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Inverse association between cancer and Alzheimer's disease analysis

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Abstract. Alzheimer's disease (AD) and cancer are the disease are seemed to be not correlated since the prior one is caused by cell degeneration and the latter one is caused by over-proliferation. However, recent research indicates that there is an inverse correlation between incident rate of infecting one disease when being diagnosed with the other. This paper evaluates the method and discoveries of the existing studies and reviews the association between Alzheimer's disease and cancer through analyzing the existing findings. As result, current researchers are focusing on the underlying reasons of the inverse relationship between the two diseases through either examining the opposite end of biological mechanisms of the two diseases, or using statistical data to find potential correlations between several risk factors and their correlation to both diseases. Although all reach the conclusion that the inverse relationship of incidence rate does exist, there is still a lack of confirmation to the existing study on which mechanism or factor is the major cause of this inverse relationship. Further research is required to expand on the existing studies by either confirming the effects of opposite ends of biological mechanism existing in both disease, or gathering more statistical data to exclude possibility of biases and deviations to provide possible explanations for the inverse relationship.

Keywords: Alzheimer's Disease, Cancer, Inverse Relationship.

1. Introduction

1.1. Introduction to cancer

Cancer, in short is the malignant uncontrolled development of cells in your body. In long, cancer has a full set of mechanism that is related to the genetics and the operation of cell apoptosis. Cell is the fundamental units of life. In a normal cell cycle, the cell undergoes controlled division and apoptosis, which is cell death, in order to allow living organisms to grow and function normally [1].

The cell division process is controlled, there is several checkpoints in cell cycle that ensures the normal growth of the cell, and there are intracellular molecules accompany with these checkpoints. The process of moving on to the next phase of cell cycle involves both positive regulation and negative regulation. In positive regulation of cell cycle, when there is designated concentration of cyclin, the cell cycle can proceed. In negative regulation of the cell cycle, there is tumor-suppressor protein that suppresses the cell division when there is abnormal DNA. It functioned through repairing the damaged DNA, otherwise trigger apoptosis to prevent the duplication of mutated genes. It also functions through blocking protein production that is essential for G1 and S phase transition [2].

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In abnormal cell cycle however, the normal regulation was being cut off with the mutation in genes that is related to cell division and apoptosis. The genes that is essential in developing abnormal cell proliferation including oncogenes, tumor suppressor genes, suicide genes, and DNA repaired genes. Each gene controls different functions, the tumor suppressor genes suppress the cell division, on the other hand oncogenes informs cell division. Suicide genes control cell death and the DNA repair genes inform the cell to repair the damaged DNA [1]. Most cancer takes long time to occur and requires several important mutations before the cell can fully transform into cancer cells [2].

1.2. Introduction to Alzheimer's disease

Alzheimer's disease is a form of neurodegeneration. Currently, there are few available therapies for Alzheimer's disease since the neurodegeneration are hard to reverse by the death of neurons, the therapies often only provide limited improvement on cognitive behavior [3]. There are several processes related to Alzheimer's disease development, two of the few important process that will be majorly discussed in this paper amyloid beta toxicity and tau protein hyperphosphorylation.

In Alzheimer's disease, the normal function of neurons in learning and memory are being impaired. Memory lost is caused by the destruction of neurons primarily start at the Hippocampus where long-term memories are form. The primary destruction of neurons in Alzheimer's disease is caused by Abeta plaque and Tau tangles. Abeta is the component studied most widely for understanding the Alzheimer's disease. Abeta is part of the amyloid precursor protein (APP), which were controlled by the APP gene. While the Abeta is a by-product during the process of APP cleavage that is helped by the enzyme Beta-secretase and cut by Gama-secretase (consist of peptide presenilin 1 and presenilin 2). This by-product Abeta may form Amyloid-B plaque that aggregates, which is associated with protein misfolding, gathering in plaques outside neurons. The mutation in APP gene and the gene that controls presenilin will cause an increase in Abeta plaques occurring. Chromosome 21 is where APP gene is found. The most mutations on APP genes that controls Beta and Gama secretase has found a positive downstream correlation on the substrate concentration of Abeta. In some research studies, Abeta is also considered an upstream of Tau tangles, which is another important risk factor for dementia which largely destruct synapses by weakening the axon fiber protein. Tau tangles are caused misfolding of Tau protein inside the microtubules of a axon, when the protein misfolds the axon's function will be impaired by its loss of structure and unable to transmit signal. There is also found an association between apolipoprotein E on the pathophysiology of Alzheimer's disease. APoE are responsible for modulating multiple brain intracellular signaling pathways. There is 3 to 15 percent increase in risk of developing late onset Alzheimer's disease when homozygosity for the APOE ε4 allele increases, there is evidence that APOE ε4 is positively correlate with the accumulation of Abeta plaque, which indicate that APOE genotype could be a Abeta mediated risk factor on Alzheimer's disease [4].

1.3. Brain cancer and its gene mutation

The brain tumors are rare, it composes only 1.4 percent of all cancers according to the CBTRUS statistical report. Most of the tumor arises in neural and supportive glial cells. There are many causes of brain tumors, and some types of brain tumors are not causing cancer. The symptoms of a brain cancer are often related to the dysfunction of normal brain functions and get worse more quickly compared to brain tumors.

There is an enzyme called Pin1 that is important in the etiology of Alzheimer's disease and human cancers. The Pin1 promotes neuronal health by restoring phosphorylated tau and amyloid precursor protein. It is also an important protein for cell division by regulating cell cycle. Both cancer and Alzheimer's disease may be correlated with the mutation of the gene that dysfunction this protein [5].

There is negative association between cancer and dementia, which may be explained by the difference in regulating the common genes and pathways. It has been shown that extensive infiltration of platelets in gliomas are responsible for bacterial invasion and act an active role in the immune system, but also release Abeta. Abeta peptide may also show an effect to suppress tumor [6]. According to the case-control study within Alzheimer disease research center cohort at Washington University in St.

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Louis, there is reduced risk of Alzheimer's disease with the participants with cancer history, and a reduced risk of cancer of participants with Alzheimer's Disease [7].

2. An overview of biological mechanisms acting in both Alzheimer's disease and cancer

While both Cancer and Alzheimer's disease may cause neurodegeneration, the inverse relationship is discovered between correlative risk of infecting cancer and Alzheimer's disease. In the evaluation of incidence of Cancer and Alzheimer's disease of Northern Italy, the risk of Alzheimer's disease in patients with cancer was 35 percent reduced and is found in nearly all sub-groups [8]. An 11 percent decrease incidence rate of Alzheimer's disease with the cancer diagnosis was associated in a review of case-control study representing 9,630,435 individuals [9]. However, the reason of this negative correlation occurring is not being fully understood in current research. Some research paper approach to this phenomenon of negative association through correlating the risk factors contributed to Alzheimer's disease and cancer to discuss the possible interpretation to the inverse relationship between the two diseases.

The author in one prior study discusses the interactions between Alzheimer's disease and many risk factors and how the alteration of cellular pathways will lead to Alzheimer's Disease. Cancer and Alzheimer's Disease are both correlated with age-related factors. They are also affected by psychosocial factors, and factors affecting the neural functions. According to Ganguli, mechanisms that regulate cell survival is the critical point of the pathophysiology in both Alzheimer's disease and pathophysiology. Both diseases are correlated with the cell pathways related to energy, immune response, DNA damage and repair, cell cycle regulation and oxidative stress [7].

The first risk factor discussed in the passage is the correlation of age. One correlative mechanism is the production of reactive oxygen species (ROS), acting as a messenger to promote cell proliferation. It is often related to age because this mechanism is often dysregulated with the age progression. In Alzheimer's disease, Abeta accumulation in the mitochondrial matrix will lead to oxidative stress and cause a high amount of ROS toxic releasing. In cancer cells, there is moderate production of ROS by mitochondria in cancer cells that leads to cell growth and proliferation. The study shows that when there is an increase in the aerobic glycolysis, while ROS is the by-product of aerobic respiration, there will be in increase in cell proliferation and cell growth thus increasing the risk of cancer development. On the contrary however, when there is decreased glycolysis, the impaired cell survival mechanisms of aged cells will likely to be promoted on its neurodegenerative processes. Another correlative factor is the p53, a protein gets involve in stopping cell division. The dysfunction of p53 is common in many cancers since it will promote uncontrolled cell division. However, it is also found that p53 participated in Alzheimer's disease when the increase of p53 activity will show an impaired function of neurons to regenerate. Also, the aggregates of Abeta plaque in neurons will stimulate the response of apoptosis with the activation of p53.

Another molecule that is correlated with both diseases is Pin1 enzyme. It catalyzes the isomerization of phosphorylated serine or threonine which when it is inhibited, the apoptosis will be induced. Thus, in Alzheimer's disease the loss of Pin1 function may result in tau and Abeta related symptoms and cell death. On the other hand, however, there will be overexpression of Pin1 in many human cancer that stimulates oncogenesis and induces chromosome instability and tumorigenesis.

The paper also discusses the microRNA in regulatory mechanisms of both the development of Alzheimer's disease and cancer. For example, miR-9-5p plays an important character in the development of brain, which is downregulated in Alzheimer's Disease patients. However down-regulated role of miR-9-5p has found to be either support or suppress tumor development. Another microRnA named MiR-34a-5p plays a role in tumor suppression. However it has an effect on synaptic plasticity and disrupt energy metabolism in neurons when it is overly expressed and increase risk for Alzheimer's disease.

Ganguli's study investigated several common pathways in Alzheimer's disease and cancer and pointed out the result of these pathways differently in situations of Alzheimer's disease and cancer that potentially explains the negative correlation of Alzheimer's disease. The overall result of this paper shows that the patients infected with Alzheimer's disease had a 42-50 percent decreased risk of having

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cancer, and people who are having cancer will have the risk of having Alzheimer's disease 35-37 percent lower [7].

Another prior paper also discusses several processes to its relation of both Alzheimer's disease and cancer. The paper discusses the cell regulation mechanism of cell apoptosis or proliferation that is correlated with the beta amyloid, which is abeta. And tau deposition. Similar to the discovery done by Ganguli, the paper focuses on some mechanisms involve in the cell cycle regulation, which for example the role of p53, Pin1 and Wnt signaling pathway are the factors that may explain inverse correlation between cancer and Alzheimer's disease. [10]

Behrens inspected that there could be biological pathways that connect the relationship between Alzheimer's disease and cancer and raises several pathways that potentially showcase the inverse relationship. Behrens believes that the most plausible explanation of this correlation is on the common mechanism on cell cycle of both diseases, which such mechanism prone the cancer cell, but more susceptible to apoptosis under factors.

One major gene identified in such cell cycle regulatory mechanism is the p53 gene. The signaling pathways of p53 are stress responsive and induce apoptosis that reacts to DNA damage. According to Res, the cost of p53 suppressing cancer formation is compromising tissue repair, which may slow down the repair of synapses and cause a higher risk of having Alzheimer's diseases. The Presence of Abeta 42 will also directly activate p53 promotor according to the mouse models, thus leading to an p53 dependent cell death. Pin1 is also a regulating protein that involves in APP regulation, which APP is the Abeta precursor protein, the deletion of Pin1 will increase the risk of Alzheimer's disease when it is having a function of strengthening the tau protein, but the overexpression of Pin1 will be related to cancer. Another signaling pathway focused by this paper is Wnt, which is important in developmental processes. The mouse model shows that the inhibition of Wnt protected the neurons at the hippocampus from Abeta. On the other hand, the deregulation of Wnt activation would raise the risk of developing cancer [10].

Behrens's study had investigated molecules that involved in cell cycle pathway which its dysfunction and normal function may generate different results according to its function, which the function of molecules may potentially explains the inverse correlation of Alzheimer's disease [10].

3. An overview on population analysis based on cancer and Alzheimer's disease diagnosis

Some other research associates this negative correlation between the risk of having either Alzheimer's disease or Cancer through analysing the patient's data on a broad scale addressing the concern that there may be potential bias align under the correlation. Collecting large scale data enable researchers to reveal insights about several risk factors that weren't considered during physical experiments. For example, like family history of Cancer and Alzheimer's disease, behaviour that increase risk for infecting both disease such as smoking, physical trauma, and other factors [11]. This broad data collection enables researchers to review multiple factors together by forming collective trends and empathize the importance of certain factors that were undermined before, and it also eliminate potential survival bias since a large scale of measurement lowers the possible risk of factors impacting the research result [12]. The survival bias is the bias that mistaken account the phenomenon occurs on a small group to the entire large population [13].

In a prior study, the carcinogenesis that was correlated in neurodegeneration in middle-aged United states adults were being examined. The population size of this cohort study includes 14583 individuals. The discovery indicates that the carcinogenesis has correlation with impairment on cognition and Alzheimer's Disease. The study set up through finding adults in United States who were born before 1949 without cancer history, then they were asked to do a self-reported physical diagnosis of any cancer during the follow-up of 16 years assess their performance of health. One measurement they use to score memory is a standardized word-list recall and proxy assessment that has a standardize average of 0 as baseline. They compared the memory change between individuals who are diagnosed with cancer during the 16 years follow-up and the individuals who remained cancer-free during the research and form a linear model [14].

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The many existing explanation for the negative association of the incidence rate between Alzheimer's disease and Cancer are explained by the opposite ends of the pathology of carcinogens and neurodegeneration processes. However, there are also concerns that this inverse association may also be caused by a selective bias that individuals who are diagnosed with cancer are relatively healthy and long-lived that protect these individuals against Alzheimer's disease. The population-based evidence enables the researchers to compare cognitive trajectories of individuals with or without the diagnosis of cancer, which aid the research on the role of cancer-altering memory function processes in aging. Population based research may also eliminate any potential factors that may be favourable in cognitive performance of certain groups of individuals [14].

In result, the population that has an incidence of cancer has a moderate rate of higher memory function. At the same time, the population also has a slower rate of decline in memory functions both before and after their diagnosis of cancer. Ten years before a cancer diagnosis, the average rate of memory decline was 10.5%. The rate is slower compared to the rate of memory decline of people without cancer throughout the study. The mean memory function of individuals immediately before diagnosing of cancer who are diagnosed at 75 years of age is higher compared with the individuals who are at similar age but without diagnoses of cancer. For individuals who are diagnosed with cancer, they have a short-term decline in memory function. After the diagnosis, however, these individuals have a slower rate of memory decline than the individuals that are cancer-free [14].

There are drawbacks in this study since the decade-long memory trajectory may be impacted with many potential social and environmental factors occurring simultaneously. On the other hand, there could be misclassification of cancer diagnosis and flawed reflection of memory scores. However, this study is valuable. According to its results, it did supports other research about the inverse association between cancer and Alzheimer's disease in many means. The discovery of slower memory decline rate before the incident of cancer associates with the correlation of decreasing risk of Alzheimer's disease. It is also the first study to evaluate the trajectories of decade-long cognitive ability of individuals before and after the diagnosis of cancer that provide information of long-term association between memory decline and cancer [14].

In the latter study, the association between cancer and Alzheimer's disease were examined. Within the same time, the study also considers majorly on the likelihood of methodological bias that may occur in studies considering the negative association between Cancer and Alzheimer's disease. This review includes 22 controlled studies that represents 9630435 individuals. According to the PRISMA reporting guideline, the study was conducted to evaluate the effect of the two diseases with attribution of potential biases. When a cancer diagnosis influences the chance of Alzheimer's Disease's diagnosis, a diagnostic bias will be likely to occur. It is thus eliminated through ascertaining the same chance of incidence rate of Alzheimer's disease diagnosis for all patients. The survival bias in researches that studied individual with cancer diagnosis before the baseline of prevalent cancer cases is really likely [9].

As result, there was a 11% decrease in incidence of having Alzheimer's disease when individuals are diagnosed with cancer. Diagnostic bias is not likely to be the explanations for the negative association found in the correlation between Cancer and Alzheimer's disease based on the Bias-adjusted meta-regressions. One limitation that may potentially impact the result of this study is that they failed to consider the patients already died based on the cause of one disease that has a high potential to be infected by the other, it also failed to eliminate random factors such as family history of cancerous mutation that may lead to a fluctuated baseline of risk of infecting cancer [9].

Each paper analyses the population data and considers the possible end of the association between Alzheimer's disease and Cancer that are impacted by many different factors. While the prior paper's main focus is on a long-term trajectory of memory decline to analyse the impact of Cancer diagnosis on incidence rate of Alzheimer's disease on people, the latter paper focuses on the inclusion and elimination of risk factors on methodology that interfere with the accuracy of the interpretation of the association between the two diseases.

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4. Discussion

Current research analyzing the negative association between Alzheimer's Disease and Cancer has several approaches, including examining the opposite end of biological etiology of both disease and a general population trend analysis that considers different factors that shows correlation between Alzheimer's Disease and Cancer.

In Ganguli's study, the biological pathways that lead to interactions between Alzheimer's disease and Cancer are being examined. which pathways and risk factors including aging, reactive oxygen species, p53 dysfunction, and Pin1 enzyme dysfunction are being analyzed and explained the opposite end of etiology these factors caused on the cases of either disease [7]. Similar structure to Ganguli's study, Behrens's research also focuses on the biological mechanisms that connect Alzheimer's disease and Cancer, and it examines the explanation of the negative correlation through certain body mechanisms.Behrens's paper showcases the different impact of mechamism of normal functioning and mal-functioning p53, Pin1 and Wnt on both Alzheimer's Disease and Cancer [10].

Both two studies approach the negative association through examining cellular pathways that potentially cause the negative association of incident rate between Cancer and Alzheimer's disease. The drawback of both study is it may be less capable of implanting the experimental data on actual population since the investigation are majorly theoretical. Which, biological mechanism explanations could be potentially be the underlying cause of the negative correlation between the two diseases, there may be many factors not being included in the experiment that lead to an incomplete explanation.

Other approaches focus on the large-scale data that indicates the correlative trend of the incidence rate between Alzheimer's Disease and Cancer. In a study done by Ospina-Romelo in 2019, the researchers primarily focus on the inverse association between Cancer and Alzheimer's disease and indicates several possible biases that constantly occur in similar research. The result indicates a congruency between the finding of this study and the research done previously about the trend of inverse relationship between the two diseases, and it also indicates that the biases are eliminated or unlikely to be the factor of such inverse trend [14]. Focusing on long-term trajectory of memory decline, however, the research paper done by Ospina-Romero in year 2020 approaches the inverse relationship between Alzheimer's disease and Cancer more focusing on the impact of the diagnosis of cancer on individual memory decline. While gathering memory scores and cancer diagnosis information throughout decade, the research ended up with a result of finding a decrease in memory decline with the individuals who has diagnosed with Cancer, indicating a lower risk of having Alzheimer's disease [9]. One major and particular flaw of both studies which analyzes population data is that it failed to eliminate potential environmental factors since the data is coming from a large pool of samples. This drawback may lead to an uncontrol attribution of factors that may indicate a trend to the researchers, but it is not the real cause of the inverse relationship. However, this is a precious approach when it counts a large sample pool that analyze the trend between the etiology of the two diseases with a base of a large population that lowers the potential of having deviation or biases.

There is a need of associating population analysis with experimental examination together to address the relationship between Alzheimer's disease and Cancer. Within the same time, the population analysis can provide researchers insights of potential factors that underlies the inverse correlation between Alzheimer's Disease and Cancer.

This particular study focusing on the relationship between Cancer and Alzheimer's disease is critical because the understanding of its relationship may provide us information on the mechanism of both diseases separately. Within the same time, the opposite endpoint of the etiology of both diseases may provide researchers ideas of treating either one of the diseases with the understanding of the correlation. On the other hand, it may raise an awareness of the use of treatment for either Alzheimer's disease or Cancer since the treatment can lead to an increase in risk to the other one.

5. Conclusion

In conclusion, by examining the current studies that are focusing on the relationship of incidence rate between Alzheimer's disease and cancer, the results show that all the current studies indicate that there

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is an inverse relationship between the incidence rate of having Alzheimer's when diagnosed with cancer, and in reverse having lower incidence rate of having cancer when diagnosed with Alzheimer's disease. While examining the existing papers, some portions of the papers demonstrated the biological mechanisms to explain the inverse relationship of the incidence rate between having cancer or Alzheimer's disease when diagnosed with the other one. Many of the molecules, including reactive oxygen species, p53, Pin1 enzyme and Wnt, are being examined since they play a big role in both diseases however demonstrates different effects due to their own function or dysfunction when being mutated. The major problem appearing in the existing studies is the lack of experimental data that supports their theory of two ends of mechanisms and undermines potential factors that may also cause the inverse relationship between the two diseases. On the other hand, many other researchers approach the negative correlation between the incidence rate of Cancer and Alzheimer's disease by analyzing population data, either on a longitudinal scale that examines the effect of aging on memory, or to examine the potential factors and biases that contribute to the study of the inverse relationship between the two diseases. The drawback is that there could be unrelated correlations that seem to indicate a trend of the inverse relationship between the incidence rate of cancer and Alzheimer's disease, and their own risk factors. This study of discovering the relationship between cancer and Alzheimer's disease provides further understanding of the mechanisms of both diseases, and lead to new insight into possible treatment to these diseases. Further research could be done on focusing the experimental data that largely controls the potential impacting factors that cannot be eliminated in population study, or did not include in the theoretical analysis done by current researchers.

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