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Article

# Decreased Expression of Alzheimer's Disease-Related Genes in Cancer May Contribute to the Inverse-Relationship-a Computational Study

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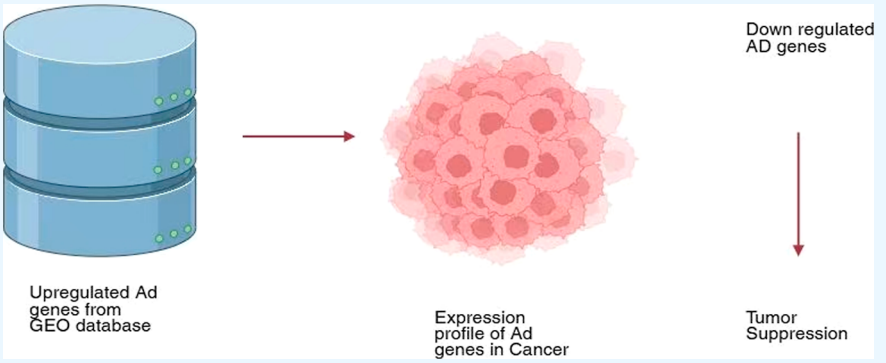


**ABSTRACT:** Alzheimer's disease (AD) has been largely prevalent among the older population. With the increasing incidence of cancer over the years, scientists have explored the relationship between these two conditions which were formerly associated with aging. Interestingly, an inverse relationship between cancer and AD has been observed in large cohort studies which has garnered substantial interest. While this inverse relationship presents a fascinating scientific puzzle, there is limited data on the molecular mechanisms that govern this phenomenon. This study aims to investigate the fundamental molecular mechanisms driving the inverse association between AD and three common cancers: breast, prostate, and colorectal cancers. Gene expression data for AD were obtained from the Gene Expression Omnibus (GEO) repository, specifically the GSE122063 data set. Differentially expressed genes (DEGs) between AD and nondemented controls were identified using the GEO2R tool. Genes associated with breast, prostate, and colorectal cancer were obtained from the Genecards database. Shared genes between cancers and AD-upregulated genes were identified using the Venny 2.1 tool. The UALCAN analysis portal was used to evaluate the mRNA expression of shared genes in cancer types. The DAVID tool, ShinyGO and SRplotter tools were used for functional enrichment analyses and gene ontology annotations. We found 20 genes upregulated in AD but significantly downregulated in breast cancer, 11 significantly downregulated in prostate cancer and 5 genes downregulated in colon cancer. Key genes were involved in pathways related to muscle structure, DNA repair, protein stability, and gene expression regulation. Three (3) of these genes, *AQP1*, *CRYAB*, and *HSPB2*, were downregulated in all three cancers and may play an important role in reduced risk of cancer development while upregulated in AD. This study serves as a foundational effort to delve deeper into the molecular connections between AD and various cancer types, using the identified genes as a promising starting point for future experimental investigations to fully elucidate the mechanisms involved in the inverse interaction and protection of AD patients against cancer development.

## INTRODUCTION

A global estimate of 416 million people aged 50 years and above have Alzheimer's disease (AD) with about 32 million of them living with dementia.[1] Dementia is the fifth leading cause of death globally and AD is the fourth leading cause of disability-adjusted life-years (DALYs) lost in persons aged 75 years and older.[2] AD is a progressive neurodegenerative condition that predominantly impacts cognitive functions, memory, and behavior. AD is marked by a decline in cognitive abilities that manifests through damaged brain cells and the loss of neuronal connections significantly impairing a person's daily life and functionality.[3] As the global population continues to age, the

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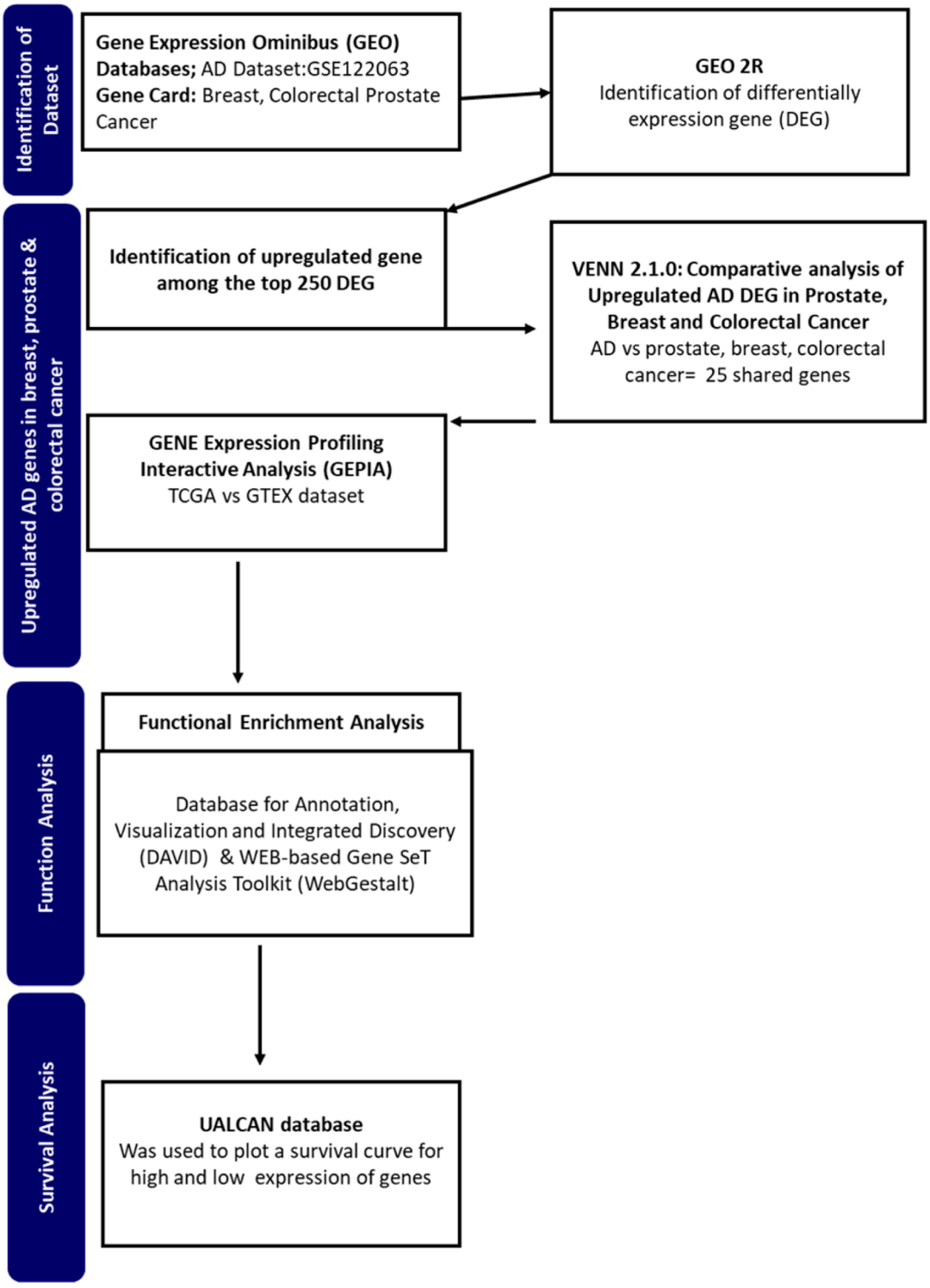


**Figure 1.** A flowchart of the bioinformatics approach used in this study. This chart summarizes the methods employed in this research.

prevalence and burden of AD is projected to rise dramatically in the coming decades.[4]

The molecular landscape of AD is manifested in two significant hallmarks: amyloid-beta (A$\beta$) plaques and tau protein tangle. However, neuroinflammation has been suggested as the third hallmark of AD.[3,5] The amyloid precursor protein (APP) is a transmembrane protein that is cleaved by secretases, leading to the production of A$\beta$ peptides, including A$\beta$40 and A$\beta$42. A$\beta$42 is more likely to aggregate and is a major component of amyloid plaques. These plaques disrupt cell-to-cell communication and trigger immune responses, resulting in inflammation. In AD, tau becomes hyperphosphorylated and forms insoluble neurofibrillary tangles (NFTs) within neurons. Hyperphosphorylated tau disrupts microtubule stability, causing neuronal dysfunction and cell death. Pathological tau can spread from cell to cell, propagating the neurodegenerative process.[6,7]

While the molecular mechanisms underlying sporadic, late-onset AD are complex and multifactorial, some diseases such as


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diabetes[8] and cancer[9] have been associated with AD pathogenesis. The relationship between AD and cancer has been a subject of increasing interest in recent years. Several studies have explored the connection between these two conditions, revealing an inverse association between the risk of developing cancer and the risk of developing Alzheimer's disease. Ospina-Romero et al., in their study, found that individuals with cancer had a slower rate of memory decline both before and after diagnosis compared to those who remained cancer-free.[10] This study followed a cohort of 14,583 adults from the Health and Retirement Study and showed that cancer survivors had a 10.5% slower rate of memory decline before diagnosis and a 3.9% slower rate after diagnosis compared to cancer-free individuals.[10] They further conducted a systematic review and meta-analysis of 22 cohort and case-control studies, representing 9,630,435 individuals and found that cancer diagnosis was associated with an 11% decreased incidence of Alzheimer's disease.[11]

The exact molecular mechanisms underlying this inverse relationship are not yet understood. However, several studies propose that shared etiological mechanisms might explain this phenomenon. The influence of genetics and specific molecular pathways that are associated with both Alzheimer's disease and cancer may have variations that affect an individual's susceptibility to either condition.[9] Additionally, pathways related to cellular growth, metabolism, and energy utilization could play a role in shaping the relationship between AD and cancer.[12] While individual studies have reported on the inverse relationship between AD and cancer, there is a critical gap in our comprehension of the specific molecular mechanisms that drive this association. It is worth noting that the relationship between AD and cancer may not be clear-cut among all types of cancers and can vary depending on various factors including the type and stage of cancer.

In this study, we delved into potential molecular mechanisms that may be responsible for the inverse association between AD and cancer. Using in silico analyses, we identified shared molecular components that potentially elucidated the inverse interaction between Alzheimer's disease and three common cancers: breast, prostate and colon cancers.

## METHODS

**Acquisition of Gene Expression Data.** We accessed gene expression data associated with AD using the Gene Expression Omnibus (GEO) data repository managed by the National Center for Biotechnology Information, USA (http://www.ncbi.nlm.nih.gov/geo/, accessed on 12 June 2023). Specifically, we used the data set with accession number GSE122063. The GSE122063 data set comprises Agilent-039494 SurePrint G3 Human GE v2 8 × 60K Microarray data showing gene expression profiles of the frontal and temporal cortex of AD, vascular dementia (VaD), and nondemented controls obtained from the University of Michigan Brain Bank. The AD and control cases in this data set had no infarcts in the autopsied hemisphere.[13] This study used 56 microarray data from 12 AD samples and 44 microarray data from 10 nondemented controls.

**Identification of Differentially Expressed AD Genes.** Differentially expressed genes (DEGs) between AD and nondemented controls were identified by analyzing the microarray data set with the GEO2R interactive web tool (https://www.ncbi.nlm.nih.gov/geo/geo2r/), accessed on 12 June 2023, within the GEO database. GEO2R uses several R packages from the Bioconductor project to identify statistically significant DEGs. This study considered the top 250 DEGs with FDR-adjusted $p$-value <0.05 and $|\log FC| \geq 1$ for further analysis.

**Identification of AD Genes Associated with Cancer.** Genes associated with prostate, breast, and colorectal cancer were obtained from the Genecards database (https://www.genecards.org/)[14] accessed on 25 June 2023. A cutoff score >4 was used to obtain the most probable genes. The Venny 2.1 web tool[15] was then used to identify shared genes between cancer (breast, colorectal, and prostate) and AD-upregulated genes.

**Analyses of AD Associated Genes' Expression in Breast, Colorectal, and Prostate Cancer.** The University of Alabama at Birmingham cancer (UALCAN) data analysis portal (https://ualcan.path.uab.edu/index.html)[16] accessed on November 2, 2024 was used to evaluate the mRNA expression of the shared genes in breast, colorectal, and prostate cancer. Gene expression data from The Cancer Genome Atlas (TCGA) containing expression data from tumor tissues and normal tissues. Statistical significance was determined by |Log 2FC| > 1 and $p$-value <0.01.

**Functional Enrichment Analyses and Gene Ontology.** The Database for Annotation, Visualization, and Integrated Discovery (DAVID) tool (http://david.ncifcrf.gov),[17] accessed on August 8, 2023, was used to perform functional enrichment analyses of the genes of interest. The ShinyGO tool (https://www.webgestalt.org/, accessed on August 8, 2023) was used to annotate each gene based on the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway to identify pertinent signaling pathways they regulate. SR plotter was used to also generate enrichment plots from gene set lists (https://www.bioinformatics.com.cn/srplot) access on November 4, 2024.

The data acquisition and analysis processes have been summarized in the flowchart in Figure 1 below.

## RESULTS

**DEGs between AD and Nondemented Groups.** Analysis of the GSE122063 data set revealed differentially expressed genes between AD and nondemented controls (Figure 2). Out of the top 250 differentially expressed genes, 77 were found to be significantly upregulated in AD compared to nondemented controls (Figure 2).

**Gene Associated with AD and the Selected Cancer.** Comparing the 77 significantly upregulated AD genes to genes associated with breast, colon and prostate cancers revealed 47, 31, and 33 genes common between AD and breast, prostate and colon cancer respectively (Figure 3). In this study we also identify downregulated AD genes associated with these cancers (supplementary Figure S1 and S2, Table S1). We hypothesized that among these shared genes, genes that were significantly downregulated in the cancers while upregulated in AD could be important in explaining the inverse association between AD and cancers. Hence, we explored the significantly downregulated genes in these cancers and found 20 significantly downregulated genes in breast cancer, 11 in prostate cancer and 5 in colon cancer (Figure 4).

**Enrichment Analysis of Significantly Downregulated Genes in the Three Cancers.** The enrichment analysis of genes that are upregulated in Alzheimer's disease (AD) and downregulated in the various cancers (breast, colon, and prostate) highlights critical biological processes and molecular functions involving key genes (Figure 5). Generally, we identified key genes involved in structural integrity, gene regulation, steroid binding, and protein quality control. The Z disc, I band, sarcomere, and myofibril are essential for muscle


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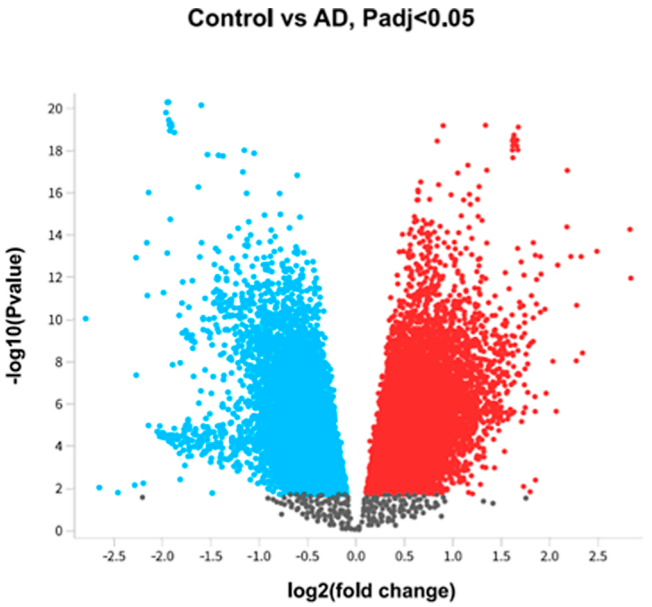


**Figure 2.** DEGs between AD and nondemented groups. Volcano plot showing DEGs between AD and nondemented controls in the GSE122063 data set. Blue dots: significantly downregulated genes, gray dots: genes with no significant difference between groups, red dots: significantly upregulated genes based on adjusted *p*-value <0.05 and |log FC| ≥ 1.

structure and function, with genes *HSPB1*, *CRYAB*, and *CSRP2* significantly enriched in these components in both breast and prostate associated genes (Figure 5A,B). These genes play vital roles in maintaining muscle integrity and resilience under stress, crucial for both neurodegenerative diseases and cancer (Figure 5A). The DNA repair complex, involving genes ATM and POLD1, is pivotal for repairing DNA damage and maintaining genomic stability, essential for preventing cancer and preserving neuronal function in AD (Figure 5). *CRYAB* and *HSPB2* are also structural constituents of the eye lens, emphasizing their roles in protein stability and structural maintenance, important for cellular resilience. *YBX1* and *NEAT1* are enriched in miRNA binding and regulation (Figure 5).

**Pathway Analysis of the Significantly Downregulated Genes in the Three Cancers.** Kyoto encyclopedia of genes and genomes (KEGG) pathway enrichment analyses were performed using the SR plotter tool for the selected genes that were downregulated in the cancers. The functional pathways analysis reveals that these genes are mainly involved in metabolic, secretory and apoptotic pathways (Figure 6). Individual genes were involved in multiple pathways. However, multiple genes were not found in a single pathway. For instance, AQP1 was involved in renin secretion pathways, proximal tubule bicarbonate reclamation and bile secretion (Figure 6A and B).

**Protein−Protein Interaction of the Significantly Downregulated Genes in the Three Cancers.** We determined the PPI network within the significantly downregulated genes identified among the three cancers (Figure 7). The gene associated with breast cancer showed two interaction networks consisting of 9 genes and 2 genes in each network (Figure 7A). Prostate cancer-associated genes also show two interacting networks consisting of 7 genes and 2 genes in each network (Figure 7B). Finally, five genes were downregulated in colon cancer, 4 of the genes formed an interaction network (Figure 7C). These interactions consist of genes that are coexpressed such as AQP1, CRYAB and HSPB2.

**Common Genes That are Downregulated among all Three Cancers.** We determined the genes that were downregulated and common to all three cancers. We found 3 genes, *CRYAB*, *AQP1* and *HSPB2* as common genes across all three cancers (Figure 8). We determined the pathways in which these genes function. CRYAB was enriched in longevity-regulating pathways and protein processing in the endoplasmic reticulum.

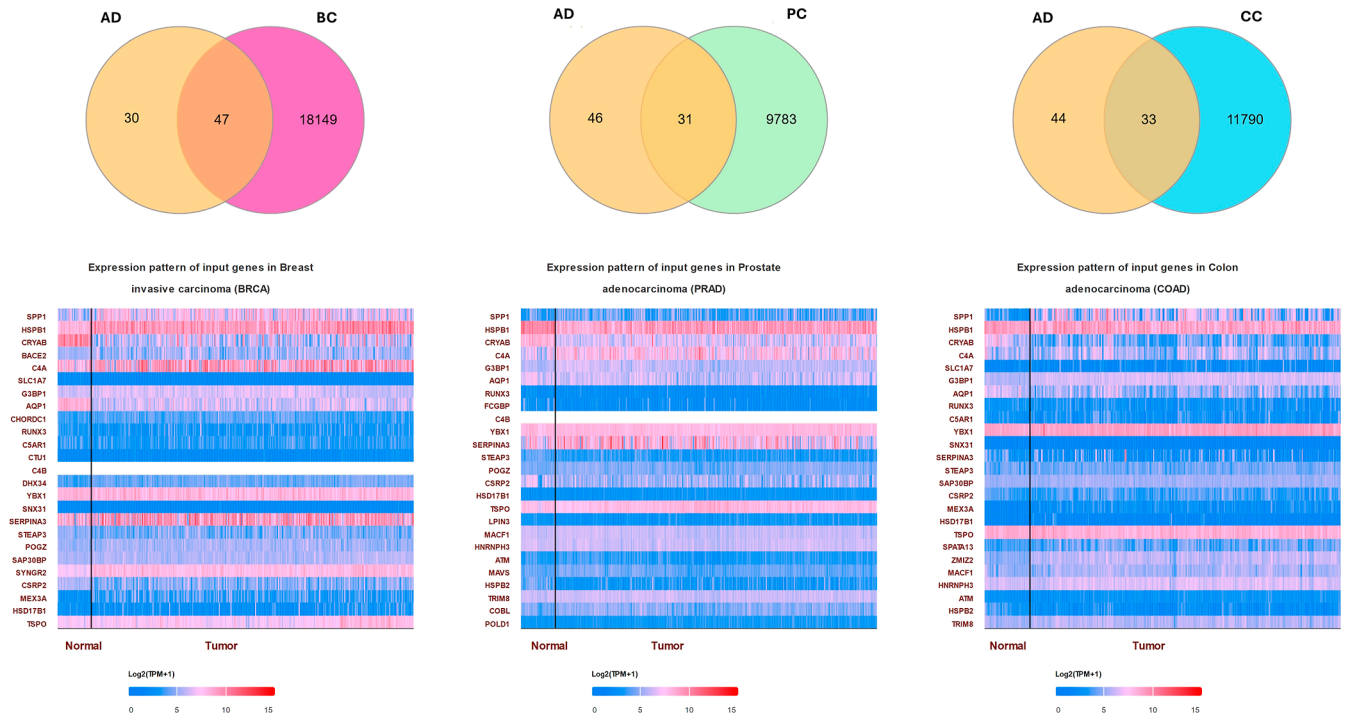


**Figure 3.** Intersection among upregulated Alzheimer's disease (AD) genes and genes associated with breast BC, colon CC, and prostate cancer PC.



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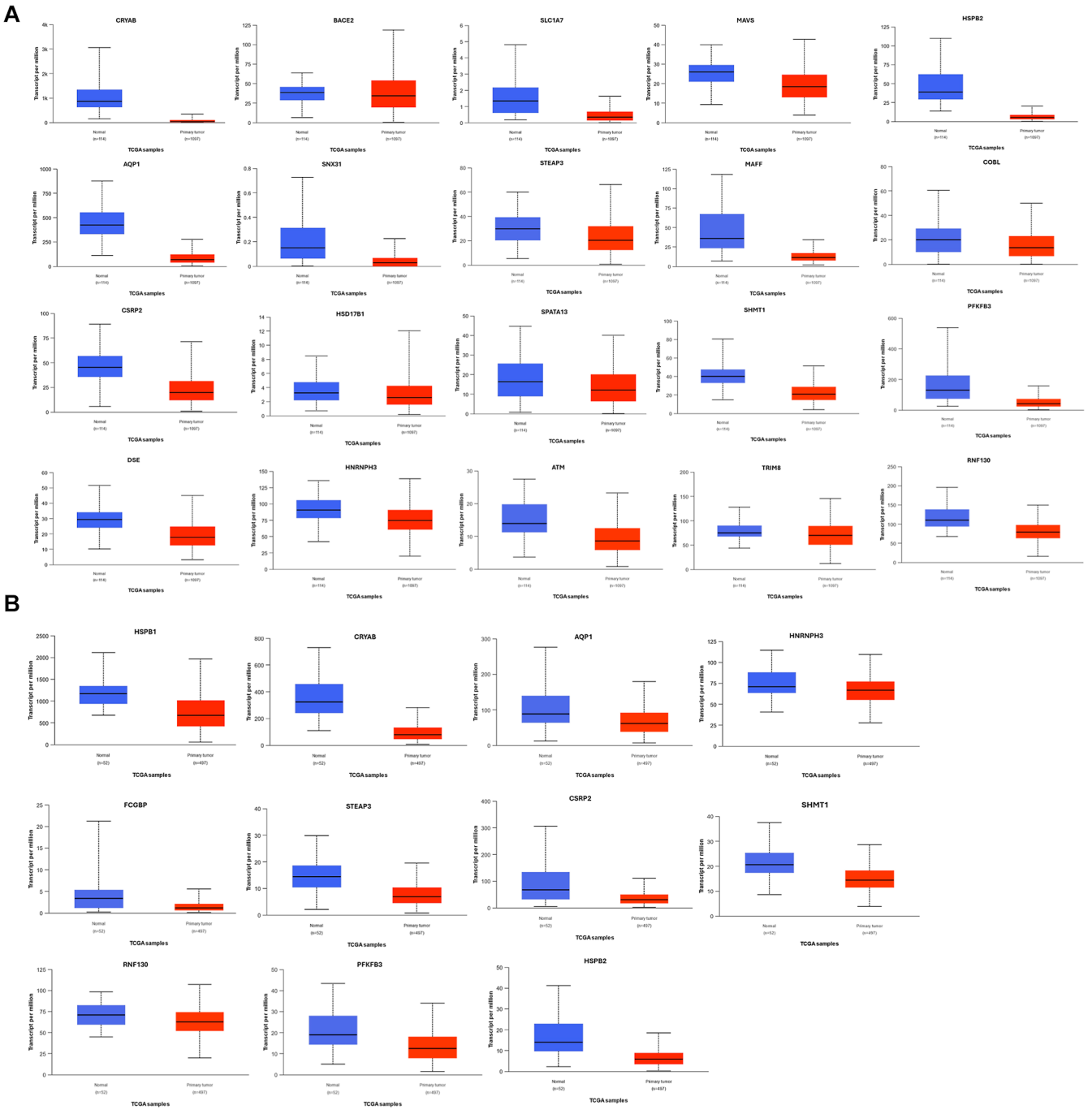


**Figure 4.** continued



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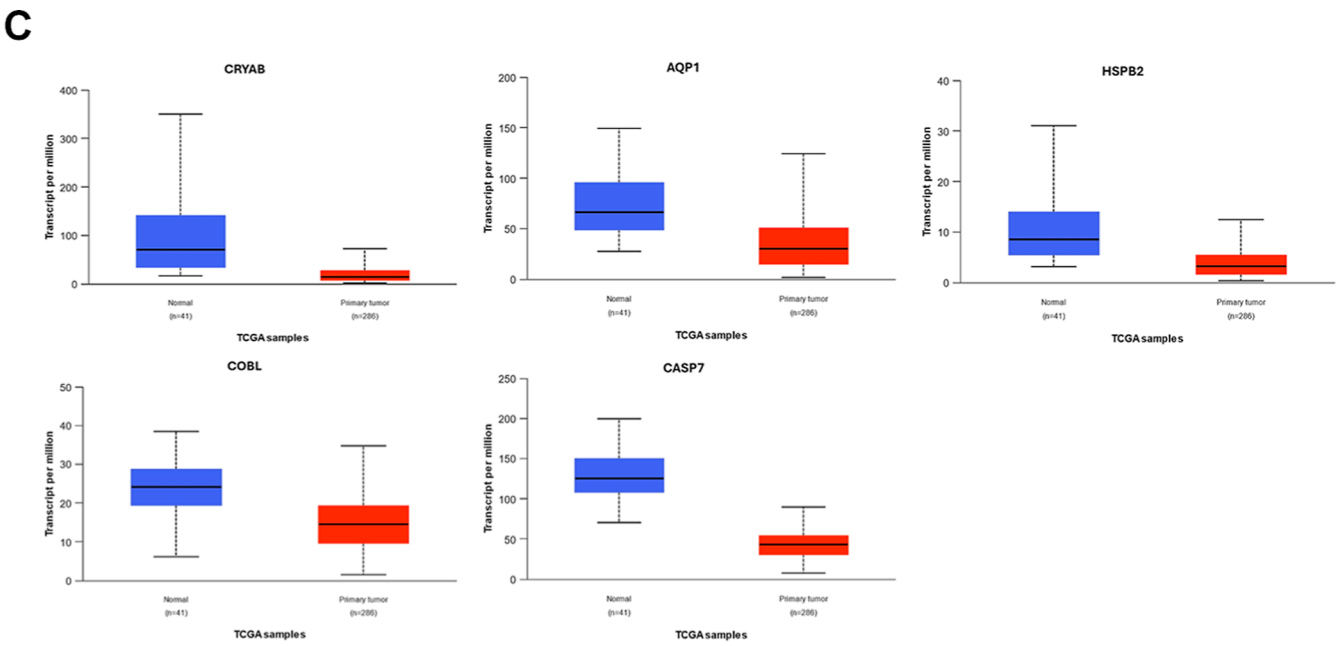


**Figure 4.** Significantly downregulated genes in the three cancers. Expression profile of significantly downregulated genes in (A) breast cancer (BRCA), (B) prostate cancer (PRAD), and (C) colon cancer. Blue—normal sample and red—tumor samples. PRAD *n* (normal samples) = 52, *n* (tumor samples) = 497; BRCA *n* (nominal samples) = 114, *n* (tumor samples) = 1097; COAD *n* (normal sample) = 41, *n* (tumor samples) = 286. Welch's *t*-test was use to analyze gene expression differences between normal and tumor samples, Statistical significance was determined by *p*-value <0.01.

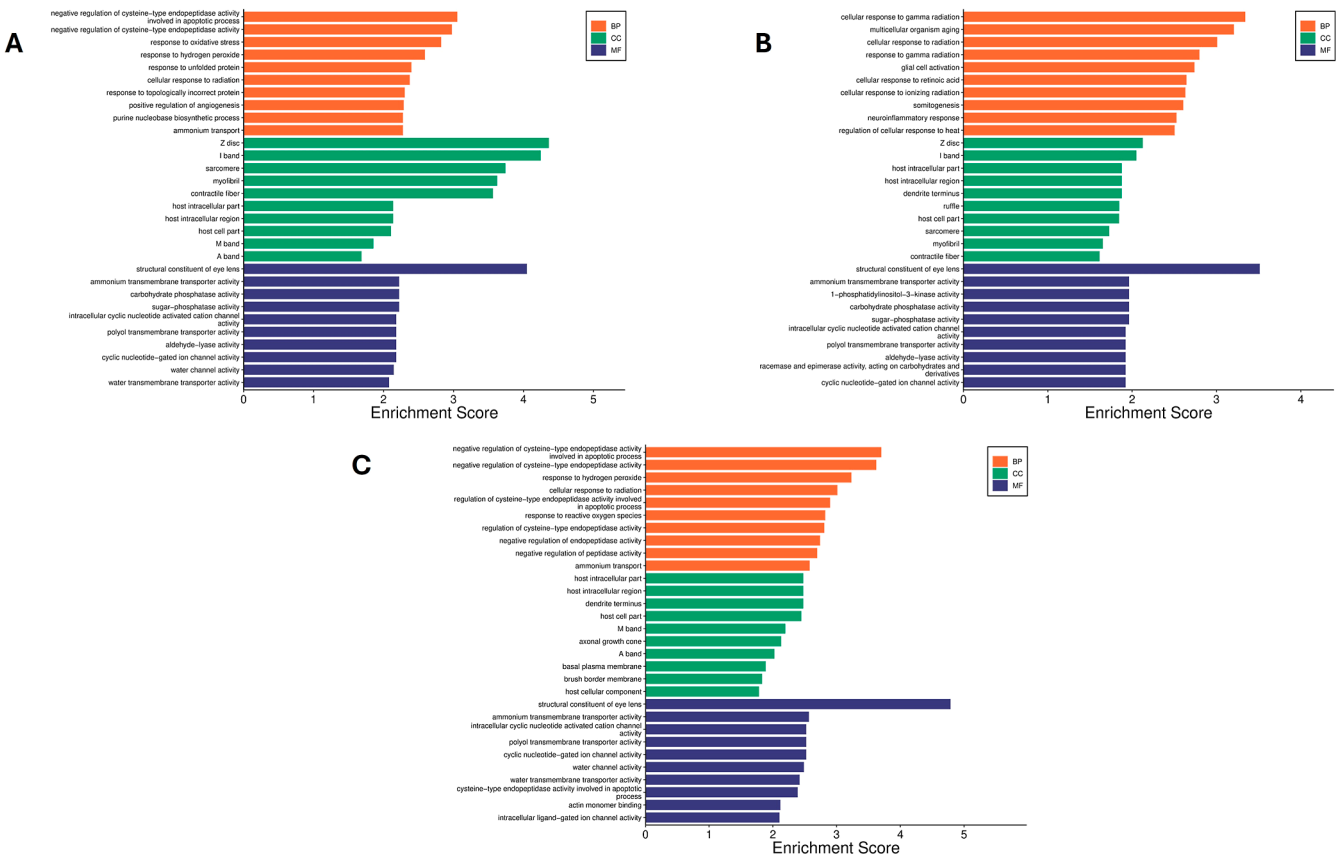


**Figure 5.** Gene ontology and pathway enrichment analysis of common genes of AD and selected cancers (breast, prostate and colon). (A) is a breast cancer downregulated gene. (B) is Prostate cancer downregulated genes and (C) is colon cancer associated genes. Biological processes (BP), molecular function (MF).

AQP1 was enriched in renin secretion, proximal tubule bicarbonate reclamation and bile secretion pathways. Finally, HSPB2 was enriched in the interaction of proteoglycans in cancers (Table 1).



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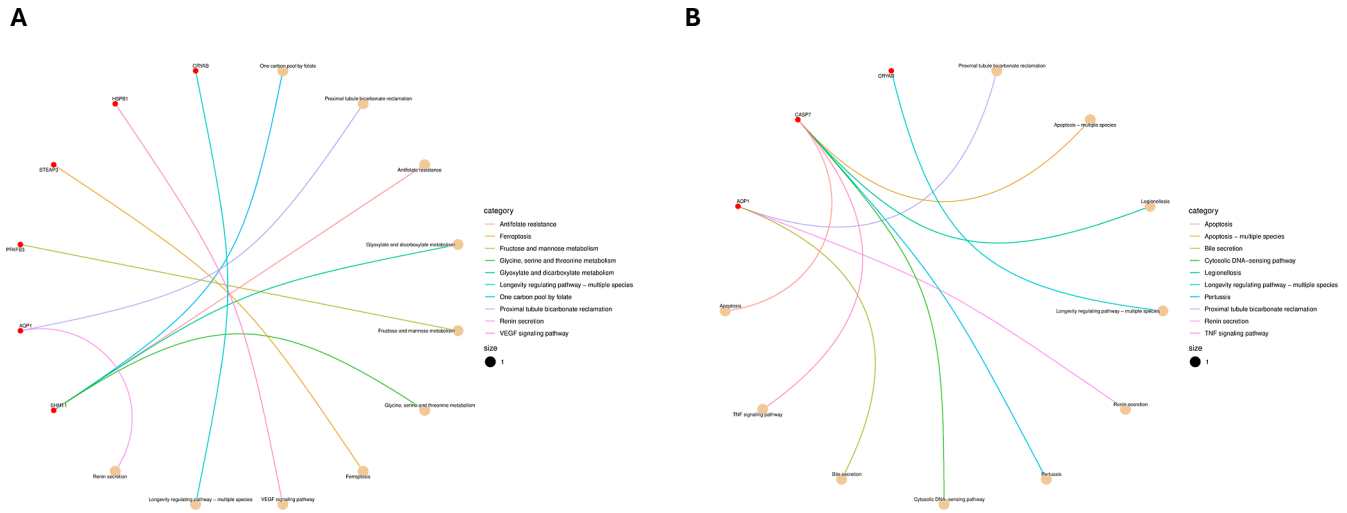


**Figure 6.** Pathways (A) and fold enrichment (B) analysis of AD genes that are significantly downregulated in breast, prostate and colon cancer.

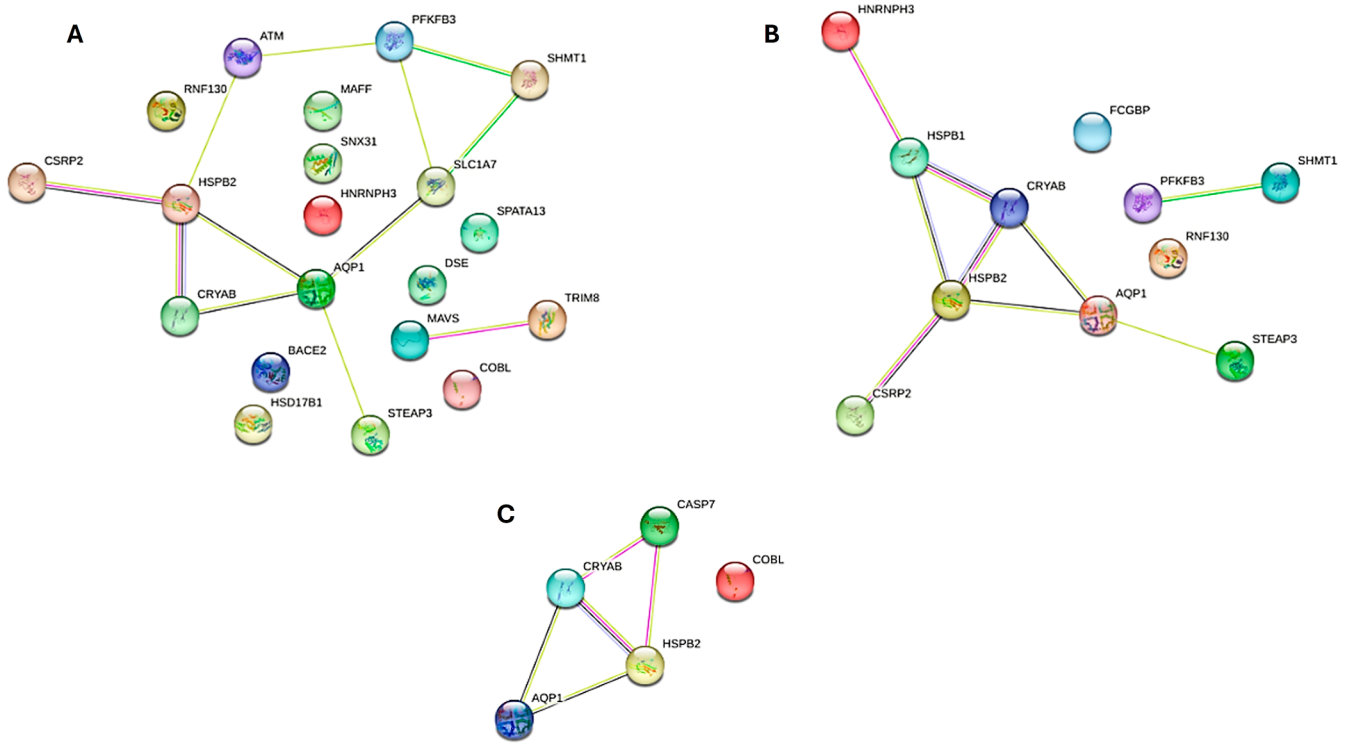


**Figure 7.** Protein−protein interaction network of the significantly downregulated genes in the three cancers. (A) represents the PPI network of the 20 significant breast cancer genes, (B) represents the PPI of the 11 significant prostate cancer genes and (C) represents the PPI network of the 5 colon cancer gene.

## DISCUSSION

Longitudinal studies have suggested a lower risk of cancer for individuals with Alzheimer's disease.[18,19] Despite this observed inverse correlation between Alzheimer's disease and cancer, the molecular drivers for this relationship remain poorly understood. This study sought to provide insight into the molecular drivers responsible for this inverse relationship and assess the potential genes that may play a role in reducing the risk of cancer development or progression in AD patients. A comprehensive understanding of these mechanisms is crucial for developing innovative treatments that could be potentially leveraged in protecting one disease against the other. A total of 25 genes were identified as shared between AD and the three cancers, with AQP1, CRYAB and HSPB2 showing differential expression patterns upregulated in AD and downregulated in cancers. These genes play critical roles in cellular stress responses, protein quality control, and gene regulation, making them strong candidates for mediating the contrasting pathologies of these diseases.

$\alpha$B-crystallin (*CRYAB*) is a small heat shock protein and is mainly expressed in astrocytes and oligodendrocytes in the central nervous system. *CRYAB* is implicated in various protein aggregation-related neurodegenerative diseases such as Alzheimer's disease.[20] From our study, the low expression levels of *CRYAB* across breast cancer (BRCA), colorectal cancer (COAD), and prostate cancer (PRAD) shed light on its role



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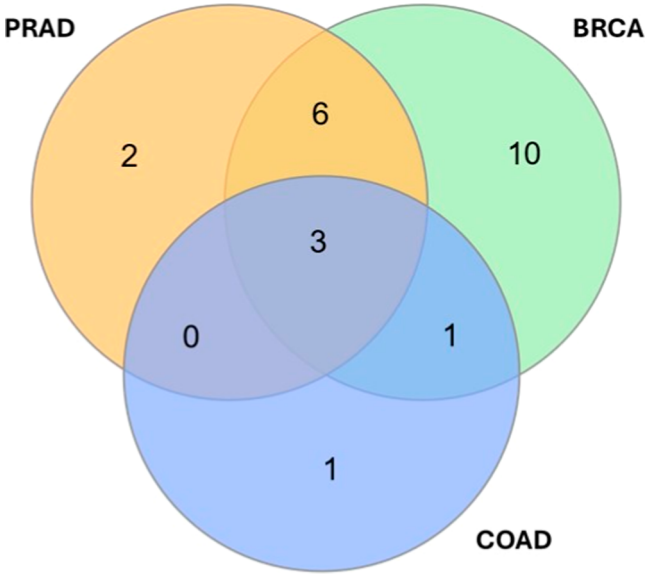


**Figure 8.** Common genes among the significantly downregulated genes in all three cancers. PRAD is prostate adenocarcinoma, BRCA is breast invasive carcinoma and COAD is colon adenocarcinoma.

in tumorigenesis. We, therefore, hypothesized that the upregulation of *CRYAB* may contribute to reducing the risk of breast, prostate and colon cancer development by enabling *MITF* activity as a tumor suppressor. For instance, **CRYAB** was associated with the longevity-regulating pathway, emphasizing its protective roles in cellular aging processes that might mitigate cancer progression while exacerbating neurodegeneration. Studies have shown that prostate cancer and nasopharyngeal cancers have a decreased *CRYAB* expression pointing at possible tumor-suppressive activity of *CRYAB* in these cancers.[21,22] Valcarcel-Jimenez et al., demonstrate that *CRYAB* act as a direct target of the Microphthalmia-associated transcription factor (*MITF*) that is responsible for its tumor-suppressive activity in prostate cancer.[23]

Similarly, **AQP1** has known roles in regulating cellular homeostasis and gene expression, respectively, providing mechanistic insights into their dual impact on neurodegeneration and tumorigenesis.[24] Aquaporin-1 (*AQP1*) is a membrane channel that allows rapid water movement driven by a transmembrane osmotic gradient. In gastric cancer, *AQP1* has been found to correlate with poor prognosis and aggressive tumor characteristics.[25] In this study, we show that aquaporin-1 (*AQP1*) which is also overexpressed in Alzheimer's disease (AD) is downregulated in breast, prostate, and colorectal cancers. Functional enrichment analyses highlighted the involvement of these genes in pathways essential for cellular health, such as protein processing, stress response, and longevity regulation. **AQP1** was implicated in metabolic pathways, including bile secretion and renal function, suggesting its potential role in creating a cellular environment unfavorable for tumor growth. These findings align with the hypothesis that shared genes might have opposing effects in the context of AD and cancer, driven by distinct regulatory dynamics. The pathway-level insights also underscore the interplay between neurodegeneration and tumor suppression. Findings from Aishima et al. and Zhuang et al., also found that the expression of *AQP1* was negatively correlated with tumor-promoting characteristics and associated with favorable prognosis in intrahepatic cholangiocarcinoma.[26,27] Moreover, they found high *AQP1* expression inhibited the invasion and migration of intrahepatic cholangiocarcinoma cells in vitro as well as inhibited lung metastasis in nude mice. This suggested that *AQP1* may play a role as a tumor suppressor in inhibiting the progression of intrahepatic cholangiocarcinoma.[26,27] The role of *AQP1* in cancer pathogenesis may be dependent on the type of cancer. *AQP1* helps in cerebrospinal fluid secretion, which is important for maintaining proper volume and pressure of the cerebrospinal fluid and protects neurons.[28] In this study, *AQP1* is under-expressed in breast, prostate, and colon cancers and we suggest a potential tumor-suppression. However, further research is essential to fully elucidate roles in these cancers.

Additionally, *HSPB2* was found to be significantly downregulated in breast, prostate and colorectal cancer tissues compared to normal tissues. *HSPB2* is a unique member of the small heat shock protein (*HSP*) family predominantly expressed in skeletal and heart muscles. Traditionally, *HSPs* have been linked to cancer development, however, *HSPB2* acts as a tumor suppressor.[29] This protein plays an anticancer role by partially restoring mutant p53 activity and promoting the expression of tumor-suppressor genes *RPRM*, *BAI-1*, and *TSAP6*.[30] *HSPB2* also repairs p53 transcriptional activity, leading to the inhibition of pancreatic cancer cell progression. Nonetheless, its role in breast cancer is debatable, with some studies reporting a tumor-suppressive role in breast cancer,[31] while others indicate a tumor-promotion role.[32] There is no report on the mechanism of *HSPB2* on colorectal cancer and prostate cancer. However, Yu et al., showed how that the expression of *HSPB2* in colorectal cancer is significantly lower than that of paired samples from adjacent normal tissues.[33] Functional enrichment and KEGG analysis revealed that *HSPB2* is also involved in the inhibition of angiogenesis in cancer. Genes like **HSPB2**, enriched in proteoglycan interaction pathways, highlight the overlap in cellular mechanisms that influence both extracellular matrix remodelling in cancer and neuronal stability in AD. Collectively, these pathways illustrate how systemic regulatory processes may underpin the inverse relationship between AD and cancer.

Despite the compelling insights provided by this study, several limitations need to be acknowledged. The findings rely solely on

**Table 1. Fold Enrichment and Pathway Analysis**[a]

| genes | fold enrichment | pathway | URL |
|---|---|---|---|
| CRYAB | 92.26209677 | longevity regulating pathway-multiple species | http://www.genome.jp/kegg-bin/show_pathway?hsa04213 |
| AQP1 | 82.90217391 | renin secretion | http://www.genome.jp/kegg-bin/show_pathway?hsa04924 |
| AQP1 | 248.7065217 | proximal tubule bicarbonate reclamation | http://www.genome.jp/kegg-bin/show_pathway?hsa04964 |
| AQP1 | 64.27247191 | bile secretion | http://www.genome.jp/kegg-bin/show_pathway?hsa04976 |
| CRYAB | 33.84763314 | protein processing in the endoplasmic reticulum | http://www.genome.jp/kegg-bin/show_pathway?hsa04141 |
| HSPB2 | 28.31806931 | proteoglycans in cancer | http://www.genome.jp/kegg-bin/show_pathway?hsa05205 |

[a]The URL leads to the KEGG pathways diagram for each gene.



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in silico analyses and require experimental validation to confirm the functional roles of the identified genes. Additionally, while this study focused on breast, prostate, and colorectal cancers, the generalizability of the findings to other cancer types remains unknown. Another limitation is the lack of patient-specific data to account for genetic and environmental factors influencing individual susceptibility to these diseases. Addressing these gaps in future studies will enhance our understanding of the molecular interplay between AD and cancer. Also, while the gene expression data sets originate from different tissues; brain for AD, and breast, prostate, and colon tissues for cancer, cross-tissue gene expression comparisons may limit direct insight into the gene expression patterns in these tissues however this have been widely used in computational biology to explore systemic disease mechanisms. The overlap in dysregulated genes between AD and cancer suggests potential systemic molecular interactions worthy of further investigation. Furthermore, gene expression pattern in brain tumor should be further investigated to find a direct correlation between AD and brain tumor for tissue−tissue validation of gene expression. This would provide a more comprehensive understanding of whether these gene expression patterns hold true in brain tumor patients as well.

In conclusion, *AQP1*, *CRYAB* and *HSPB2*, which are significantly upregulated in AD patients are downregulated in breast, prostate and colorectal cancer. We hypothesized that these genes act to reduce the risk of cancer development in AD patients and are at least partly responsible for the low incidences of breast, prostate and colorectal cancer. We suggest here that the upregulation of *AQP1*, *CRYAB and HSPB2*, in AD may contribute individually or in combination to reducing the risk of cancer by activating different pathways. However, the extent of protection against cancer development, progression and survival may be varied among different cancers. There may be a more complex molecular interplay between AD and the development and progression of cancer that may explain the observed inverse relationship between the two diseases in large cohort studies. *Additionally, we recommend that, the exact role these genes play in the inverse relationship should be investigated experimentally.* Therefore, this study serves as a preliminary study to further explore the molecular relationships between different types of cancers and AD using these identified genes as a potential starting point for experimental investigations.

## ■ ASSOCIATED CONTENT

### Data Availability Statement

No new data was created.

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c11571.

Expression analysis of down regulated AD genes in breast, prostate and colon cancer. Supplementary Figure 1. Intersecting genes between the downregulated gene set list in Alzheimer's disease and the upregulated genes set list in the three cancers Supplementary Figure 2. Expression pattern of between downregulated genes in Alzheimer's disease and prostate cancer, colon cancer and breast cancer. Supplementary Table 1. Significantly downregulated genes in Alzheimer's disease which are significantly upregulated in the three cancers. Supplementary Figure 3. Expression pattern of HSPB2 in normal tissue and several cancer cases. Supplementary Figure 4. Expression pattern of CRYAB in normal tissue and several cancer cases. Supplementary Figure 5. Expression pattern of AQP1 in normal tissue and several cancer cases. Supplementary Table 2. Significant genes common to all three cancers which are downregulated in Alzheimer's disease (PDF)

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### Author Contributions

#B.K. A. and S.B.A. authors contributed equally to this work. Conceptualization, B.K.A, S.B.A., K.F., J.W.; methodology and data analysis, E.L.L, B.K.A, K.F. J.T.Q; data validation, J.W., S.B.A., J.T.Q.; data visualization, E.L.L, S.B.A, K.F., B.K.A., writing—original draft preparation, K.F., B.K.A, E.L.L.; writing—review and editing, J.T.Q., S.K., S.B.A., J.W., B.K.A; funding acquisition, J.W.


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### Notes

The authors declare no competing financial interest.

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