications/literature. The implications of the results were discussed, and potential mechanisms underlying the long-term effects of secondary asbestos exposure on mesothelioma risk were explored.

Hypothetical results:

Longer duration and higher intensity of secondary asbestos exposure were positively correlated with an increased risk of mesothelioma. Participants with more than 10 years of secondary asbestos exposure had a 3-fold higher risk of developing mesothelioma compared to those with less than 5 years of exposure.

Discussion:

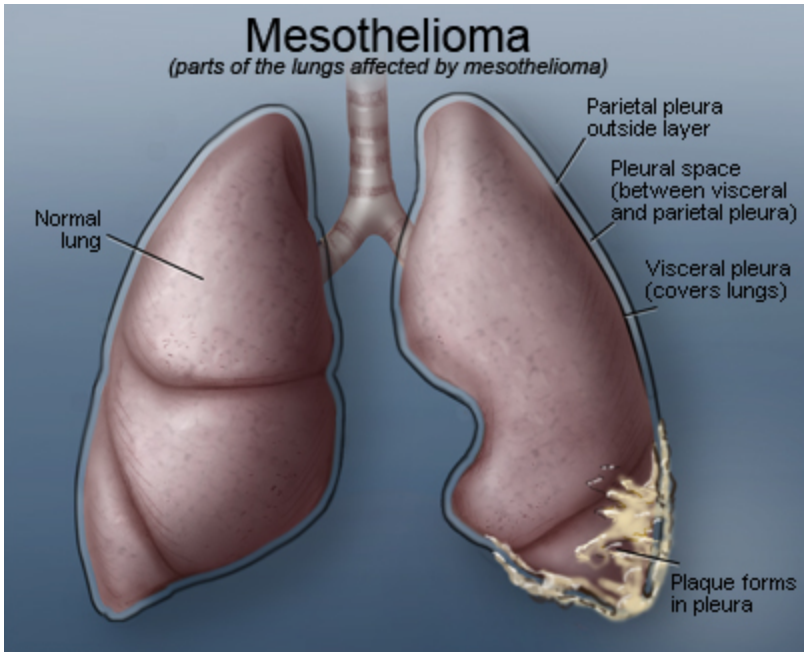
Historical Asbestos use:

The first industrial revolution began from the period 1760 to1830 (Britannica, 2023). Many technological innovations facilitated the production and distribution of goods such as textiles. Asbestos gained significant popularity, especially in Great Britain. As powered machinery and steam power became more and more prevalent, so did the need for an efficient and effective way to control the heat needed to create and power the machines. Asbestos served as a perfect insulator for high-temperature products like steam

pipes, turbines, ovens, and kilns; all things that helped facilitate the Industrial Revolution. By 1900, doctors started reporting lung sickness and pulmonary fibrosis in patients who had worked in asbestos textile factories and asbestos mines. These workers inhaled or ingested asbestos fibers during their daily activities, leading to the development of mesothelioma over time (Hardy, 2016). Additionally, they were housed in cramped living areas with poor ventilation trauma from machinery. To make matters worse, this is where secondary exposure can arise (La, Morte, 2017). By WWII, asbestos was being used in the shipping industry (as insulation to components subjected to high heat), the automobile industry (as brake and clutch lining), and in the construction industry (in a wide variety of products including insulation, siding, and cement) (Hardy, 2016).

Occupational exposure:

Construction workers have been identified as a high-risk group due to their potential for prolonged and direct exposure to asbestos-containing materials (ACMs) commonly found in construction sites. Asbestos is utilized extensively in various construction materials, such as insulation, roofing materials, flooring, and pipe insulation, due to its excellent heat resistance and durability. Consequently, construction workers who handled or came into contact with these ACMs were at a heightened risk of inhaling or ingesting asbestos fibers, leading to the development of mesothelioma over time. Furthermore, the nature of construction work itself exposes workers to conditions that increase the likelihood of asbestos exposure. During renovation, demolition, or maintenance activities, older buildings or structures containing ACMs are often disturbed, releasing asbestos fibers into the air. This can result in inhalation by construction workers who are present on-site, leading to asbestos fiber retention in the lungs and subsequent mesothelioma development. Inadequate safety measures, such as the lack of proper containment, ventilation, or personal protective equipment, further exacerbate the risk for construction workers. The asbestos fibers cause this tissue to inflame, leading to scar tissue plaques forming on the surface of the protective lining. It is within this scar tissue that malignant mesothelioma tumors begin to grow. When asbestos fibers are ingested they can develop into peritoneal mesothelioma, which forms within the abdominal lining (peritoneal lining) (University of Pennsylvania, n.d). Another contributing factor is the long latency period associated with mesothelioma development. Construction workers may experience asbestos exposure early in their careers, but the disease can take several decades to manifest. As a result, cases of mesothelioma among construction workers are often diagnosed many years after the initial exposure, making it challenging to establish a direct causal link and identify specific sources of exposure.



Emily, W. (2017) Mesothelioma [Image]

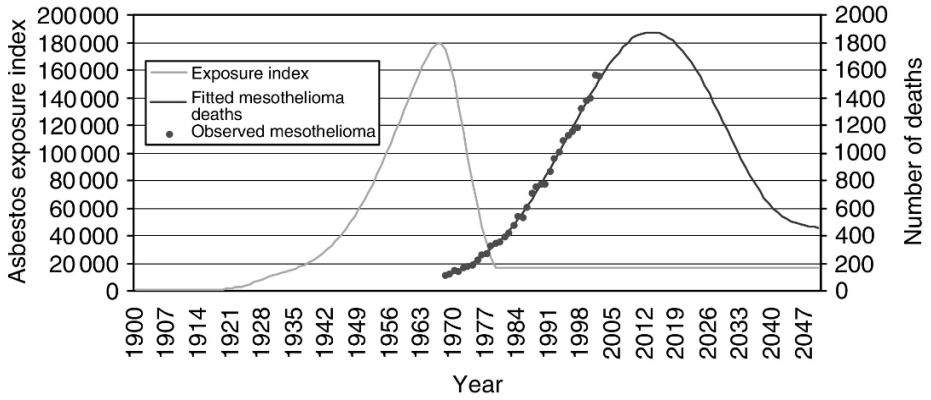
Regulatory Measures:

Many countries including Great Britain have begun to regulate and ban the use of asbestos due to health concerns. Some of these include, Asbestos (Prohibitions) Regulations 1985, *Control of Asbestos Regulations 2006*, The Asbestos (Prohibitions) (Amendment) Regulations 1999, and Asbestos (Licensing) Regulations 2012. Moreover, Great Britain has implemented strict control measures for handling asbestos-containing materials (ACMs) and requires licensing for certain activities involving asbestos. The Control of Asbestos Regulations 2012 (CAR 2012) sets the legal requirements for managing asbestos in non-domestic premises. This includes provisions for risk assessments, training, and the safe removal and disposal of asbestos. The regulations also require dutyholders to conduct thorough asbestos surveys to identify the presence and condition of asbestos in buildings. Appropriate management plans are developed to minimize the risk of exposure. These measures have helped in identifying and safely managing asbestos-containing materials in various settings, such as workplaces, public buildings, and schools. Great Britain has taken steps to ban the import, supply, and use of all forms of asbestos. The ban (came into effect in 1999), prohibits the use of new asbestos in any construction or refurbishment projects. This ban has significantly reduced the risk of exposure to asbestos fibers during building activities and has contributed to the overall decline in mesothelioma cases. The Health and Safety Executive (HSE) in Great Britain has actively promoted awareness about the dangers of asbestos and the proper management of asbestos-containing materials (Health and Safety Executive, n.d). Employers are required to provide appropriate training to workers who may come into contact with asbestos as part of

their job duties. This emphasis on education and training has led to increased awareness and improved safety practices. The implementation of these regulations, along with ongoing efforts in raising awareness and providing guidance, has been effective in reducing asbestos exposure and subsequent mesothelioma cases in Great Britain.

Future projections:

It is predicted (from the study) projected a continuous rise in mesothelioma cases in Great Britain, peaking at around 2,500 cases per year around 2020-2025. This upward trend was attributed to historical asbestos consumption patterns and the long latency period between exposure and disease manifestation. The study also highlighted the changing age distribution of mesothelioma cases. While older age groups (75 years and above) were initially more affected due to historical exposure, the burden was expected to shift towards younger age groups over time as a result of lower asbestos exposure levels in recent decades. The study emphasized the significance of occupational asbestos exposure, which accounted for the majority of mesothelioma cases. Workers in high-risk industries, such as construction, shipbuilding, and insulation, were identified as particularly vulnerable to asbestos-related diseases (Hodgson et al., 2005).



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Conclusion:

Great Britain remains one of the leading countries with the highest mesothelioma incidence. Primarily due to historical uses, current occupations, secondary exposure to asbestos, and previous lack of regulations.

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Review Article

Photodynamic Therapy for the Treatment of Malignant Pleural Mesothelioma

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Keywords: Photodynamic Therapy, Mesothelioma, Alternative Treatment

Abstract:

This literary review provides an overview of the principles and applications of photodynamic therapy (PDT) in mesothelioma treatment. PDT selectively targets and eliminates cancer cells through the administration of a photosensitizer drug followed by laser light exposure. The localized treatment generates reactive oxygen species, inducing cytotoxic effects and promoting an immune response against cancer cells. While PDT shows promise, its effectiveness can be influenced by factors such as disease distribution and the presence of residual disease. The potential complications and side effects associated with PDT are highlighted to emphasize the importance of patient education, monitoring, and appropriate management. Overall, PDT offers a novel therapeutic approach for mesothelioma, holding the potential to improve patient outcomes and survival rates when used in combination with other treatment modalities.

Introduction:

Malignant mesothelioma is a rare and aggressive cancer that primarily affects the protective lining of the lungs, heart, and abdomen. It is mainly caused by long-term exposure to asbestos fibers, which leads to the development of cancerous cells within these linings. Despite advancements in conventional treatments such as surgery, chemotherapy, and radiation therapy, the prognosis for mesothelioma remains poor, with limited survival rates and significant side effects. In recent years, photodynamic therapy (PDT) has emerged as a promising alternative treatment modality for mesothelioma, offering a novel approach that combines light activation and a photosensitizing agent to selectively destroy cancer cells while minimizing harm to healthy tissue.

The Process:

Photodynamic therapy (PDT) is a well-established treatment approach for mesothelioma that utilizes light-activated drugs to selectively target and eliminate cancer cells. It involves the administration of a photosensitizer drug followed by exposure to laser light.[1] The photosensitizer is absorbed by both healthy and cancerous cells, but cancer cells retain it for a longer duration. After a suitable interval, laser light is applied, activating the photosensitizer and triggering a series of events that lead to cancer cell destruction. PDT offers the advantage of selectively accumulating within malignant cells while sparing healthy tissue.

Upon activation, the photosensitizer generates reactive oxygen species, which induce cytotoxic effects, including shrinking tumor blood vessels and stimulating an immune response against cancer cells. This localized treatment can be precisely targeted to specific areas, such as the lungs, and can be repeated as needed. In the management of mesothelioma, PDT is often utilized as part of a multimodal treatment strategy, combining various therapies to improve patient outcomes and overall survival. The procedure involves two key steps: photosensitizer injection and subsequent exposure to laser light. It can be performed intraoperatively, and the length of hospitalization and recovery varies depending on the specific surgical procedure combined with PDT. Clinical trials have demonstrated the effectiveness of PDT when combined with mesothelioma surgeries like extrapleural pneumonectomy (EPP), pleurectomy and decortication (P/D), and radical pleurectomy. Additionally, PDT can be combined with other therapies such as chemotherapy, radiation therapy, or immunotherapy as part of an individualized treatment plan.

Multimodal Treatment:

Malignant pleural mesothelioma (MPM) has a short median survival period of approximately 12 months.[2] Many patients with MPM are not eligible for definitive surgery at the time of diagnosis due to factors such as comorbidities, advanced age, or the presence of unresectable disease. However, among eligible MPM patients, surgery as part of a multidisciplinary treatment approach has been associated with improved survival compared to nonsurgical modalities. The currently employed surgical procedures for definitive treatment include extrapleural pneumonectomy (EPP) and radical or extended pleurectomy. EPP involves the en-bloc resection of the parietal pleura, lung, pericardium, and diaphragm, while radical pleurectomy involves resecting all pleural surfaces and visible disease while preserving the lung. EPP is considered more oncologically aggressive, leaving behind less microscopic residual disease, and enables better administration of adjuvant hemithoracic radiotherapy. Radical pleurectomy offers improved lung function preservation and lower perioperative morbidity and mortality rates.

Clinical Trials:

In a randomized phase III trial conducted by the National Cancer Institute, PDT was evaluated in combination with maximum debulking surgery and postoperative immunochemotherapy for MPM patients.[3] The trial results found that combining PDT with surgery and postoperative immunochemotherapy did not show significant improvements in recurrence patterns, median survival, or progression-free time. The presence of macroscopic residual disease after surgery may have limited the effectiveness of PDT. In another phase II study, patients with early-stage MPM had a median survival of 36 months, while those with advanced disease had a median survival of 10 months after undergoing EPP

or pleurectomy followed by PDT.[4] The dose of PDT was found to impact overall survival. Different PDT approaches were explored, with one study showing durable tumor control but increased toxicity, while another using a different PDT agent demonstrated improved median survival and reduced tumor regrowth.[5] University of Pennsylvania researchers conducted studies on intraoperative PDT for MPM, finding that in a recent study of 38 patients who underwent radical pleurectomy and intraoperative PDT, the majority achieved complete resection.[6,7] The cohort had a median survival of 31.7 months, with epithelial histology patients experiencing a median survival of 41.2 months, but progression-free survival was only 9.6 months, suggesting a potential immune response to microscopic residual disease induced by PDT.

In these studies, varying results were found. While one trial found that the combination of PDT and surgical treatment showed no results, another trial found this approach effective. The type of photosynthesizing drug and the presence of residual disease after surgery was found to cause varying effectiveness of PDT. However, in the majority of trials the use of PDT has increased the survival survival period for patients with pleural MPM.

Limitations of PDT and Additional Applications:

It should be noted that PDT may be unsuitable for certain patients due to blood diseases, cancer spreading to distant sites, large tumor size, or severe respiratory distress. Additionally, with cancer that has spread throughout multiple organs and is far from the skin’s surface, unlike surgical options, PDT is not the most effective treatment.[8] However, it is still a valuable treatment approach that can be used to treat many conditions and diseases. PDT is not limited to mesothelioma and can be used for various conditions, including acne, psoriasis, age-related macular degeneration, and several cancers such as skin, lung, brain, bladder, pancreas, bile duct, esophagus, and head and neck. PDT has demonstrated efficacy in treating bacterial, fungal, and viral infections by triggering the body's immune response. It is also utilized for pancreatic cancer, bile duct cancer (cholangiocarcinoma), esophageal cancer, and certain skin diseases, including precancerous skin changes and nonmelanoma skin cancer.[9]

Early and Late Onset Side Effects:

Early side effects of PDT include pain or discomfort during light activation, burning sensation, and erythema (redness) in the treatment area. Swelling, edema, and blisters may also occur, particularly in areas with a thin or delicate skin layer. In some cases, these early effects can lead to delayed wound healing. Other observed complications include photosensitivity reactions, which can manifest as sunburn-like symptoms, and ocular sensitivity, causing discomfort in the eyes when exposed to light. Late

side effects of PDT are less common but can still occur. Skin changes, such as hypo- or hyperpigmentation, scarring, or fibrosis, may develop over time in the treated area. In certain cases, persistent erythema or telangiectasia (dilated blood vessels) can be observed. Patients may experience itching, dryness, or sensitivity in the treated skin. In rare instances, the occurrence of secondary malignancies has been reported, although the association with PDT remains unclear.[10] The severity and frequency of these side effects can vary depending on factors such as the photosensitizer used, light parameters, treatment site, and individual patient characteristics. Proper patient selection, adequate light dosimetry, and comprehensive follow-up are crucial to minimize the risk of complications and manage any adverse effects that may arise. The study emphasizes the importance of patient education, including providing detailed information about potential side effects and measures to mitigate them. Close monitoring and appropriate management of complications are essential to ensure optimal outcomes and patient satisfaction with PDT treatment.

Conclusion:

Photodynamic therapy (PDT) has emerged as a promising alternative treatment modality for malignant mesothelioma. It offers a selective and localized approach to destroy cancer cells while minimizing harm to healthy tissue. PDT can be combined with surgical procedures such as EPP and radical pleurectomy, enhancing treatment outcomes in eligible patients. However, the efficacy of PDT may be influenced by factors such as the extent of residual disease, depth of penetration, and dose of photosensitizer. Clinical trials have shown mixed results regarding the addition of PDT to surgical interventions, with some studies demonstrating improved survival and reduced tumor regrowth. Adverse effects of PDT include early complications like pain, erythema, and swelling, as well as late effects such as skin changes and ocular sensitivity. Proper patient selection, light dosimetry, and post-treatment monitoring are essential for minimizing complications and optimizing outcomes. Further research is needed to refine PDT protocols, improve patient selection criteria, and investigate combination therapies to enhance the effectiveness of this treatment modality. Overall, PDT shows promise as an adjunctive therapy for malignant mesothelioma, offering a potential avenue for improved patient outcomes in the future.

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Literary review

Genetic Links to Mesothelioma

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Keywords: Mesothelioma, genetic markers, early diagnosis, prognosis factors, survival rate

Abstract

Mesothelioma is a deadly and incurable cancer of the mesothelial tissue. Currently the only known definitive cause is asbestos exposure; however, recent studies into the disease have revealed a lot about the genetic links involved in the disease. This literature review will discuss genes and genetic markers involved in risk factors, diagnosis, and prognosis of mesothelioma and the power they have to create better outcomes for patients. Through the research conducted it can be understood that the CDKN2A, NF2, and BAP1 genes when mutated or inactive are risk factors for Mesothelioma.[21] Therefore, knowledge of risk factors can be an advantage for early diagnosis, because symptoms can be recognized earlier with the pre-known information that someone has a high chance of developing mesothelioma. Also, people with genetic risk factors when diagnosed with mesothelioma have a seven times better long term survival rate, this is probably attributed to a higher chance of the cancer being caught in earlier stages.[3] Likewise, there are many genes that indicate the presence of mesothelioma through the genetic markers they release into the blood. Some of these markers include glucose transporter 1 (GLUT1), insulin-like growth factor 2 mRNA-binding protein 3 (IMP3), BRCA1-associated protein 1 (BAP1), and methylthioadenosine phosphorylase (MTAP). Of the many markers MTAP with CDKN2A is the best for mesothelioma because it is very specific and sensitive.[7] These markers are also key for innovation because they are being used in the creation of novel blood tests. Additionally, the gene ALK which is found in idiopathic cases and can be used for targeted therapy. Genes like ALK are the key for more effective and targeted therapies.[13] The genes related to mesothelioma are being used in new diagnosis frameworks and the gene profiling is also being incorporated in the diagnosis and prognosis process.

Introduction

Many people in the world can name someone that has been affected by cancer. Although the world is filled with many kinds of cancer, some are more common than others, and there are some forms of this genetic disease that are still largely a mystery. Mesothelioma is a form of cancer that is still not fully understood because of its rare nature. Mesothelioma is cancer of the mesothelium, and can occur in the pleural, abdomen, pericardial region. However, pleural mesothelioma is the most common kind resulting in almost 80% of cases according to ASCO.[12] The only definitively known cause for this cancer is a naturally occuring mineral called asbestos, which was very commonly used in the 20th century, and 80 percent of cases are attributed to asbestos. Most often asbestos is inhaled and over a period of 20 to 60 years it results in Mesothelioma in the lung region. Additional indirect contact with asbestos can also cause cancer, but the cause of mesothelioma among people without exposure to asbestos and other such minerals is still not fully understood. Although researchers have countless questions and theories as to why it occurs, many just classify mesothelioma that is not attributed to asbestos and related minerals as idiopathic or spontaneous.[4,1] Nevertheless, there is

enormous research being done into genes that put one at a genetic disposition for mesothelioma as well as those affected when mesothelioma develops in idiopathic instantace. In sight into genes that put one as a genetic disposition for mesothelioma can allow the cancer to be caught earlier and expand life expectancy, while identifying genes related to the disease can help customize therapy drugs making them more effective. The problem lies in the fact that not all genes that are involved with mesothelioma are discovered and many still remain a mystery, however using the limited knowledge of the genes that are researched, scientists can draw connections to solutions and create better outcomes for Mesothelioma patients. The countless genes linked to Mesothelioma can be split into three groups, unique genes found in patients with the disease, genes that put one at risk, and genes that serve as markers for diagnosis. Through analyzing the genes involved in mesothelioma this review will convey the important role they play in understanding the disease.

Genes that put one at a genetic disposition for mesothelioma

Mesothelioma, like all cancers, is a genetic disease, although the cancer's genetic risk factors are few and still being researched, scientists have been able to isolate a couple genes. The CDKN2A, NF2, and BAP1 genes when mutated or inactive are risk factors for Mesothelioma.[21] Initially, when BAP1 is mutated in the germinal state (embryo) it puts one at a close to 100% risk of developing cancer in their life, also 30% of people with a mutated BAP1 gene develop Mesothelioma.[14] An article in *The American Journal of Surgical Pathology* outlines how testing for mutations in BAP1 through FISH showed a loss of the BAP1 gene in 7/26 cases or close to 27% off cases.[15] Although this may sound insignificant, only 0.16% of all cancer diagnoses are attributed to mesothelioma.[10] In the big picture if we take a pool of 10,000 people with a mutated BAP1 gene, it is likely that 3000 of those people will develop mesothelioma. On the other hand, if you take a pool of 10,000 people at random with and without mutated BAP1 who have cancer only about 16 of those people will have mesothelioma. This means that people with a mutated BAP1 have a 187.5 times high chance of developing mesothelioma compared to someone with cancer having mesothelioma. Additionally, NF2 mutations are another mutated gene present in mesothelioma cases. About 30%-50% of all mesothelioma cases have mutated NF2 genes present, making it the most common gene mutation in mesothelioma.[8] Although mutations differ they can be present in the form of deletion and insertion. In a study published in the *Lung Cancer Journal* scientists observed that 40% of all mesothelioma cases presented with mutations of NF2. The researchers studied the NF2 cases and identified that insertion and deletion lead to inactive genes, causing the mutations. This allowed the conclusion that inactivation of the NF2 was essential for the formation of mesothelioma, and in mesothelioma cases without NF2 mutations the gene was inactivated by phosphorylation.[8] However, what makes NF2 mutation different is that it is observed in mesothelioma however not seen in lung cancer, making it unique to mesothelioma.[17] Finally, deletion of CDKN2A is also a prevalent gene in mesothelioma, studies found that in over 74% of cases there was homozygous deletion of CDKN2A.[11] Given the

rarity of mesothelioma, research is more limited, however as more research is being done into genes that put one at risk for the disease it allows the individuals to be better informed of their condition. CDKN2A, NF2, and BAP1 are some of the more common genes that are a risk factor for mesothelioma, individuals with these genes are at a genetic disposition for the disease, this means that as more genes linked to the disease are discovered more people can be made aware of their risk for mesothelioma. Knowledge of risk allows people to be screened earlier for the disease; therefore, if they do develop the disease it enables the cancer to be caught earlier and in turn increases survival time.

Genetic advantages to Early diagnosis

Mutations in certain genes can put one as a slightly better survival rate than those without because of factors such as earlier detection, better prognosis, and possibly a genetic advantage.[14,3,4] One common gene that is looked into is BAP1 because it is commonly passed down from generation to generation. Researchers at the University of Hawaii Cancer Center found that people with germline BAP1 who developed mesothelioma have a greatly improved survival rate with a medium at six to seven years. It was found that the survival rate was increased because they responded very well to their prognosis, and some even lived 10-20 years with the cancer.[14] To be exact, scientists found that patients with germline BAP1 have a 7 times better long term survival rate. Analysis of data shows that people with the BAP1 mutation have a median 5 year survival rate, while those without BAP1 have a median survival rate of less than 1 year.[3] Although the exact factors that lead to this increased survival rate were not looked into, it is safe to assume that early detection played a role given people had knowledge of their disposition for mesothelioma. Research shows that early detection greatly improves survival chances, hence people with genetic mutations linked to mesothelioma development can be tested earlier and more frequently increase the chance that if one does develop mesothelioma it is caught early. New tests are being developed such as blood tests to enable detection of mesothelioma earlier on. For example, Mesomark® is a blood test that tests for biomarkers in the blood. Markers such as SMRP which are released by mesothelioma cells into the bloodstream long before detectable symptoms appear.[4] As testing and therapy drugs for mesothelioma become more advanced, people with genetic risk factors for mesothelioma are able to be tested earlier and more frequently. In addition, if the mutated genes are identified more curated therapies can be administered creating better prognosis.[4] Science is rapidly advancing, specifically in the innovation of newer and better methods of diagnosis and prognosis. Hence, with genetic mutations linked to mesothelioma identified, it allows both the patient and the scientist to have better outcomes, by adapting to the risk and allowing for a greatly improved life expectancy through early diagnosis.

Markers that indicate presents of Mesothelioma

Often the only strategy for mesothelioma diagnosis is biopsy, however alternative strategies exist such as testing for markers in the blood displayed by the tumor. There are many markers of mesothelioma , however, to be able to test for mesothelioma effectively the gene must be specific for mesothelioma and also sensitive. In a literature review by the ACS, it is explained how markers such as glucose transporter 1 (GLUT1), insulin-like growth factor 2 mRNA-binding protein 3 (IMP3), and BRCA1-associated protein 1 (BAP1) is highly specific for mesothelioma, but come with trade-offs.[7] Firstly, GLUT1 and IMP3 are both traditional markers for mesothelioma diagnosis, but are not very effective when tested alone, because of their low sensitivity at 21% and 37% respectively. However when the immunoexpression of both GLUT1 and IMP3 was tested for there was a 45% sensitivity.[5] Although sensitivity of GLUT1 and IMP3 greatly improved when both immunoexpression are tested for, it is not the most effective solution. Secondly, BRCA1-associated protein 1 is also a marker for mesothelioma and studies show that it stains negatively in 67% of cases however it has low sensitivity in sarcomatoid tumors.[7,17] The downside is that in some cases BAP1 expression was lost, making it an unidentifiable factor. The cause for the loss of the BAP1 expression is not exactly known, scientists had concluded that because of this unique quality of BAP1 it is a bad marker for diagnosis but has the possibility of identifying subtypes of the disease for prognosis. It has recently been discovered that the surrogate marker methylthioadenosine phosphorylase (MTAP) is both highly sensitive and specific for mesothelioma making it a great marker to test for.[7] MTAP is a surrogate marker with the deletion of CDKN2A, making the deletion of both highly unique to mesothelioma. CDKN2A is often mutated in mesothelioma patients, since it is a gene that puts one at a genetic disposition for the disease, therefore when coupled with MTAP it becomes highly specific to mesothelioma.[6] In today's world, biopsy is one of the only ways to identify mesothelioma, however this is a invasive and extensive methode; therefore, testing for biomarkers in immunoexpression is a less invasive strategy which although has much improvement needed, the advances made in identifying the biomarkers is the first step. The identification opens countless doors. Although today MTAP coupled with CDKN2A is the best identifier, as more biomarkers are discovered using the most sensitive and specific one for mesothelioma is key for making diagnosis the most effective it can be.

A unique gene linked to idiopathic Mesothelioma

Although a good amount of the genes linked to mesothelioma are known, still a lot remains a mystery in idiopathic cases especially involving kids and young adults with no asbestos exposure. In such cases testing is being done. One unique gene found in children and young adults is Anaplastic Lymphoma Kinase (ALK). In a study done at the National Institutes of Health in Maryland, participants who were diagnosed with mesothelioma before they turned 40 were tested for ALK through FISK.[13] This group of participants are significant because it takes 20-60 years from the time of asbestos exposure to develop mesothelioma; however some of the participants in the study were

only 14. Since asbestos is the only confirmed known cause of mesothelioma, everyone below 20 with the disease most likely has an idiopathic case. Likewise, since everyone in the study is below 40 at the time of diagnosis it is highly probable that a large number of the people in the study have cases not linked to asbestos. In the study 6% or two out of the 32 of the group tested positive for ALK. The positive tests arose from a 14 year old female and a 27 year old male, both had idiopathic cases. Researchers believe that such information is beneficial because it allows for patients with mesothelioma and also the presence of ALK to receive therapy targeting the ALK such as tyrosine kinase inhibitors targeting ALK.[13] ALK is just one of many genes that are present is mesothelioma and when identified can be used to curate more targeted treatments. As evident from the evidence, genes like ALK are not gene specific allowing them to be tested for and used in a wider range of people. Genes like ALK can be the step needed to treat mesothelioma more effectively in both idiopathic and non-idiopathic cases.

Novel diagnosis methods utilizing genetic markers

Mesothelioma's main underlying problem other than that its incurable nature is the fact it is so incredibly hard to diagnose. However novel techniques to diagnose it are being implemented, utilizing genomes and profiling. In this section just two of the many techniques that are being developed are discussed; however, these two techniques are unique because they utilize genetics in two very different ways, and both have huge potential to change the way we diagnose mesothelioma. First, researchers from Pakistan are using the genetics of a person to evaluate their mesothelioma risk and do further testing. Currently prognosis factors such as performance status, age, and sex of the patient are the most substantial however none of these factors are heavily unique to mesothelioma. The scientists conducted a study using a very large public database of mesothelioma patients, they used artificial intelligence to analyze the information. Analysis of the data showed novel mesothelioma factors including Pleural lactate dehydrogenase, C-reactive protein, and pleural albumin. The scientists hope to use this information to create a new framework for diagnosis making mesothelioma easier to catch.[2] Using computers to assist with diagnosis is extremely effective since AI is rapidly advancing. Utilizing this method, with time more prognosis factors can be found, and allow for the revision of the framework to make it more effective. Studies show that AI involvement in diagnosis streamline diagnosis and improve clinical outcomes.[9] Secondly, gene expression profiling in mesothelioma. Profiling of mesothelioma in general showed that marked up-regulation of energy, protein translation, and cytoskeletal remodeling pathways were present These novel markers can be incorporated to identify mesothelioma more effectively but also they can be targeted in .[7] For example, methods such as a two-gene prognostic score (2-PS) which incorporate genes are able to utilize information from gene profiling. The 2-PS uses a model incorporating two genes to show survival rate. The first test with this system was done with GOLT1B and MAD2L1, since currently those two genes are revealed to be the best indicators of survival rate. However, as gene profiling of

mesothelioma advances better genes are revealed and can be used in 2-PS to gain more accurate results.[19] Currently, 2-PS has only been applied to mesothelioma a limited number of times, but further testing can allow for scientists and doctors to use 2-PS in a wider range of factors linked to mesothelioma.

Conclusion

In all, a clear and deep understanding of the genes involved in mesothelioma are key to a more effective diagnosis and prognosis of the disease. Novel and breakthrough research is the key to breaking the code to all rare diseases, not just mesothelioma. The science and research community must continue to work to study and unravel the genes involved in mesothelioma. Mesothelioma is a rare and incurable cancer to this day, even with the constant advances in technology. Although the asbestos related cases are understood to a level, sporadic cases still remain a mystery. Understanding genes linked to risk, diagnosis, and prognosis are essential.

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Non-Asbestos Related Mesothelioma

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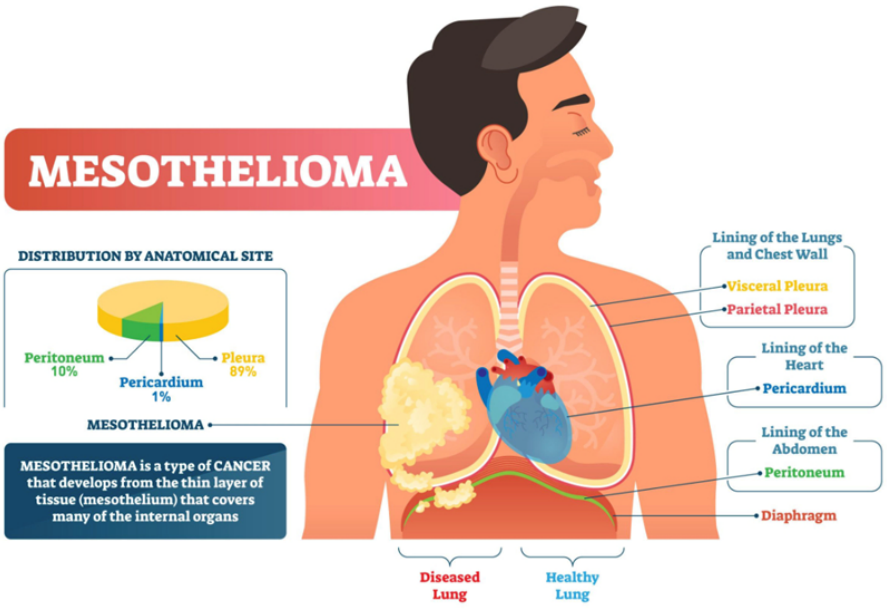
Keywords: Cancer research, Mesothelioma, Erionite, Gene disposition, Bap1 mutation, Radiation, Radiotherapy

Abstract:

Mesothelioma is a rare condition that involves the Growth of malignant tumors on the mesothelium, the thin protective lining of the Lungs, stomach, and heart. Mesothelioma primarily affects the lungs caused by the inhalation of carcinogens such as the widely known and accepted cause of mesothelioma, Asbestos exposure. However, relatively recently researchers have located multiple new Risk factors for mesothelioma, such as exposure to the natural mineral known as Erionite. Erionite is a natural forming mineral just like asbestos and is often found in volcanic ash and gravel production as well as naturally formed underground where miners may become exposed to the harmful carcinogen. The amount of Erionite exposure related mesothelioma cases does not fill the 30% of non-asbestos related mesothelioma cases, other elements such as certain genetic dispositions. The Bap1 gene controls and prevents the growth of tumors in the body, many patients who have contracted mesothelioma have been found to be related to a Bap1 gene mutation, this mutation effectively eliminates the protection against tumors and lead to patients being way more susceptible to developing mesothelioma. Bap1 mutation may allow for supplementation to the growth of tumors and formation of mesothelioma however there have been instances where minerals such as asbestos and Erionite have not been found in a patient That has developed Mesothelioma However The mutated Bap1 gene is present leading researchers to question if the gene itself can cause the Deadly cancer. The more uncommon occurrence believed to cause mesothelioma is radiation therapy, Cancer patients who have undergone chest radiotherapy have later developed mesothelioma due to the heavy doses of radiation. Overall, Asbestos is the widely believed the sole cause of mesothelioma however roughly 30% of cases are not related to Asbestos at all and some possible risks are the Erionite exposure, Gene dispositions and mutations, and Radiation therapy.

Introduction:

Mesothelioma, a rare and very aggressive form of cancer, asbestos has long been considered as the cause of mesothelioma. However, more recent studies have revealed that nearly 30% of Mesothelioma cases are completely unrelated to asbestos exposure. This revelation has sparked many scientist's interests and prompted further exploration into the lesser-known causes and risk factors of this devastating disease. Mesothelioma primarily affects the thin protective lining of organs such as the lungs, heart, and Figure 1abdomen, is notorious for its long period of latency often spanning several decades between exposure and first sign of symptoms. The cause, traditionally linked to asbestos, a mineral that naturally occurs and is used extensively in infrastructure, construction, and shipbuilding. However, many cases of Mesothelioma have been found to have no connection to asbestos which poses a perplexing challenge for clinicians and medical researchers. (Professional, n.d.)



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The emergence of these non-asbestos related cases has raised critical questions regarding their underlying cause and if there are any new risk factors many researchers are investigating the mechanisms that are

triggering mesothelioma development, multiple new factors have been believed to cause non-asbestos related cases these factors include:

Erionite exposure: Erionite, a naturally occurring mineral like asbestos often found in volcanic ash and sometimes used in gravel production, has been identified as a potential cause of mesothelioma in certain geographical regions. Areas with high Erionite deposits such as parts of Turkey and the United States of America have reported an increase in mesothelioma cases not related to asbestos. (Dogan, A., Dogan, M., & Hoskins, J. A. (2008))

Genetic disposition: Emerging evidence suggests that certain genetic mutations and variation can render individuals to be more susceptible to the development of mesothelioma even with an absence of Asbestos. Research is currently being undergone to identify the specific genes and genetic pathways responsible for the development of mesothelioma. Research has pointed to more cases of mesothelioma occurring in individuals lacking the Bap-1 gene and some cases where mesothelioma develops without asbestos or Erionite exposure. (Selby, K., RN. (2023b))

Radiation and environmental hazards: Radiation therapy that targets the lungs and chest area has been found to cause the growth of tumors on the mesothelium. Other environmental hazards such as "natural" exposure to large doses of radiation have been found to cause multiple types of cancer as well as mesothelioma.

The complex web of non-asbestos exposure related cases requires a lot of collaboration amongst researcher's clinicians and public health experts. The goal is to provide more thorough diagnostic strategies, targeted therapies, and enhance knowledge and prevention efforts for these devastating diseases.

"The asbestos problem affects everyone" John Engler

In this article we will delve deeper into the non-asbestos related mesothelioma cases exploring the latest research into the matter as well as breakthroughs and challenges faced by medical professionals in the quest to understand and prevent this deadly disease. Through a comprehensive examination of

epidemiological studies, genetic investigations, and case reports will shed light and awareness onto the little-known causes and risk factors for mesothelioma. By broadening our understanding of the disease and expanding knowledge regarding the Diagnostic approach, we move closer to providing targeted treatments and effective management options for patients affected by mesothelioma regardless of asbestos exposure.

The impact of Erionite exposure:

The most common Mesothelioma cause other than asbestos is Exposure to a mineral known as Erionite, Erionite belongs to the Zeolite group and is similarly structured like asbestos is slowly becoming known for its potential health hazards, in particular its connection to mesothelioma. Erionite can easily enter the lungs if the mineral is agitated enough to become airborne. ((*Erionite: An Emerging North American Hazard | Blogs | CDC*, 2019)). Erionite is structurally like asbestos and has been found in various regions across the globe most notably would be locations containing volcanoes and volcanic ash since erionite can often be found in Volcanic ash as well as certain mines in Turkey and the United States. This poses significant health risks to those that meet it Either through volcanic ash or mining, Erionite deposits have been reported in most countries across the globe however it is only in the three villages of the Cappadocia region turkey where environmental exposure to erionite has been proven to directly cause an epidemic of mesothelioma however the other erionite deposits have a high possibility to cause a similar epidemic if exposure occurs. Dogan, A., Dogan, M., & Hoskins, J. A. (2008). Samples of the Erionite deposits from the three villages using a High-resolution field Emission SEM showed microstructures of Bundles Fibers and Fibrils which are very important physical properties of fibrous erionite minerals. These fibers being very similar to the asbestos fibers were compared in terms of numbers of fibers. According to research by A. Umran Dogan, assuming that the lung burden of fibers in the human mesothelium victim is approximately 1 mg, and the hazardous fibers are around 1 μm in diameter and 10 μm long, the 1 milligram would contain roughly 40 million asbestos and 50 million erionite fibers. These microstructures of erionite draw attention to the connection between surface area and volume to the carcinogenicity of the mineral. Once more, A Umran Dogan concluded that “the larger surface area to volume ratio and their relationship to the carcinogenicity of the mineral. The larger surface area creates a wider platform for mineral–cell interaction and thus more possibilities of proliferative transformation of mesothelial cells.”.

The Three villages experienced roughly between 7-16% of their population develop mesothelioma due to the mining of nearby erionite that was carried on clothing back to the village. Inhalation of Erionite

fiberscan often lead to disposition in the lungs, often triggering chronic inflammation and the formation of reactive oxygen species. These processes, coupled with the genotoxic effects can result in DNA damage and chromosomal aberrations, ultimately leading to the development of mesothelioma. A study by (Carbone et Al, 2011) and another article (Dogan er al, 2008) investigated the biological mechanisms underlying Erionite carcinogenicity and found that Erionite fibers have a very high binding affinity for the same cell receptor, as asbestos fibers, simply this interaction promotes tumor growth like the reaction of Asbestos once it enters the body. Further research on Animals who had been exposed to the mineral supported the previous Claim that Erionite can and does cause mesothelioma.

The recent studies have started to shed light on the dangers of Erionite exposure and how common Erionite is found for example the many deposits found in the Western America as seen below.

From Sheppard (USGS), 1996.

New preventative measures have been taken in an attempt to reduce exposure to the harmful toxin such as restrictions on mining operations involving the Mineral and the ban on its usage domestically. However, awareness of the presence this mineral has is very limited and most of the populace does not know of its existence, as such actions must be taken to inform the people such as identifying where the deposits take form and implementing like what they did in Cappadocia screening procedures for those within the vicinity of the health risk who may have been exposed directly or indirectly. Furthermore, just like asbestos the ban on obtaining, using or making contact with the mineral is in place however the problem lies in the fact that the mineral and its potential health risks is not well known to the populace. just as with the reduced usage and mining for asbestos erionite exposure is and will further need to be more regulated in workplace environments and effective safety protocols is vita; furthermore, developing safer alternatives to erionite-containing materials, such as construction and insulation can greatly reduce the risks of mesothelioma and effectively stop the spread of Erionite exposure (Metintas et al 2010).

Genetic disposition and its role in Mesothelioma

Although mesothelioma is widely believed to be caused by the inhalation of toxic minerals such as asbestos and Erionite, another potential risk has been identified and researched. The risk is Genetic dispositions, a Gene called the Bap1 which is responsible for creating and controlling Tumor growth throughout the body. The Bap1 gene also regulates a channel that moves calcium inside cells. With gene damage or mutation, calcium levels drop. As this happens cancer risk is higher from carcinogens such as asbestos (Selby, 2023c). This gene has been found to be mutated in a significant number of mesothelioma patients especially the Three villages in turkey however due to the village's smaller population and many kin marriages the gene seems to present in most of the villagers. Other research has compared two families one of which over half were positive for mesothelioma whereas the other had only one instance of mesothelioma. The family that had more cases was found to have mutated Bap1 genes whereas the family with only one case was lacking this mutation. With this information researchers have concluded that this gene mutation occurs in nearly 70% of mesothelioma cases where only 20% of cancers correlates with the Bap1 gene. This allows the Gene to be a possible target for prevention therapy.

Researchers have posed the question is mesothelioma hereditary and whilst this Bap1 gene mutation is hereditary it does not directly cause mesothelioma it only supplements the progression and development of the disease allowing mesothelioma to present itself earlier and develop faster. Typically, mesothelioma occurs later in life with asbestos fibers laying in wait in some cases 50+ years. Bap1 gene can also be used as a screening tool. The national cancer institute studied genetic risk and potential solutions in 2019. Senior investigator Dr Hassan studied the gene in similar instances. "This is an important, long-term study that could have implications not only for a patient, but for family members, too," Hassan said."Progress can be made in terms of prevention and early detection." When and if doctors locate a Bap1 mutation, they can provide steps to lower mesothelioma risk such as avoiding workplace exposure and Tobacco use can decrease the incidence of disease. The use of genetics to prevent mesothelioma has been more popular recently with many detection devices revolving around the testing of genes and genetic disposition. For example, through Dr. Michele Carbone Healthy Bap1 levels and repaired calcium channels led to positive chemotherapy results. (Selby, 2023d)

Radiation and environmental hazards

Some cancers that affect the chest region are treated using Radiation therapy to both shrink and "kill" the cancer tumors however there have been multiple instances where radiation therapy has caused Mesothelioma to develop doing the opposite of "Killing" the disease. According to the mesothelioma veterans center There are two main ways that someone can obtain "mesothelioma from radiation therapy one of which is Radiation exposure, particularly to the radioactive substance Thorium dioxide, which was used with X-rays to diagnose health conditions between the 1920s and 1950s, may increase the risk of developing mesothelioma" Penn Abramson Cancer Center. The other is Radiation Treatment for other cancers scientists are starting to believe that patients who receive radiation therapy for other cancers may have an increased risk of mesothelioma. The reason being that radiation typically harms cancerous and non-cancerous cells ``***Radiation*** exposure may cause mesothelioma, such as when a patient has previously received radiation therapy for lymphoma." American Society of Clinical Oncology

This research has been indecisive, and researchers have only drawn theories that radiation can cause mesothelioma specifically however other cancers have been connected to radiation therapy there are few cases where mesothelioma develops due to radiation therapy. (Dryfoos & Dryfoos, 2021) Other environmental dangers also relate to exposure to radiation However the exposure varies from cases like Chernobyl where heavy doses of radiation infect the body, however in this case that is the least of someone's worries. Other natural exposure to radioactive material can cause various cancers, one of which is mesothelioma.

Conclusion:

More research is needed before scientists can narrow down the exact non-asbestos related causes for mesothelioma, however throughout the past 15 years efforts to discover other harmful minerals and chemicals has drastically improved leading to the discovery of one risk factor being erionite exposure. Erionite, a similar material to asbestos that is naturally formed and found in various locations around the world, has caused the development of mesothelioma in many people, especially in rich erionite locations such as Turkey. Although 30% of mesothelioma cases are not related to mesothelioma, Erionite only makes up somewhere between 7-16% of cases, so what are the other risk factors? Although it has not been the preliminary focus, research into genetic factors has greatly increased leading to the discovery that the bap1 gene mutations have been found within a majority of mesothelioma cases and in rare

instances mesothelioma will crop up without asbestos or Erionite involved leading to believe the gene mutation alone may be the cause as-well as an inhibitor to the disease. Other risks associated with the disease would be radiation exposure such as patients that receive radiation therapy for the chest have been found to develop mesothelioma as a result although rare enough cases have occurred for the risk factor to be associated with the cancer. Furthermore, certain environmental risks are present through chemical gasses and Metal materials that can be breathed into the lungs. Long exposure to such materials such as small zeolites, a type of mineral, has led to the development of the disease. Although roughly 70% of mesothelioma cases are directly related to asbestos exposure, the other 30% have been and currently are Being thoroughly researched, these findings have allowed scientists to warn people of the newfound risks and causes of the cancer as well as the treatments and preventative measures available to those at risk. Overall, there are many risk factors for the disease that are not common knowledge and warnings are needed to inform more of the public of these risks in hopes to lower mesothelioma cases significantly.

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Mesothelioma Prognosis

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Keywords: Mesothelioma, Cancer, Asbestos, Treatment

Abstract:

Mesothelioma is a rare type of cancer that mainly targets the lungs through the inhalation of asbestos particles. Asbestos is a mineral fiber commonly found in rocks and soil, and was often used for construction during the 1970s. It takes a considerable amount of time for the development of cancer cells after enough asbestos exposure. However, careful consideration must also be noted because nearly eighty percent of all mesothelioma cases start with asbestos exposure. Possible and available treatment options range from getting surgery, radiation therapy and chemotherapy. Most of the time, a combination of two treatment methods work more effectively than sticking to one option. Emerging treatments such as immunotherapy and vaccine therapy expand the field of mesothelioma research and allow hope for the cure of mesothelioma to be found in the future.

Introduction:

Mesothelioma is a rare type of cancer that mainly targets the lungs, but can also affect the heart, abdomen and testicles. The most common type of mesothelioma is Pleural Mesothelioma, which is contracted through the inhalation of asbestos exposure. Asbestos is a mineral fiber commonly found in rocks and soil. Before the 1970s, due to its strength and heat resistance properties, asbestos was used in a lot of building constructions for insulation as well as a fire retardant. Typically, asbestos exposure is rare, so the only way asbestos fibers can be released is through the damaging or disturbing of asbestos-containing products. It takes a considerable degree of asbestos exposure to cause diseases where asbestos particles lie in the tissue lining of the mesothelium, eventually leading to the development of mesothelioma. However, careful consideration must also be noted because asbestos exposure accounts for nearly eighty percent of all mesothelioma cancer cases. The development of mesothelioma takes a long period of about fifteen to fifty years, which isn't the most ideal because most cases of mesothelioma are diagnosed in its late stages. The early symptoms of mesothelioma include shortness of breath, coughs, fatigue, and chest pain. The average life expectancy after mesothelioma diagnosis is around four to eighteen months, but there have been cases of patients who lived past the ten-year mark. While mesothelioma is still incurable, possible treatment options are available. The treatment options include surgery, radiotherapy and chemotherapy, but the treatment plan is decided based on the stage of cancer patients are in as well as other health

conditions like age, gender, blood chemistry, and cell type. This literary review aims to go into more detail about the prognosis for Pleural Mesothelioma and possible treatment options as well as emerging treatments that may be more effective at killing the cancer cells.

Treatments for Mesothelioma:

Surgery for Mesothelioma

Of the few treatment options available, surgery is often a more prevalent choice. Surgery for mesothelioma may be done in an attempt to cure the cancer by getting rid of existing cancer cells inside the patient's body. This is otherwise known as potentially curative surgery. Most of the time, however, surgery cannot fully cure a patient of their mesothelioma due to the possible fact that all cancer cells may not be removed during surgery. Surgeons have no way of telling the full extent of the spread of the cancer cells, which makes it difficult for the surgery to be completely successful. Thus, potentially curative surgery is mostly performed to help the patient live longer. The aforementioned type of surgery may be more suitable for the earlier stages of mesothelioma. In cases where the cancer has spread too far and the patient is too ill for a large-scale surgery, palliative surgery may be performed to help relieve the pains of the cancer for the patient. The goal of a palliative surgery is to ease the pain, rather than remove any cancer cells or cure the cancer.

Extrapleural pneumonectomy (EPP)

One type of a potentially curative surgery is Extrapleural pneumonectomy (EPP). EPP is only done when surgeons think that a cure is possible and the cancer may be removed completely. However, as it is a very big operation, only experienced surgeons may perform on healthy patients. The patient must be in rather good health and suffer from no other illnesses to endure the effects of EPP. About 1 in 3 patients face complications when going through EPP. This is because during an EPP, the surgeon removes the lungs, diaphragm, pericardium and nearby lymph nodes that are affected by the cancer. Man-made materials then replace the diaphragm and pericardium after they are removed.

Pleurectomy/decortication (P/D) and Debulking (partial pleurectomy)

Moving on, one type of palliative surgery is Pleurectomy/decortication (P/D) + Debulking (partial pleurectomy). In a P/D surgery, only the affected tissues lining the chest wall, lung, mediastinum and diaphragm are removed. The lung and diaphragm muscles do not get removed, and there aren't any man-made materials that replace the removed tissues. In a debulking surgery, the main goal is to remove as many of the cancer cells as possible. Typically, less tissues are removed in a debulking when compared to a P/D. Both of these surgeries aim at lessening the pain of the cancer and allow the patient to breathe better.

Radiation Therapy for Mesothelioma

Radiation therapy tends to be harder to use when it comes to treating mesothelioma due to the fact that the cancer cells usually grow in large concentrations, but improved methods of technology and tools have made this treatment more effective at killing cancer cells. New methods of radiation therapy allow better execution of high-energy x-rays, and can be used in a few different ways. One of the most uses of radiation therapy is after surgery to kill cancer cells that were missed during operation. This is also known as adjuvant radiation therapy. In addition, this procedure can also be used "to ease symptoms of mesothelioma such as shortness of breath, pain, bleeding, or trouble swallowing" (American Cancer Society). The aforementioned treatment is called a palliative procedure, which is similar to a palliative surgery. In addition, the delivery of radiation rays during the execution process is completely painless and safe.

External beam radiation therapy (EBRT) and intensity-modulated radiation therapy (IMRT)

External beam radiation therapy (EBRT) is the most common type of radiation therapy. This is done by projecting radiation into the affected areas inside the patient's body from an x-ray machine outside. Possible radiation damage can be done to nearby healthy cells. However, the penetration of a high energy source damages the DNA of the cancer cell, along with shrinking the size of the tumor and preventing future occurrences of the cancer cells. With the new and more advanced intensity-modulated radiation therapy (IMRT) doctors can treat the cancer cells more precisely by using different beams of radiation rays in certain areas of the cancer. This procedure surpasses the use of EBRT by targeting affected areas more precisely and reducing the amount of side effects or damage done to nearby healthy tissues and organs.

Brachytherapy

Brachytherapy is another type of radiation therapy. During the brachytherapy procedure, instead of using an outside radiation source, the radiation source is directly put inside the patient's body, either right in the cancer area or near the cancer area. A 2020 study published by the National Library of Medicine found that patients in their early stages of cancer had overall longer survival rates after going through radiation therapy combined with other treatment options.

Chemotherapy for Mesothelioma

Chemotherapy is often used alongside surgery or radiation therapy to treat mesothelioma. Different anticancer drugs are used in different ways to kill cancer cells in the body. Doctors have yet to figure out the best drugs and the best ways to use them, so drugs paired with either surgery or radiation therapy make the best treatment option for some patients. Usually given in cycles, the period of time for treatment is between three to four weeks, followed by a resting period to allow the patient's body to recover. In the case that chemotherapy can be paired with surgery for the cancer, doctors will have the patient take the drug before surgery in an attempt to shrink the size of the cancer cells and lower the risks that the cancer will spread to other parts of the body. This is also known as neoadjuvant therapy. Adjuvant therapy, which also involves taking drugs with surgery, is the use of drugs after surgery to kill any small areas of cancer that were not removed during the operation. Chemotherapy may be used with radiation therapy if surgery cannot remove the cancer cells.

Systemic chemotherapy and intrapleural or intraperitoneal chemotherapy

The two main ways in which drugs are given to patients is through either systemic chemotherapy or intrapleural or intraperitoneal chemotherapy. In systemic chemo, the drug is injected into the blood through a vein in which the drug then travels through the bloodstream to reach wherever the cancer cells are to kill them. In intrapleural chemo, the drug is directly placed into the chest area through a tube that is placed in the body through a small incision in the chest. Similarly, in intraperitoneal chemo, the drug is delivered to the abdomen by a tube through a small incision in the abdominal wall. Intrapleural or intraperitoneal chemo may be more effective than systemic chemo based on the fact that the drugs travel directly to the designated area in said type of chemotherapy. Through systemic chemo, the drugs travel through the bloodstream and multiple parts of the body, which may negatively affect other healthy parts of the body. Hyperthermic chemotherapy, the act of heating up drugs before they are placed into the patient's body, aids in the drug working better at killing cancer cells in the body.

Emerging Treatments for Mesothelioma

Some examples of emerging treatment options for mesothelioma include immunotherapy and gene therapy. Although the emerging treatments cannot be used on their own, paired with older treatments make them more effective at killing the cancer cells. More and more research has been done to target mesothelioma, and a final breakthrough happened in 2020 when the FDA approved the immunotherapy combination of Opdivo and Yervoy. This acceptance would be the very first treatment of mesothelioma to be accepted in sixteen years.

Immunotherapy

Immunotherapy, the act of taking drugs that influence immune cells in the body to attack and destroy cancer cells, is a new but effective treatment for mesothelioma. An improved immune system allows a better job of fighting cancer cells in the body. The newly approved combination of Opdivo and Yervoy drugs in 2020 has improved and lengthened a patient's overall survival rate with mesothelioma. Dr. Bernardo Goulart at the Seattle Cancer Care Alliance further accentuated the success of Opdivo and Yervoy by explaining that "the disease is subject to the harnessing of the immune system. This will open many doors." When used with other treatments like chemotherapy, the survival rate of the patient is undeniably going to be longer. The usage of immunotherapy is also more beneficial than chemotherapy when brought into comparison, as results have shown that there are fewer side effects with immunotherapy, and a stronger immune system fights better than any other medical treatments such as drugs.

Vaccine Therapy

Vaccine therapy is a rather new treatment method for mesothelioma that works alongside immunotherapy to fight cancer cells. Once injected into the body, the vaccine would instruct the immune system to create antibiotics to fight cancer cells. Paired with immunotherapy treatments, the body becomes stronger in its defense against the invasion of cancer cells. A clinical trial arrived at the conclusion that patients who received the WT1 vaccine had an overall median of 4.8 months longer survival rate than patients who received the placebo sample.

Conclusion:

While the complete cure for mesothelioma is yet to be found, more and more treatment options are becoming available with advancements in technology and breakthroughs in discoveries. Surgeries, radiation therapy and chemotherapy remain stable operations as immunotherapy and vaccine therapy will soon become available treatment options to all mesothelioma patients. Available treatment plans will also depend on the individual patient's stage of cancer and body condition. Certain treatments may work better on specific individuals based on how each patient's body reacts to different treatments. All in all, the field of research for the cure of mesothelioma has a long way to go, and it is important that doctors receive support in their development of possible effective solutions.

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Literary Review

Non-Asbestos Factors That Can Impact Mesothelioma

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Abstract:

Mesothelioma is a form of cancer found throughout the human body. The most common cause of mesothelioma development is exposure to asbestos, a material often used in construction and building materials. However, asbestos exposure is not the only factor that can influence the development of mesothelioma. Other environmental factors include exposure to zeolite minerals like erionite, and radiation exposure. An etiological factor is the SV40 virus, which has millions of cases globally due to infected polio vaccines. The last factor to be discussed in this paper is the genetic component behind this disease. BAP1 is especially apparent, but mutations and variations in the genes of other tumor suppressants/DNA-repairing proteins can increase the likelihood of mesothelioma development. This paper aims to display the other factors that can induce mesothelioma development in order to broaden research past asbestos exposure.

Introduction:

Mesothelioma is a type of cancer, most notably caused by asbestos, found throughout the body. The mesothelium is a thin tissue layer that covers most of the body's internal organs, and in cases of mesothelioma, it is the mesothelium that is affected by this cancer. There are various types of mesotheliomas as well, with pleural in the lungs, peritoneal in the peritoneum/abdomen, and pericardial in the heart (1). This rampant and life-threatening cancer is often associated with asbestos, a popular material used in building houses in the mid-20th century, but it is not always artificially induced. There are also naturally occurring silicate materials/minerals that can cause mesothelioma, such as asbestos and zeolites, even when they are not used in construction. Mesothelioma is considered to be an uncommon cancer, with only about 3000 cases being diagnosed each year in the United States according to a statistics study done by Michelle Whitmer under Asbestos.com (2). Due to the latency period of mesothelioma development, it is possible that symptoms of mesothelioma won't appear until after 20-60 years after the initial exposure, according to RN Karen Shelby at Asbestos.com (3). However, there are many other instances in which mesothelioma was contracted naturally from various sources besides inhalation of asbestos-based construction materials, and this paper looks to examine these sources and their impacts on mesothelioma development.

Zeolites:

One of the most popular cancer-causing zeolites is erionite, which can be found naturally in volcanic ash (4). The mineral is similar to asbestos in that both are silicone-based and can cause mesothelioma when individuals come into contact with it. However, the Environmental Protection Agency does not consider erionite one of the six asbestos fibers to be regulated by the US (4). Exposure to erionite can cause fibrogenic lung disease, lung cancer, and mesothelioma. The risks of this exposure were not discovered until a study of Turkish villages came out in the 1970s. These villages utilized erionite in the majority of their building materials and were in turn hit with waves of mesothelioma and other cancer-related diseases because of it. In a research study conducted by researchers at Hacettepe University on 84 patients exposed to erionite or asbestos in rural Turkey, all the patients had some level of pleural thickening (5). Pleural thickening has been studied and observed to be closely tied with pleural mesothelioma by Mary Ellen Ellis under Mesothelioma.net (6). Pleural masses were found in 52% of the patients studied in Turkey, which again indicated high levels of malignant pleural mesothelioma in this population exposed to erionite/asbestos. Though this study took place in Turkey, erionite has been observed in 12 different US states (4), which proves why this research is relevant and pressing. Furthermore, a study carried out by researchers at the University of South Florida, Saint Elizabeth Health Center, and GATA Haydarpasa Training Hospital observed patients with mesothelioma exposed to erionite (E-MPM) and asbestos (A-MPM), and they determined that those exposed to erionite were 14% more likely to have died by the end of the study compared to those exposed to asbestos (7). Throughout the study, the same remained true, as there were fewer E-MPM individuals that survived in each stage of mesothelioma compared to A-MPM individuals. The prevalence of this mineral paired with its association with mesothelioma should not be ignored, and it shows that not all mesothelioma is caused by asbestos. We cannot focus solely on asbestos, and broadening the research will help prevent mesothelioma before it is even needed to be treated.

Radiation:

Another cause of mesothelioma that is not related to asbestos exposure is radiation therapy. Most notably found in children undergoing chemotherapy, radiation-induced mesothelioma can manifest in different ways. Whether it is pleural mesothelioma in the lungs or pericardial in the heart, there is an observed positive relationship between the two variables proven by a study carried out by researchers at various universities on the non-asbestos causes of mesothelioma (8). In these cases, radiation therapy to treat adolescent tumors was most often in the case of lymphoma, germ cell neoplasms, and breast cancer.

After receiving radiation therapy, the children would enter a latency period between 5-50 years and would develop mesothelioma within that time frame. When therapy is done through thorotrast administration, the $^{232}ThO_2$ deposits in organs (8). This radioactive substance has been linked to prolonged alpha-ray emission and slow decay, as well as tumor development. Beyond children, radiation also poses a risk to those exposed in occupational settings. At the Idaho National Engineering and Environmental Laboratory, energy workers faced an increased risk of mesothelioma development between 1946 to 1990 when the data was analyzed by researchers at the University of North Carolina (9). This heightened risk was due to the excessive exposure the workers recreationally faced when nuclear demolition and processing took place. Furthermore, there are also cases of those exposed to radiation through X-Ray diagnostic exams because of exposure to thorotrast during treatment. One factor to be considered, however, is the fact that these radiation therapies have changed over time to include less harmful substances like thorotrast. Though the risk of developing mesothelioma is still there, it is currently the most effective option to treat the aforementioned cancers/tumors according to Kenneth E Rosenzweig, who analyzed radiation therapy for malignant mesothelioma (10). However, there has recently been some research using other methods to treat tumors instead of radiation therapy, which could significantly reduce mesothelioma cases in these radiation-exposed patients.

SV40:

Simian Virus 40 (SV40) is a potential etiological cause of mesothelioma. SV40 is most commonly found in Macaque monkeys, and it is a DNA polyomavirus, meaning that most of its hosts are mammals or birds. While the virus mostly infects host species that are immunocompromised, there are instances in which nonhost species have been infected. SV40 has also been established by Michelle Carbone at the University of Hawai'i Cancer Center and others as a transforming virus that can cause human mesothelial cells in vitro to transform after infection (11). This transforming ability is mainly observed in rodents and is tumorigenic or tumor-causing. SV40 has infected humans through injections of the polio vaccine and was especially prevalent in vaccines dating back to the mid-20th century. One such example was the Salk poliovirus vaccine, which was administered from 1955 to 1963, and was contaminated with SV40 according to researchers at the University of Colorado (12). The vaccine failed to inactivate SV40 in the same way it inactivated polio, and further testing allowed researchers to determine that SV40 could infect humans, and that it could promote tumor growth as well. Even before this vaccine, SV40 naturally circulated around the human population, but it is estimated that hundreds of

millions of people were globally exposed to SV40 by this vaccine between 1954 and 1963 (11). Scientists began to study the relationship between SV40 and mesothelioma and found SV40 tag proteins in mesothelioma cases. The data is relatively conflicting, however, and some laboratories are unable to find the tag proteins for SV40 in their mesothelioma cases. Despite the inability to establish a causal relationship, there may be other ways to explain why the tag proteins are found in mesothelioma cases. One hypothesis is that SV40 is instead a passenger virus for mesothelial cells but does not cause tumorigenesis. The confusion regarding SV40's role in mesothelioma displays how much attention has been put toward studying asbestos. Instead, researching other potential causes of mesothelioma, like SV40, can help prevent more cases of mesothelioma in the future.

Genetic Inheritance:

The final non-asbestos related factor to be discussed that plays a role in mesothelioma development is genetic predisposition. The genetic risk factors to be discussed are either low-risk or high-risk, each still impacting the patient's potential contraction of mesothelioma. A review done by researchers at Università del Piemonte Orientale found that a low-risk genetic factor is 10 to 15-fold less likely to cause development of malignant pleural mesothelioma (MPM) compared to asbestos exposure (13). However, a large number of these low-risk factors can increase the likelihood of developing MPM, and it can exemplify the effects of asbestos exposure. High-risk genetic factors tend to include mutations of proto-oncogenes or other tumor-suppressor genes. The lack of regulation towards cell growth causes the development of tumors/cancers, including mesothelioma. The most studied high-risk factor in the development of MPM development is BAP1 and the disease BAP1-TPDS (13). This disease has an autosomal and dominant pattern of inheritance, and individuals that contract it have a higher risk of developing tumors/mesothelioma. Mesothelioma is the second highest reported cancer in individuals with this mutation, placing after uveal melanoma. This genetic disorder also causes an increased risk of breast cancer, cholangiocarcinoma, and neuroendocrine tumors just to name a few. The age in which MPM is present is similar between individuals with this disorder and patients that are exposed to environmental risk factors recreationally and occupationally. Women with this mutation are more likely to contract mesothelioma compared to men, which is reversed in the general population, according to researchers at Ohio State University that reviewed Bap1 predisposition syndrome (14). Though Bap1 is the most heavily researched gene linked to MPM development, CDKN2A, PALB2, BRCA1, FANCI, ATM, SLX4, BRCA2, FANCC, FANCF, PMS1, and XPC all also have a role in predisposition to mesothelioma (14). These genes all have a role in the HRR pathway, concerned with DNA repair. When one of these genes is mutated, then DNA repair can be hindered or slowed. This leads to cancer development because there is

a lack of proteins to repair DNA damage, and cancer cells can replicate uncontrollably. The role of genes in the development of cancers is not to be overlooked, especially in the case of mesothelioma, where these genetic predispositions can pair with environmental exposure to cause an increased or synergistic effect.

Conclusion:

Mesothelioma is a type of cancer that can appear throughout many organs in the body. Though asbestos is a common cause of mesothelioma development, there are other factors that are often overlooked. Exposure to erionite is like asbestos in many ways, as they are both silicate-based minerals that are used in construction, but erionite exposure can be slightly more deadly. Radiation exposure is another environmental factor that can increase the development of mesothelioma, with patients being exposed during therapy, recreationally, or even occupationally. SV40 has been linked with mesothelioma, but there is not yet enough evidence to establish a causal relationship between the two. Lastly, there are genetic factors that may pose a risk or increased likelihood of mesothelioma development. High risk factors are similar to asbestos exposure in terms of risk of MPM development, but too many low-risk factors can have heightened effects as well. Overlooking these factors in favor of asbestos would only hurt mesothelioma research in the future, and it is important to take all variables into account when discussing topics like these.

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