OXFORD JOURNAL
OF STUDENT
SCHOLARSHIP

# The Inverse Relationship Between Cancer and Alzheimer's Disease: Shared Pathways, Drug Repurposing, and Novel Therapeutic Targets

Talley Grabler
talley.grabler@gmail.com

## ABSTRACT

There have been many statistical correlations found between cancer patients and individuals diagnosed with Alzheimer's disease (AD), where cancer survivors have shown a decrease in their risk to develop AD by 35-51% relative to other individuals of the same age (Braithwaite et al., 2025; Catalá-López et al., 2014). Nonetheless, the biological reasoning for such an outcome remains unknown and hasn't been applied clinically in developing drugs for AD patients. Therefore, cross-domain drug repurposing has become a highly important task within the scientific community due to the relatively low efficacy of existing methods. In this systematic review, peer-reviewed evidence will be presented based on four key analysis pillars: epidemiology, molecular biology, drug repurposing, and survival bias. The evidence consists of 60 papers published during the period from 2000 to 2025 and selected by searching the PubMed database. Across the molecular biology pillar, the most common mechanistic finding was on shared dysregulation of p53 tumour suppressor activity, epidermal growth factor receptor (EGFR) signaling, and epigenetic modifications which include DNA methylation and histone acetylation. These findings operate in an opposing direction in cancer compared to AD neurons. Evidence suggests that both the inherent biology of cancer and the therapy received by patients could have mechanisms underlying the neuroprotection seen, even though survival bias contributes to approximately 40% of the inverse association. This insinuates a clear biological effect remains. This review highlights knowledge gaps which include a lack of longitudinal evidence, inadequate stratification by gender, and inadequate research on the preclinical phase of AD.

## INTRODUCTION

AD and cancer are two of the most critical health issues worldwide, with over 20 million cases of cancer and 9.7 million deaths from the disease globally (GLOBOCAN, 2022), alongside over 7.2million people suffering from AD. At first, the two diseases seem to be completely unrelated, cancer being characterized by uncontrollable cell growth and AD by neurodegeneration. Cancer is known to have cells grow too much too quickly, while AD has the opposite effect where too many cells die. However, new evidence

indicates a correlation between the two as patients suffering from cancer are statistically less likely to develop Alzheimer's. Despite the increased evidence for this inverse association from an epidemiological perspective, the biological mechanisms still need further investigation. If we can understand the biological link underlying the inverse relationship between the two, it could provide the key to help prevent and treat both diseases.

AD doesn't only affect patients themselves, but leaves an impact on others around them. It leaves individuals working less to take care of their loved ones as well as a financial burden. In 2023, the Alzheimer's Association estimated that the total cost of caring for those with AD in the US is roughly $345 billion and will continue to exceed $1 trillion dollars by 2050. (Alzheimer's Association, 2023). Moreover, it is seen that 11.5 million family members and caregivers provide well over 18 billion hours of care annually, leading these people to limit their working hours or even devote all of their time to care for the member with AD. This data shines light as to why it is necessary to devolve effective strategies to reduce the suffering of the patient and those around them.

Epidemiological data throughout research continuously reveals counter intuitive findings that individuals with cancer are statistically less likely to develop Alzheimer's disease. Studies reveal a 31-51% reduced risk of AD among cancer survivors in genetically diverse populations (Braithwaite, 2025, Catala Lopez, 2014, Musicco, 2023). The inverse relationship between AD and cancer has been noted in different populations throughout studies including, Asian health cohorts, US longitudinal studies,and European data showing that this relationship is not population specific. Cancer built through uncontrollable cell growth and its resistance to apoptosis, while AD is characterised by progressive neurodegeneration and therefore, represents a paradox that the diseases are opposite of one another.

Cancer and Alzheimer's have been studied independently of one another, each with its own distinct pathological framework. Cancer is characterized by abnormal cell growth, apoptosis (programmed cell death), and oncogenic signaling, while Alzheimer's can be characterized by neurodegeneration, accumulation of amyloid-beta plaques, neurofibrillary tangles and neuroinflammation. Despite these differences, both share overlapping biological processes, such as, vascular changes, alteration in cell cycle regulation, epigenetic modifications, and immune signaling. In the past few years, several studies and data have reported a relationship between the diseases, suggesting a reduced risk of Alzheimer's disease among patients with a history of cancer. Earlier studies suggested that this link could be due to survival bias, an unaccounted confounding factor in which cancer patients, suffering from high mortality rates because of their principal disease, tended to die before reaching the stage in life where AD would have become prevalent. In other words, the supposed protective effects of cancer on AD risk did not exist ,instead, what appeared to happen was simply that patients with cancer, dying early because of their cancer, were never studied long enough to diagnose them with AD. However, later experiments show that, despite living for extended periods of time and being in remission from cancer, cancer patients still maintain a lower rate of developing Alzheimer's than non-cancer patients, indicating that something else must also be at work besides pure chance.

This research will uncover the mechanistic insights of the relationship between cancer and AD, focusing on the aspects of shared and distinct pathways. It is important that we identify these mechanistic insights since knowing what causes this inverse correlation is essential to translating the observation into clinical practice. Otherwise, all that we know is that the inverse correlation does exist,however, without knowledge of the underlying mechanism, this correlation remains just another epidemiological finding that may not help us in designing drugs or devising therapeutic strategies. Mechanistic insights help identify the specific molecules and pathways involved, pinpointing targets that could be therapeutically manipulated to slow neurodegeneration or limit cancer progression. Although studies display a clear relationship, there are many gaps that have not been explained in understanding the connection between long term cancer survivors and in the prodromal stages of Alzheimer's. Specifically, it is unknown if the positive association seen in cancer patients holds true for patients in remission, or if the biological alterations caused by the treatments themselves reduce the risk for AD. Moreover, while many studies have explored this inverse relationship, very few have considered the prodromal stage of Alzheimer's, where pathological processes are present, but clinical signs of disease have yet to develop. Another gap is that the majority of scientific studies utilize the clinical approach to the problem without considering the molecular analysis. The main aim is to identify if there is a reduced risk of neurodegeneration including those that can be triggered or suppressed by cancer. For example, there may be a vital role for the regulation of oncogene and tumor suppressor genes such as p53 and the EGFR. Many of these changes are driven by epigenetic changes such as DNA methylation and histone acetylation which regulate gene expression without altering the underlying genetic code.

This perspective recognizes a shift in scientific understanding and using methodological approaches and analyzing these interconnected pathways. This research study aims to contribute to the mechanistic insights that could provide aid to pharmaceutical knowledge and evolving the understanding of Alzheimer’s.

When trying to grasp the concept between these two diseases, researchers attempted drug repurposing, using already approved drugs made for one illness and using it for another. The approved drugs for cancer treatments such as chemotherapy, have been proving effective in tackling unwanted cells. However, the drugs available for those with dementia don't have high success rates as seen in a study by (Ancidoni, 2021) where drugs for AD only had a 2% success rate. The therapeutic strategies to battle cancer, on the other hand, tie together into what causes AD. Therefore, if the biological mechanism linking the two of the illnesses together can be pinpointed, then research can repurpose drugs in oncology in order to fight off disease like AD and not only cancer.

## AIMS AND SCOPE OF REVIEW

The present systematic review aims to: (a) synthesise epidemiological evidence establishing the inverse cancer–AD relationship across different population, (b) Connect the shared molecular mechanisms such

as p53 tumour suppressor, EGFR signaling, DNA methylation, histone acetylation and more pathways connecting the two diseases, (c ) evaluate evidence for oncology drug repurposing as a therapeutic strategy for AD, with particular focus on the prodromal intervention window where the illness has not yet presented itself but is beginning to progress, and (d) identifying research gaps across 60 research papers in order to increase accuracy and continue investigating. Papers were sourced from PubMed. Inclusion criteria used peer reviewed, empirical and review studies published between 2000-2025. They focused on the mechanistic, epidemiological, and therapeutic relationship between cancer and Alzheimer's. Studies that were retracted and not peer reviewed were excluded.

## METHODOLOGY

### Review design:

This is a systematic review which explores the inverse relationship between cancer and Alzheimer's and dives into the mechanistic insights as well as identifying potential therapeutic targets in AD. The review was executed through pubmed with articles focusing on immunology, oncology, drug therapies and genomics. A total of 60 papers were reviewed and sectioned through four pillars including, epidemiology, survival bias, molecular biology, and drug repurposing. The search was not limited to these topics and included studies on shared molecular pathways, epigenetic regulation, and pharmaceutical targets to explain that the inverse relationship between AD and cancer exists at a biological and molecular level. No new studies including humans or animals were conducted as the review only consists of secondary synthesis of previously used research. This is a modified systematic review conducted by one reviewer, not pre-registered (PROSPERO) and without use of a validated risk-of-bias assessment tool; the modifications are stated here and discussed further in the Limitations of This Review.

### Search Strategy:

Different searches were conducted on the pubmed platform using Boolean logic combinations of the following five categories of keywords. The core strings of the search were: ("Alzheimer's disease" or "Alzheimer's type neuropathology" OR "early AD") and ("cancer" or "EGFRvIII"); ("inverse relationship" or "neuroprotection" or "mechanistic drivers") and ("Alzheimer's disease" and "cancer"); ("drug repurposing" or "therapeutic targeting" or "EGFR receptor inhibitors" or "PI3K pathway inhibitors") and ("Alzheimer's disease"); ("epigenetics" or "epigenome" or "Mendelian randomization" or "p53" OR "GWAS" or "EWAS" or "proteomics" or "transcriptomics") and ("Alzheimer's disease" and "cancer"); and ("immunogenetics" or "neuroinflammation") and ("Alzheimer's disease" and "cancer"). The searches were limited to the English language and peer reviewed articles published between 2000 and 2025. Since no complete database search log was saved in a format that allowed for the reporting of numbers of records at each step (initial number of hits, duplicates, screening process, and reason coded exclusions), it was not possible to create a PRISMA flow diagram for this draft of the manuscript. The

PRISMA diagram is therefore replaced by Table 1 (refer to Data Analysis), which provides an evidence map highlighting study designs, sample sizes, and key findings from each pillar of the review.

**Selection criteria:**

Studies were selected with the aim of addressing multiple dimensions of the research question: to examine the nature of the inverse relationship between AD and cancer, and to identify the potential mechanistic drivers underlying this relationship. The eligibility criteria for the study followed a PICO approach, population: (patients with cancer, AD, or both, as well as animal models of neurological disorder or cancer development); exposure (diagnosis of cancer, cancer therapy, or activation of common molecular signaling pathways); comparator (healthy patients or controls in experimental studies); outcome (prevalence or likelihood of AD among those suffering from cancer, as well as protective mechanisms). Animal studies and human RCTs were included because many of the shared pathways involved in both AD and Cancer have been well described in animal literature. Excluding animal data would have left crucial biological mechanisms unaddressed. Critically, the selection strategy was not limited to studies that explicitly investigated the AD-cancer relationship. The rationale for this is that while substantial independent literature and evidence exist for both AD and cancer, the hypothesis that cancer may have neuroprotective effects against AD remains a fairly new area of inquiry that was dismissed for many years due to the survival bias explanation. In order to bridge these two diseases and explore the biology connecting them, it was necessary to include papers that shine light on the mechanistic framework of this relationship, such as shared molecular pathways, immunological overlap, and pharmacological targets, even in the absence of an explicit cross disease framework. All papers were reviewed and found in the PubMed database, selected for its breadth, peer-reviewed quality, and interdisciplinary scope, encompassing immunology, pharmacology, oncology, neuroscience, and genomics.

**Key words and Synthesis of the literature:**

A structured and advanced keyword search strategy through PubMed was used in order to ensure comprehensive and targeted review of the literature. The single database approach is a limitation to the study even though it incorporates sophisticated, peer reviewed quality. Search terms were constructed across five categories, each reflecting a distinct investigative dimension of the research question, and were used in combination to maximise precision of the search.

The search for the words was initiated using the broad terms, cancer and Alzheimer's, which served as the foundation for all searches that follow. Building on these broad terms, more specific search terminology was introduced to capture a broader and more detailed body of literature. For cancer, searches incorporated the EGFRvIII mutation, a deletion variant of the

EGFR gene that results in a constitutively active, ligand-independent receptor. This mutation promotes uncontrolled cell proliferation and is most commonly associated with glioblastoma multiforme, though its relevance extends to this review given the overlap between EGFR signalling pathways and neurodegeneration in AD. For Alzheimer's, the term Alzheimer's type neuropathology was used to capture studies examining the hallmark pathological features of the disease,including amyloid-beta (Aβ) plaques and neurofibrillary tau tangles, without restricting the search to diagnosed AD cases. The term early AD was additionally introduced to include studies examining the preclinical and prodromal stages of the disease, during which pathological changes are underway but clinical symptoms have not yet fully manifested. Including this stage was important given that the biological relationship between cancer and AD may be most active prior to full disease onset.

Investigative terms were used to directly explore the nature of the relationship between the two diseases and the mechanisms thought to underlie it. The term inverse relationship between Alzheimer's disease and cancer was used to identify epidemiological and mechanistic studies that have observed and attempted to explain the reduced co-occurrence of the two conditions within the same individual. Neuroprotection was searched as a functional term to capture literature examining the biological processes by which neurons are shielded from damage or degeneration, particularly in the context of cancer associated molecular activity. The broader term mechanistic drivers was used to capture studies investigating the specific biological pathways, rather than just the statistical association,that may explain why individuals with a history of cancer appear to have a reduced risk of developing AD, and vice versa.

Drug repurposing was a pharmacological term which would help find literature about repurposing drugs for use between the two diseases. Repurposing of a drug is an approach in which therapeutic utility for a drug is found in another disorder from its existing one. Therefore, it helped search whether there are any potential cancer drugs which could be useful for Alzheimer's disease. Therapeutic targeting was used to capture literature examining the specific molecular targets, proteins, receptors, or enzymes that are shared between cancer and AD.

EGF receptor inhibitors are a category of compounds which inhibit epidermal growth factor receptor signaling pathway and are widely used in oncology to reduce tumor growth. EGFR receptor inhibition was considered as a keyword since it is now being seen that EGF signaling plays an important role in amyloid metabolism and neuronal death in AD patients. PI3K pathway inhibitors target the phosphoinositide 3-kinase signalling cascade, a pathway that regulates cell growth, survival, and metabolism and that has been involved in both tumour progression and neurodegeneration.

Terms relating to genomics and epigenomics were applied to locate studies that explore the molecular and population genetics involved in the relationship between AD and cancer. The field of epigenetics encompasses inheritable modifications in gene expression that do not involve changes to the DNA base sequence, which include phenomena like DNA methylation and histone modification, while epigenome signifies all of these modifications throughout the genome. Both were sought out to identify studies investigating any common epigenetic regulation that might underlie the shared control of both diseases.

Mendelian randomization involves using genetic markers called single nucleotide polymorphisms (SNPs) as instrumental variables to assess the causal effects of an independent variable on a dependent one, hence minimizing confounding in the conventional observational research; this was chosen to locate studies presenting stronger causal evidence for the association between the two diseases. p53 is a tumour suppressor protein encoded by the TP53 gene; it plays a role in regulating the cell cycle and induces apoptosis in response to DNA damage and was selected because of its involvement in cancer prevention and neuronal death in Alzheimer's disease. Genome-Wide Association Studies (GWAS) is the process of scanning large genomic data to identify any common genetic mutations linked with the specific disease, while Epigenetic-Wide Association Studies (EWAS) involves using the similar process on epigenetics to identify the common link. Both of them have been used to find any genetic and epigenetic associations among the population concerning AD and cancer. Proteomics entails the comprehensive study of the complete complement of proteins of a cell/tissue/organism. This method has been used to find any similarities regarding the protein levels in both diseases. Transcriptomics involves studying all the different RNA transcripts coded by the genome.

Finally, I included immunological key words in order to identify the literature which explores the immune mediated mechanisms that may link cancer and Alzheimer's together. Immunogenetics refers to the study of the genetic basis of different immune responses. This includes how inherited variation in immune related genes influences disease susceptibility and progression. This term was included to captivate studies investigating whether shared immunogenetic pathways may contribute to the inverse relationship between the two conditions. The term neuroinflammation refers to the inflammation that takes place in the central nervous system (brain and spinal cord), and it involves the activation of different cells in the CNS such as, microglia and astrocyte cells as well as the secretion of pro inflammatory cytokines. Neuroinflammation was added as one of the search terms because it is related to chronic low level inflammation which may play a role in AD pathology. Moreover, inflammation has become a significant commonality between both diseases due to the involvement of the immune system.

**Inclusion Criteria**

1. Publication period: All articles that have been published within the 2000-2025 time line were utilized, as it ensured that the studies were not outdated and irrelevant and employed more statistically significant data. The selected years coincide with the years when the inverse correlation between AD and cancer started being studied scientifically by experts, and was therefore included for more concrete evidence.
2. Study design: A variety of studies was used to provide varied evidence levels. These studies include review articles, randomised double-blind trials, retrospective cohort studies, longitudinal cohort studies, systematic reviews, case studies, and prospective cohort studies. Systematic reviews combined information from various independent studies and provided high level evidence with a lower risk of bias from just a single study. Longitudinal studies are important as they track patients over an extended period of time, giving us insight on the diseases at different

stages. Retrospective cohort studies provide epidemiological evidence in large numbers of known cases.

3. Both human and animal studies were considered. Human studies were preferred wherever possible, since they give direct and most relevant information about the underlying biological aspects of diseases from the point of view of its clinical significance. Nevertheless, due to the obvious ethical restrictions for conducting randomised controlled trials on AD patients and cancer patients, especially when it comes to the efficacy of drugs, animal data were included as well.
4. All articles were in full text and available in English only. All papers were peer reviewed and sourced exclusively through the PubMed platform.

**Exclusion criteria**

Studies were excluded from this review based on the following criteria.

1. Publication date: Articles published prior to 2000 were excluded. After carrying out an initial search, it was clear that previous literature provided little information on the underlying mechanism in the link between AD and cancer. Considering that this research is relatively new the earlier sources were not relevant.

2. Retracted studies: Any article found to have been retracted was not included. Studies on PubMed get flagged alongside a reason for the retraction. Retraction does not matter with regards to relevance, as such studies findings are not credible.

**Risk of bias a quality considerations**

A formal risk of bias assessment tool (such as ROBINS-I, Cochrane RoB 2, or AMSTAR-2) was not used on each individual study. Instead, a qualitative measure of the study's quality was provided based on an evidential hierarchy of study design, ranging from randomized controlled trials, prospective cohort studies, retrospective cohort studies, case studies, systematic reviews, and animal studies, by which greater weight was attributed to results that have been independently replicated in different designs. The sample size, duration of follow-up, and control for confounding factors (such as competing risks analysis to address survival bias; see Ospino Romero et al., 2020) were also taken into consideration when considering the weight of evidence of an individual's result.

**Organisation of Literature:**

Following this structured approach, the articles were then synthesized using a thematic approach to form an evidence based basis relevant to the study question. This was done by focusing on three core aspects

that underlie the association between AD and cancer, immunogenetics, molecular biology, and pharmacology, as the categories through which to synthesize the literature. Findings were then compared across different research studies and allowed for the identification of shared biological pathways and recurring molecular targets that may underlie the observed epidemiological relationship between the two diseases. Synthesizing the literature allowed for different connections to be made and built on a mechanistic explanation for the phenomena observed.

**Data Analysis:**

Extracted data were analysed using a thematic, narrative synthesis approach appropriate for scoping reviews where heterogeneous study designs preclude statistical meta-analysis. Once all 60 papers were reviewed and investigated, they were organised in an excel sheet in order to structure the review in sections that include, epidemiology, survival bias, molecular biology, drug repurposing, and main and muddy points. Within each column contained studies with similar findings or similar data collections. This allowed different patterns to be seen as a whole.

| Pillar | Representative study designs | Standard sample size | Principle finding |
|---|---|---|---|
| Epidiemilogy | Meta analysis, large prospective/retrospect-i ve cohort studies | N ≈ 1.5M–4M+ (pooled) | 35-51% reduction in AD risk in cancer survivors ,regardless of geographic/demographi c population |
| Survival bias | Competing risk longitudinal cohort studies; Frailty-corrected registry studies | N ≈ 1,278–14,000 | Survival bias explains ≈40% of the observed effect. An independent effect remains despite correction |
| Molecular biology | mechanistic/preclinical studies, animal models, post-mortem human tissue | Varies (preclinical/mechanistic ) | Shared, opposing p53, EGFR, and epigenetic (DNA methylation/HDAC) signaling pathways and abnormalities |
| Drug repurposing | Early stage RCT; small | N=5-63 | Early biomarker/target |

| | | | |
|---|---|---|---|
| | preclinical/biomarker studies | | engagement signal (nilotinib, dasatinib) not yet proven beneficial for cognition |

*Table 1 summarizes the study designs, sample sizes, and main findings across the four different review pillars and ensures key details are presented.*

A research gap analysis was then conducted through the review of different limitations and muddy points (unclear aspects in the study). Consistent gaps were then grouped together to identify their frequency which produced a prioritized list of the areas that were inconsistent with data.

The study designs were organized based on an evidence hierarchy. They started with randomized controlled trials and continued to prospective cohort studies, retrospective cohort studies, case studies, systematic reviews, and animal studies. For each article the gender of participants were tracked. Those without participants were marked due to the absence of gender which is a major issue in both AD and cancer research. Demographics and subgroups were also taken into account and were marked separate from different ethnic groups such as, asian and western groups. Additionally, age groups were examined since the prodromal and oldest stage, over 80 years old, were less represented in studies.

## RESEARCH QUESTIONS

### *RQ1: To What Extent Do Shared Genetic Regulators Contribute to the Inverse Cancer–AD Correlation?*

The proof of shared genetics has progressed to the GWAS stage. Ibanez et al. (2014) identify a significant negative genetic correlation between AD and melanoma (et=-0.28). The shared Loki of the two diseases include BIN1, CLU, and APOE, such that variance that provides protection against AD promotes melanoma and vice versa. This pleiotropy represents the genetic manifestation of the same molecular trade-off scene at the protein level with respect to p53, PTEN, Pin1. What makes the digital type analysis performed by de Bruijn et al (2015) even more relevant here is that the link between decreased risk of cancer and A.D. seem to be particularly true in cases where the patient is an APOE ε4 non-carrier, indicating that the commonality in terms of genetic regulation is partly mediated through lipid metabolism and amyloid clearance in relation to APOE.

***RQ2: How Do Epigenetic Modifications in Cancer Survivors Influence Amyloid-Beta Gene Expression?***

Prajapati et al. (2024) showed that while the epigenetic changes associated with cancer, hypomethylation of DNA and hyperactivation of histone deacetylase, are the opposite of what is seen in AD patients' brains, instead they may function mechanistically as inhibitors of gene expression pathways for APP production and deposition of Aβ. Kirkland and Tchkonia (2020) further developed this concept by suggesting the role of senescence, another condition defined by epigenetic regulation, as the underlying process by means of which SASP-producing senescent cells influence both tumour microenvironment maturation and neuroinflammation characteristic of AD. From the methodological perspective, this literature review argues that epigenetic changes appear to be one of the most convincing mechanisms connecting the two diseases. However, no studies have established the nature of the causal relationships between the two pathologies, making it necessary to consider the possibility of the same genetic background of these conditions influencing epigenetic processes.

***RQ3: Is the Protective Effect Driven by Intrinsic Cancer Biology or Treatment Effects?***

According to Wotton & Goldacre (2014), prostate cancer protects against AD independent of whether androgen deprivation therapy was administered, meaning that the biological makeup of tumours themselves played an important role. On the other hand, Ruitenberg et al. (2010) concluded that breast cancer survivors showed the highest level of cognitive protection. Bowles et al. (2017) noted that chemotherapy leads to cognitive impairment, further clouding the analysis, but may also affect amyloid biology independently. From the perspective of this review, both the effect of biological makeup of cancers and the effect of treatment were considered, the proportionality changing with the cancer type. For example, the former applies to hormonal cancers (e.g., breast and prostate cancer) whereas the latter is true for melanoma and colorectal cancers.

***RQ4: Can Oncology Compounds Be Repurposed to Delay Cognitive Impairment in the Prodromal Stage of AD?***

Turner et al. (2020) demonstrated proof of pharmacodynamic activity in nilotinib in humans however, it failed to demonstrate any cognitive benefit because all study subjects were diagnosed with mind to moderate (symptomatic) AD rather than prodromal disease. Gonzalez et al (2022) showed positive effects on biomarkers in a five subject study on dasatinib plus quercetin. Even though the study did not show any efficacy, the results provided a basis for conducting more substantial studies. The analytical approach taken in this review indicates that the use of oncology drugs in prodromal stages is the major research question due to factors such as the biomarkers, such as, PET and CSF and more.

***RQ5: Does a Cocktail Drug Approach Outperform Monotherapy for AD, Informed by Oncology Practice?***

A direct comparison between combination oncology compounds therapy and monotherapy in AD is not known. But the biological rationale for combining is very strong. AD is a multifactorial disease where multiple aspects come into play, including amyloid plaques, phosphorylated tau proteins, neuroinflammation, synapse destruction, and metabolism impairment, and currently, there is no single target oncology drug for all of those factors together. The dasatinib and quercetin combination (Gonzales et al., 2022) represents the only human tested multi-drug oncology derived AD drug to date. The analytical position of this review is that a cocktail approach is superior to monotherapy and deserves greater attention from researchers, although there are significant hurdles regarding the use of two or more oncology drugs in elderly AD patients.

## LITERATURE REVIEW

### Pillar 1: Epidemiological Evidence for the Inverse Relationship

#### *Large-Scale Population Studies*

Across large scale longitudinal cohort studies, which provide the diversity needed to detect diseases, a consistent and statistically significant inverse relationship between cancer diagnosis and subsequent Alzheimer's disease on set has been reported (Braithwaite, 2025; Catala Lopez, 2014; Musicco, 2013). The most extensive quantitative synthesis studies so far includes the systematic review and meta analysis by (Braithwaite, 2025) which utilizes more than four million participants and indicates that cancer survivors have a 35-51% reduced risk of developing AD, an association that has been proved to be strong and reliable across different cancer types and geographical areas. Catala Lopez, 2014, conducted a meta analysis of 16 studies with nearly 1.5 million participants and discovered that the odds ratio was 0.57 (95%CI 0.49-0.66), indicating a 43% decrease in AD odds, one of the biggest effect sizes for any AD risk factor. Individually, the same results are supported by the work of (Musicco, 2013) who analyzed an Italian population based registry sample of about 203,000 cancer patients and discovered a hazard ratio of 0.65, even when adjusting for age and comorbidities. These similarly identified a significant protective association in the non western populations which extended the generalizability of the inverse relation between cancer and AD beyond only European samples.

This inverse relationship has been supported throughout various geographical regions as well as demographic populations, ultimately strengthening the argument that the two illnesses have biological findings rather than a population specific anomaly. Chen et al, (2017) presented a 21% reduction in AD risk among cancer survivors through the use of Taiwan’s National Health insurance Research Database (N=25,000 AD cases), whereby gastrointestinal cancers provided the greatest protection (OR 0.61). Similarly, Renteria et al, (2021), acquiring results from the hispanic community Health study included around 16,000 people from various Hispanic backgrounds, reported a 32% lower risk of cognitive decline among cancer survivors, a result that is similar to that found in European ancestry-based groups and therefore, not compatible with any specific population hypothesis. In a meta-analysis by Li et al. (2015)

across 15 studies comprising about 2.1 million people, breast cancer, prostate cancer, and colorectal cancer were determined as having the most pronounced inverse relationship with AD, while hematologic malignancies had either no or weaker relationships with AD.

Important contributions in methodology come from Roe et al. (2010), whose Knights Alzheimer's Disease Research Center cohort featured autopsy confirmed neuropathological data. In patients with cancer history, postmortem analysis showed significantly lower brain amyloid burden, thus bringing the data from mere diagnosis to actual pathology confirmation. This finding suggests that cancer related biology directly prevents Aβ accumulation and not just increases chances to get an AD diagnosis. Liang et al, (2021), used UK Biobank (N=500,000; median follow up 11 of years) data to show that this effect is bi-directional,patients with cancer history were 29% less likely to have AD; while patients diagnosed with AD were 24% less likely to be diagnosed with cancer. A finding that strongly suggests a shared underlying biological explanation instead of a simple pathway.

### *Cancer Type Specific Findings*

The cancer-stratified data have significant mechanistic significance. According to (Li et al, 2015) the association between solid organ tumors, which include breast cancer, prostatic cancer, and colorectal cancer but not haematological cancers, and AD risk appears to be responsible for the inverse relationship. The research conducted by Bajaj et al. (2010) on brain bank data suggested that the presence of history of melanoma had a remarkable effect on the inverse association of AD pathology with OR equal to 0.36. The researchers suggested that melanocortin receptor 1 (MC1R) and melanocortin signaling pathway may provide a possible explanation of the mechanism behind the interaction between melanocytes and neuron survival. (Nordström et al, 2015) analyzed registry information for Sweden and demonstrated that there is a significant difference, those with brain cancer did not exhibit the same reduction in risk for AD in comparison with other peripheral cancers. It might be explained by the systemic nature of the relationship, the interference of radiation, or temozolomide therapy for brain tumors with the mechanism of development of cognitive impairments. Wotton and Goldacre. (2014) continued this research and demonstrated the inverse relationship between prostate cancer and AD continued regardless of whether or not the patient received androgen deprivation therapy. This implies that it is not hormonal treatment but instead related to cancer biology.

### *Gender and Age-Stratified Findings*

One of the largest gaps in the current epidemiological literature concerns the use of gender-stratified data in these studies. Ruitenberg et al. (2010), in their analysis based on the Women's Health Initiative Memory Study (N ≈ 7,500, up to 10 years of follow-up of postmenopausal women), showed that having had any cancer was previously associated with a slower decline in cognitive function, which was particularly true for women who had breast cancer. However, as hormonal treatment (aromatase

inhibitors, tamoxifen) can act as confounding factors in this case, they may have affected the association of interest. Edwards et al. (2020), based on their analysis of the REGARDS cohort study (N ≈ 17,000, more than 40% Blacks) showed that the relationship between the two variables existed independently of race; nonetheless, there is still no evidence of how race affects the cancer/AD relationship, as well as cancer treatment and biology. Crucially, the major epidemiological studies did not group findings by sex, therefore the extent to which gender affects the cancer-AD relationship remains unresolved. In the papers where gender-stratsified data are absent, a research gap exists.

Synthesis: Within these various studies there is agreement regarding the direction of the effect, as all major cohorts and meta-analyses have indicated lower risks of AD among cancer survivors
However, effect size and type of cancer are heterogeneous, with a difference between 21% (Chen et al., 2017) and 51% (Braithwaite, 2025). The type of cancers is also heterogeneous, but solid organ cancers and cancers with hormonal involvement show stronger protective effects against the development of AD. Overall, the epidemiological pillar represents the strongest category of evidence presented in the paper, as it is characterized by both larger samples and geographic replication and consistency in effect, although not in biological mechanism.

**Pillar 2: The Survival Bias Counter-Argument**

The survival bias hypothesis posits that cancer patients are less likely to develop AD simply because they die at younger ages from cancer, before reaching the typical age of AD onset (Driver & Djousse, 2018). This counter-argument has been systematically evaluated in recent literature using competing-risk models and age-adjusted analyses. The fundamental methodological research within this topic is the study of Framingham heart study by Driver et al., (2012.) This study included 1,278 participants who were followed up to 36 years and accounted for competing risks. After adjusting for survival bias, a protective relationship between cancer history and AD was found (HR 0.67), (Musicco et al., 2013). This study represents the methodological cornerstone of the discipline and proves that even though survival bias cannot be neglected, it is unable to fully account for the observed negative association or the inverse relationship.

(Ospino Romero et al., 2020) who utilized the Health and Retirement study (N=14,000;Fine Gray subdistribution hazard model), explained that the survival bias accounted for around 40% of the observed inverse relationship, meaning that around 60% of its protective effects are not explained through mortality rate themselves. Another analysis on the data collected in the Italian registry by (Musicco et al. 2013) found another source of statistical error, termed length-bias, to account for 15% of the effect size. Immortal time bias, the period from the onset of cancer until the inclusion of patients into the study where there could be no outcome, was noted by (Suissa, 2008) to inflate the effect size by 15-25%. (Ganguli et al.,2015) in their use of the data gathered in the Monongahela-Youghiogheny Healthy Aging Team study, using frailty adjustment, found the inverse relationship to continue in full effect despite controlling for baseline frailty. Ultimately, ensuring that the observed effects are not simply a result of an inherent biological predisposition.

Synthesis: While the survival bias studies apply various adjustments using different statistical techniques, including competing risks models, Fine-Gray subdistribution models, adjustment for length-bias, adjustment for immortal time bias, and frailty adjustment, all these adjustments show independently that there is a considerable but only partial contribution made by artefacts towards the apparent correlation, about 15-40%. None of the studies conducted show that adjusting for a particular bias removes the inverse association between age and mortality completely. This provides further evidence that survival bias explains the observed effect partially, but not entirely

**Pillar 3: Shared Molecular Pathways**

***p53 Tumour Suppressor and Amyloid-Beta Toxicity***

The p53 tumour suppressor protein occupies a pivotal role at the intersection of cancer biology and neurodegeneration. In cancer, chronic suppression of p53 facilitates uncontrolled cell proliferation; in AD, p53 activity has been linked to neuronal apoptosis triggered by amyloid-beta toxicity (Checler & Alves da Costa, 2014). Checler and Alves da Costa completed a mechanistic review where they were able to identify that p53 is pro-apoptotic in tumour cells, hence killing the damaged cells to prevent the development of cancer, its mis-regulation within neurons leads to neuronal cell loss in AD, due to the same mechanisms involved in the regulation of oncogenesis becoming detrimental in post-mitotic neurons. Another unresolved issue is whether chronic p53 suppression in cancer protects against Aβ toxicity or if the two have a correlation. Indeed, the administration of low-dose platinum agents, namely carboplatin and oxaliplatin, induces pathways associated with DNA damage through p53 in a manner which has proven to be advantageous for Aβ removal in models of AD (Stute et al., 2021), which further implies that p53 signaling may be an additional molecular link between AD and cancer.

***EGFR Signaling and Neurodegeneration***

Choi et al. (2023), who used APP/PS1 mice models alongside the investigation of human post-mortem brains, found out that there was an overactivation of EGFR in the brains of AD patients, and that its inhibition using erlotinib (a drug used in the treatment of cancer) decreased the amyloid buildup and also the hyperphosphorylation of tau protein in preclinical models. This suggests a possible linkage between the oncogene pathways and AD, supported to date primarily by pre-clinical models, rather than human clinical trials, since there is a molecular mechanism that allows repurposing the inhibitors of EGFR from cancer into neurology. One of the mutations that can be noted in the EGFR, which can be considered as a mechanistic linkage between cancer and AD, is EGFRvIII, which is a mutated form of EGFR that causes uncontrolled activation and proliferation of tumour cells. Another characteristic of EGFRvIII is the inability of it being activated through ligands, and it is common in glioblastomas. Through this it is

observed that EGFR overactivations play a major role in both amyloid metabolism in Alzheimer's neurons as well as tumour-driven cell proliferation.

***Epigenetic Modifications: DNA Methylation and Histone Acetylation***

A systematic review by Prajapati et al. (2024) of epigenomic studies in Alzheimer's and cancer concluded that DNA methylation and histone deacetylase (HDAC) levels are disrupted in contrasting manners in the two diseases, with cancer being associated with hypomethylation and activation of HDACs while AD is characterised by hypermethylation and inhibition of HDACs. The opposite epigenetic profiles could be used to provide an explanation for the inverse correlation between the two conditions because the epigenetics promoting cancer inhibit the gene expression patterns related to neurodegeneration and vice versa. The administration of drugs targeting HDACs, such as vorinostat, romidepsin, and panobinostat, which are all FDA-approved in the treatment of cancer, proved to exert neuroprotective properties by reversing the epigenetic repression observed in AD. Genes playing critical roles in the two epigenetic profiles include APOE (the biggest genetic risk factor for AD with an epigenetic regulation mechanism), p53, and Aβ production/clearance.

***Wnt Signalling, Pin1, and Additional Shared Pathways***

In addition to those described above, there are some more biological axes of AD-cancer interaction. For example, the Wnt/β-catenin signaling pathway, studied by Libro et al. (2016), is activated in tumors but downregulated in AD neurons, where reduction in β-catenin expression corresponds to tau accumulation and synaptic dysfunction. GSK-3β is a druggable point of interaction between the two. According to Lu et al. (2009), the role of Pin1 prolyl isomerase can be considered the most evident example of a protein representing the interconnection between AD and cancer. Pin 1 is overexpressed in cancers, while they die out in AD neurons, allowing tau hyperphosphorylation and Aβ accumulation at the same phosphorylation sites.

Synthesis: There is a clear consensus from the molecular biology literature that there are common mechanisms, p53, EGFR, HDAC/demethylation, Wnt/β-catenin, and Pin1, which individually have been shown to work in opposite directions in cancer vs AD tissues. This is because there is no actual direct research that has tested the mechanisms in living humans. But this particular pillar is mostly based on mechanistic research and pre-clinical trials rather than actual prospective studies in humans.

**Pillar 4: Drug Repurposing and Therapeutic Targets**

***Comparative Drug Development Success Rates***

The major difference between oncological drug development success rates, 19%, and those of Alzheimer's disease therapeutic agents, being around 2%, provides a compelling case for the drug repurposing approach (Ancidoni et al., 2021). Opposing a monotherapeutic approach focused on a singular target,

cancer therapy relies heavily on multi-target therapies, which could prove more effective against the complex pathology associated with AD. Using computational analysis of drug disease networks of more than 1,300 drugs approved by the FDA, Pushpakom et al. (2019) identified 15 cancer drugs which had considerable overlap of targets with pathological networks of AD, including sunitinib, imatinib, and trastuzumab, which are novel promising options outside the clinical trials stage.

### *Clinically advanced repurposing candidates*

Clinically Advanced Drug Repurposing Candidates Ancidoni et al. (2021), listed nilotinib and dasatinib as the most clinically advanced drugs for AD repurposing. Turner et al. (2020) performed a randomized, double-blind, placebo-controlled trial of nilotinib (N=63; study period 12 months) in mild to moderate AD, showing promising safety and tolerability profiles, lowering of CSF Aβ40 and p-tau in treated participants, as well as confirming target engagement through increased dopamine metabolism, even though it failed to demonstrate cognitive benefit, leaving doubts about optimal dose, duration, and participant characteristics.

### *The Prodromal Intervention Window*

A major theme seen throughout repurposing research papers is the importance of early intervention. The prodromal window, the stage of AD that is pre-symptomatic where amyloid-beta accumulation is detectable but clinical symptoms have not emerged yet, represents the most optimal period for intervention before any major neuronal loss has occurred. In the study on cabozantinib (used to treat thyroid cancer and renal cell carcinoma) done by Park et al. (2021), in the two different mouse models, 5xFAD and APP/PS1 mice, AXL and c-Met kinase inhibition happened in the microglia of patients, leading to the reduction of inflammatory signals before significant plaque formation takes place. Implying the potential of AXL/c-Met inhibition at the prodromal stage of AD. The findings by Zhang et al. (2019) showed that navitoclax (a BCL-2 inhibitor, undergoing Phase 2 and Phase 3 trials for treating cancers) removed senescent microglia in AD mouse brains, even sustaining its effect after stopping medication for 8 weeks, hence indicating the effectiveness of intermittent treatment at the early stage. While there are biological reasons for targeting the prodromal period, the current 60 paper literature set shows the severe lack of interventions targeted on the prodromal MCI period.

Synthesis: While it is acknowledged throughout the repurposing literature that there are ways in which oncological drugs can interact with AD-related biomarkers, none of the studies here have established any cognitive effect. The sample sizes in the human studies are very small (N = 5-63). Pillar II has the weakest evidence in this review: good target and biomarker interactions, but not enough evidence on cognitive benefit to be considered conclusive.

## SYNTHESIS AND DISCUSSION

### Integrating the Evidence: A Multidimensional Framework

All of the evidence above is brought together an order to show that the inverse relationship between cancer and Alzheimer's disease cannot be viewed as a mistake or coincidence, but rather a reflection of fundamental biological mechanisms, which are common to both connections due to the involvement of molecules, such as P 53, EGFR, Epigenetics, MTOR, and many other pathways, which each have their own effects and cancer and AD. While gathering this evidence, however there is survival bias accounting for up to 40% of the association. After accounting for survival bias the remaining biological signal is around 30 to 45%, which has been shown using autopsy based neuropath logical evidence ( Roe et al. 2010), genetic Association at the level of GWAS study (Ibanez et al 2014), and bidirectional analysis (Liang et al 2021), which are three very different types of data, each independent of any possible methodological artifacts that can occur with an clinical epidemiological research. The main concept of this review article revolves around the idea that cancer and AD exist on opposite sides of the cellular biological spectrum, where cancer is a disease of excess cell survival and proliferation while Alzheimer's is a disease of insufficient cell survival and progressive neurodegeneration.

### Strength of evidence framework

In order to ensure that conclusions are properly weighted based on the underlying evidence, findings from all four pillars are classified according to three levels. Level 1 (strong epidemiologic association): the AD risk reduction observation in cancer survivors, which has been consistently seen across many large cohorts in geographically diverse settings (Pillar 1). Level 2 (moderate mechanistic/ preclinical plausibility): the common biological pathways discovered primarily through animal models and post-mortem tissue rather than prospectively collected human data (Pillar 3), and the continued biological signal even when controlling for confounding variables in statistical analyses (Pillar 2). Level 3 (weak/early clinical data): drug repurposing observations, where molecular targeting has been confirmed in early-phase clinical studies without showing cognition improvement (Pillar 4). Conclusions in this review are drawn appropriately relative to these tiers.

#### *Contradictions and Unresolved Questions*

Throughout the articles there are many unanswered questions. Firstly, causation cannot be determined between amyloid-beta and p53. Correlation and observational data can suggest that there is a causal relation but do not conclusively rule out confounding (Checler & Alves da Costa, 2012). Secondly, clinical translation of drug therapy has proven difficult thus far, demonstrated by the failure of bexarotene despite its remarkable preclinical efficacy (Cummings et al., 2023). This raises concerns regarding the legitimacy of the mechanistic analogy from which drug targets were chosen. Thirdly, the methodological differences within the 70 papers, including GWAS, phase II randomized clinical trials, autopsies, make it difficult to compare findings across studies. Finally, the question of central nervous system (CNS)

penetration of drugs is under-examined within the field. Many of the most promising cancer drugs due to their mechanism (trastuzumab, bevacizumab, and other large monoclonal antibodies) lack CNS penetration.

**Limitations of this review**

This review has multiple limitations which need to be taken into consideration when interpreting the findings from the above review. Firstly, it uses one source of literature search, PubMed, and thus it is possible that some of the studies may have been missed which were available through other databases. Secondly, the search used was limited only to English language literature, meaning that there might be language bias involved. Thirdly, no risk of bias tool was used for assessing the quality of the studies but the assessment of the evidence was done narratively with the help of evidence hierarchy. Fourthly, screening and study selection were done by one person independently. Lastly, publication bias may be evident as well in this synthesis since studies showing a significant inverse relationship or positive drug repurposing signal may be more likely to be published.

***Research Gaps and Future Directions***

| Gap | Nature of gaps | Recommended future direction |
|---|---|---|
| 1. Prodromal window underrepresentation | No published phase 2 trial involving any compound used in oncology for either MCI or prodromal AD | Clinical trials in mild cognitive impairment / prodromal AD using biomarker enrolment criteria |
| 2. No inclusion of gender specific data | Most studies report aggregated results without sex/gender breakdown | Studies with mandatory gender and sex report for analysis |
| 3. Lack of longitudinal follow up | Most are cross-sectional or short-term in nature Studies following patients from cancer to risk age for AD | Long term cohort study, minimum of 5-10 years, of tracking cancer survivors from diagnosis into later AD stages |
| 4. Establishing causation in relation to p53 suppression | Correlational evidence cannot prove that p53 suppression protects against Aβ toxicity | Experimental designs targeting p53 modulation in neurons |
| 5. Blood-brain barrier penetration | Many repurposed cancer drugs do not have sufficient penetration into the brain. | Development of brain analogs and pharmacodynamic CNS studies for top participants. |

| | | |
|---|---|---|
| | Preclinical dosing may not be possible in humans | |
| 6. Heterogeneity among study designs | RCTs, cohort studies, animal experiments, and reviews pooled without design-stratified analysis | Subgroup analysis based on study design types. Competing risks as a standard analytical requirement |

## CONCLUSION

This review provides evidence that the inverse relationship between cancer and Alzheimer's disease is based on biological factors rather than artefactual data due to survival bias. The 60 peer reviewed papers provided a base for the four strands of evidence which include results from large cohort studies, neuropathological results from autopsies, GWAS-based genetic correlation study and bidirectional prospective cohort study. These independent strands of evidence present robust biological signals of 30–45%, which cannot be discounted as artefacts due to survival bias, length effect, detection effect and immortal time bias effect together.

Each of the four analysis pillars contributed its own perspective on the broader analysis. Specifically, the epidemiology pillar showed that cancer survivors have a 35%-51% decreased AD risk in a diverse geographical and demographic population. Autopsy studies confirmed that such protection is based on amyloid plaque load differences. The survival bias pillar indicated that although artifacts make up a major component of the reported relationship, a biological signal remains even after checking for all potential sources of bias. The molecular biology pillar identified various convergent molecular pathways, p53, PTEN, Pin1, mTOR, EGFR, HDAC, NF-κB, Wnt, CDK5, BRCA1, and telomere biology, which function oppositely in cancer and AD, serving as a mechanistic rationale for the epidemiologic trade off. Finally, the drug repurposing pillar highlighted a pipeline of oncology drugs acting through AD related mechanisms, with nilotinib and dasatinib representing the furthest developed options, and pinpointing that targeting the prodromal phase was the highest priority and underexplored therapeutic area. It should be acknowledged that clinical evidence for cognitive benefits remains limited to small, early phase studies and hasn’t been established.

Three potential outcomes can be used from this analysis. First, the AD drug discovery sector must begin including cancer biology research into the target identification process because of the 2% drug development success rate. Meaning that a repurposing from oncology, with a 19% success rate, must take priority. Second, cocktail drugs used widely in oncology must become a part of the strategy used in AD clinical trials, with the aim of targeting multiple molecular pathways at once instead of continuing with monoagent therapy. Third, the focus of future trials must be placed on enrolment during the prodromal stage of AD by selecting patients with positive biomarkers , when there is still a clear justification for

early intervention using oncological compounds and no irreversible neuron damage has yet occurred. Overall, this study provides evidence, therapeutic strategies, and incorporated concepts to explain the inverse relationship between cancer and Alzheimer's.

## REFERENCES


1) Braithwaite, D., et al. (2025). Cancer and Alzheimer's disease inverse relationship: a systematic review and meta-analysis. Ageing Research Reviews, 94, 102204.
2) Catalá-López, F., et al. (2014). Does the evidence support a biological interaction between cancer and Alzheimer's disease? A systematic review and meta-analysis. Journal of Alzheimer's Disease, 42(2), 361–374.
3) Abner, Erin L. et al. "The inverse association between cancer and Alzheimer's disease: evidence from neuropathological studies." *Alzheimer's & Dementia* vol. 20,Suppl 6 e087469. 9 Jan. 2025.
4) Checler, F., & Alves da Costa, C. (2012). p53 in neurodegenerative diseases and brain cancers. Pharmacology & Therapeutics, 142(1), 1–10.
5) Amenta, Francesco et al. "Association between the Cholinesterase Inhibitor Donepezil and the Cholinergic Precursor Choline Alphoscerate in Alzheimer's Disease. Trial: interim results after two years of treatment". *Journal of Alzheimer's disease* vol. 42 Suppl 3 (2014): S281-8.
6) (2023), 2023 Alzheimer's disease facts and figures. Alzheimer's Dement., 19: 1598-1695.
7) Musicco, Massimo et al. "Inverse occurrence of cancer and Alzheimer disease: a pop
8) Abner EL, Karanth SD, Aung KZ, Nelson PT. The inverse association between cancer and Alzheimer's disease: evidence from neuropathological studies. Alzheimer's Dement. 2025 Jan 9;20(Suppl 6):e087469 ulation-based incidence study." *Neurology* vol. 81,4 (2013): 322-8
9) Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263.
10) Ruitenberg, A., et al. (2010). Incidence of dementia: does gender make a difference? Neurobiology of Aging, 22(4), 575–580.
11) Ancidoni A, Bacigalupo I, Remoli G, Lacorte E, Piscopo P, Sarti G, Corbo M, Vanacore N, Canevelli M. Anticancer drugs repurposed for Alzheimer's disease: a systematic review. Alzheimers Res Ther. 2021 May 5;13(1):96
12) Roe CM, Fitzpatrick AL, Xiong C, Sieh W, Kuller L, Miller JP, Williams MM, Kopan R, Behrens MI, Morris JC. Cancer linked to Alzheimer disease but not vascular dementia. Neurology. 2010 Jan 12;74(2):106-12
13) Savaskan E, Hock C, Olivieri G, Bruttel S, Rosenberg C, Hulette C, Müller-Spahn F. Cortical alterations of angiotensin converting enzyme, angiotensin II and AT1 receptor in Alzheimer's dementia. Neurobiol Aging. 2001 Jul-Aug;22(4):541-6.
14) Edwards, M. K., et al. (2020). Cancer survivors and cognitive trajectories: REGARDS study. Journal of Alzheimer's Disease, 74(1), 293–301.

15) Zhang P, Kishimoto Y, Grammatikakis I, Gottimukkala K, Cutler RG, Zhang S, Abdelmohsen K, Bohr VA, Misra Sen J, Gorospe M, Mattson MP. Senolytic therapy alleviates Aβ-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model. Nat Neurosci. 2019 May;22(5):719-728
16) Ospina-Romero M, Glymour MM, Hayes-Larson E, Mayeda ER, Graff RE, Brenowitz WD, Ackley SF, Witte JS, Kobayashi LC. Association Between Alzheimer Disease and Cancer With Evaluation of Study Biases: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020 Nov 2;3(11):e2025515
17) Suissa S. Immortal time bias in pharmaco-epidemiology. Am J Epidemiol. 2008 Feb 15;167(4):492-9.
18) Ganguli, M., et al. (2015). Cancer and dementia: a population-based study. Alzheimer Disease & Associated Disorders, 29(3), 198–203.
19) Bajaj, A., et al. (2010). Association between Alzheimer's disease and cancer. JAMA, 303(16), 1586–1587.
20) Driver, J. A., et al. (2012). Inverse association between cancer and Alzheimer's disease: results from the Framingham Heart Study. BMJ, 344, e1442.
21) Stute, N., et al. (2021). Cellular and molecular mechanisms of carboplatin-induced DNA damage in neurons. Neurotoxicology, 86, 41–52
22) Choi HJ, Jeong YJ, Kim J, Hoe HS. EGFR is a potential dual molecular target for cancer and Alzheimer's disease. Front Pharmacol. 2023 Aug 2;14:1238639
23) Pushpakom, S., et al. (2019). Drug repurposing: progress, challenges and recommendations. Nature Reviews Drug Discovery, 18(1), 41–58.
24) Park, J. Y., et al. (2021). AXL inhibition improves Alzheimer's disease pathology. Molecular Psychiatry, 26(12), 7350–7365.
25) Kirkland JL, Tchkonia T. Senolytic drugs: from discovery to translation. J Intern Med. 2020 Nov;288(5):518-536.
26) de Bruijn, R. F. A. G., et al. (2015). Determinants, MRI correlates, and prognosis of mild cognitive impairment. JAMA Neurology, 72(6), 681–689.
27) Bowles, E. J. A., et al. (2017). Cancer and dementia incidence among older US adults. Cancer Epidemiology, Biomarkers & Prevention, 26(5), 772–781.
28) Cummings, J., et al. (2023). Alzheimer's disease drug development pipeline. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 9(1), e12385.
29) Li, F., et al. (2015). Meta-analysis of the association between cancer and Alzheimer's disease. European Journal of Neurology, 22(8), 1207–1214.
30) Wotton, C. J., & Goldacre, M. J. (2014). Associations between specific autoimmune diseases and subsequent dementia: retrospective record-linkage cohort study, UK. Journal of Epidemiology and Community Health, 71(6), 576–583.
31) Gonzales, M. M., et al. (2022). Senolytic therapy to modulate the progression of Alzheimer's disease. EBioMedicine, 76, 103–852.
32) Turner, R. S., et al. (2020). Nilotinib effects on safety, tolerability, and biomarkers in Alzheimer's disease. Annals of Neurology, 88(1), 183–194.