Am J Cancer Res 2023;13(10):4961-4975
www.ajcr.us /ISSN:2156-6976/ajcr0152151

Original Article

GSK3β rs3107669 polymorphism implicates chemotherapy-associated retrospective memory deficits in breast cancer survivors

Wen Li[1,2,3*], Chen Gan[1,2,3*], Sheng Yu[1,2,3*], Jian Xu[1,2,3], Lingxue Tang[1,2,3], Qiang Li[2,3], Zhenwei Zhu[2,3], Huaidong Cheng[1,2,3]

[1]*Department of Oncology, The Second Hospital of Anhui Medical University, Hefei 230601, Anhui, P. R. China;* [2]*The Third School of Clinical Medicine, Southern Medical University, Guangzhou 510500, Guangdong, P. R. China;* [3]*Department of Oncology, Shenzhen Hospital of Southern Medical University, Shenzhen 518000, Guangdong, P. R. China.* [*]*Equal contributors.*

Received July 11, 2023; Accepted October 8, 2023; Epub October 15, 2023; Published October 30, 2023

Abstract: Glycogen synthase kinase-3β (GSK-3β) plays an important role in the development of neurodegenerative diseases. However, the underlying effect of GSK-3β polymorphism on chemobrain in cancer survivors is unclear. This study aimed to evaluate the correlation between GSK-3β polymorphism and chemotherapy-associated retrospective memory deficits in breast cancer survivors. The difference in GSK-3β gene expression between breast cancer patients and healthy controls was confirmed using bioinformatics technology. All participants (197 with breast cancer and 40 healthy controls) underwent prospective and retrospective memory tests, and five single-nucleotide polymorphism loci of GSK-3β (rs3107669, rs1154597, rs334543, rs334558 and rs3755557) were genotyped from peripheral blood. Breast cancer survivors had memory impairment after chemotherapy (P<0.0001). The expression difference of the GSK-3β gene was determined through bioinformation analysis, and a genotype frequency difference of GSK-3β rs3107669 was found between the breast cancer and healthy control groups. GSK-3β rs3107669 was a genetic risk in comparison to the healthy controls (OR=0.382; 95% CI=0.186-0.786; P=0.009). Breast cancer with the GSK-3β rs3107669 (C/A+A/A) genotype was a protective factor for chemobrain (Beta=-0.306; 95% CI=-5.556~-2.145; P<0.0001) from multiple linear regression. The C/A+A/A genotype carrier performed better on the retrospective memory test than the C/C genotype (z=-4.302, P<0.0001). Breast cancer patients with chemotherapy who also carried the GSK-3β rs3107669 (C/C) genotype more easily presented cognitive deficits. The GSK-3β rs3107669 polymorphism was a feasible genetic risk factor for chemotherapy-associated retrospective memory impairments in breast cancer survivors.

Keywords: Glycogen synthase kinase-3β (GSK-3β), polymorphisms, retrospective memory, breast cancer, cognitive

Introduction

In 2023, there will be approximately 290,000 new cases of breast cancer in the United States, accounting for approximately 31% of new cancer cases, surpassing lung cancer as the most common major cancer in women [1]. Although cancer mortality has continued to decline, the global incidence rate of breast cancer still has shown an upward trend, which has been far higher than that of other cancers in developing countries (55.9‰) [2]. With the continuous improvement of the diagnosis and treatment of breast cancer, the 5-year survival rate of breast cancer is as high as 90%, which is far higher than that of other cancers [3]. Chemotherapy is the most important treatment for breast cancer and can prolong the survival time of patients while presenting neurocognitive changes [4]. According to reports, 75% of patients experience cognitive impairment during chemotherapy, and up to 35% of patients continue to have this symptom even years after the end of chemotherapy [5]. This kind of learning, memory and attention impairment in cancer patients with chemotherapy is collectively called “chemobrain” [6]. The exploration and mechanistic research of “chemobrain” is a hot

issue in the field of oncology and mainly focuses on female breast cancer [7]. The main characteristic of "chemobrain" was that it had significant heterogeneity. Janelsins et al. [8] found that 45.2% of breast cancer patients complained of cognitive decline after chemotherapy, while 10.4% of healthy controls complained of cognitive decline in a large sample of research data. Up to 60% of breast cancer patients have cognitive problems during chemotherapy, and negative emotions such as anxiety and depression can be seen everywhere, which seriously affect quality of life [9].

Prospective memory (PM) and retrospective memory (RM) are the two main aspects of human memory. PM was defined as the memory of future intentions, such as remembering to go to school [10]. In contrast, RM refers to remembering past events, such as knowledge recollected [11]. Memory impairment is one of the characteristics of chemobrain in breast cancer. Previous findings indicated that approximately 23.3% of breast cancer patients had language memory impairment after chemotherapy [12]. Verbal memory deficits were observed in breast cancer patients treated with doxorubicin and cyclophosphamide based on a chemotherapy regimen [13]. Changes in brain network dynamics are the root cause of the deterioration of memory and executive function in breast cancer patients after chemotherapy [14]. Our group found that memory impairment was the main feature in breast cancer patients following chemotherapy [15]. At the same time, the heterogeneity of chemobrain in different molecular types of breast cancer was confirmed [16].

Genetic susceptibility was found in chemobrain for breast cancer [17]. Small et al. [18] found that carriers of the COMT Val genotype were more likely to have impaired cognitive function in breast cancer patients receiving chemotherapy. The APOE gene is highly involved in neuronal repair and neural plasticity after brain injury. APOE ε4 allele carriers were associated with cognitive decline in aging and Alzheimer's disease patients [19]. Koleck et al. [20] found that breast cancer patients with the APOEε4 genotype had significant deficits in language learning memory, as well as visual learning memory performance. Ahles et al. [21] thought that the APOEε4 genotype had a long-term effect on cognitive decline in breast cancer survivors. Our team found that the COMT rs737865 polymorphism could aggravate RM impairment in triple-negative breast cancer patients [22]. Therefore, we had reason to believe that genetic polymorphisms related to cognitive function were involved in the composition of chemobrain.

Glycogen synthase kinase 3β (GSK3β) is highly expressed in the brain, is involved in the formation of Alzheimer's disease (AD) and plays an important role in synaptic plasticity, memory formation and neuronal survival [23, 24]. GSK3β gene polymorphism was associated with cognitive function. It was found that the GSK3β rs3755557 polymorphism in the Han population might be associated with susceptibility to schizophrenia and cognitive dysfunction [25]. Mateo et al. [26] found that the GSK3β gene rs334558 polymorphism increased the risk of cognitive deficits in late-onset AD. Kettunen et al. [27] found that GSK3β (rs334558 and rs1154597) polymorphisms were associated with high-level T-tau and low expression of Aβ42, while the rs3107669 CC genotype was accompanied by lower MMSE scores in AD patients. Bai et al. [28] convinced that the GSK3β gene 334558 polymorphism could affect changes in brain network structure in patients with mild cognitive decline. Hohman et al. [29] even more provided genetic pathological evidence of GSK3β rs334543 involvement through autopsy of brain tissues from AD patients. Unfortunately, the correlation between GSK3β gene polymorphism and chemobrain had not yet been involved in the study.

However, the specific mechanisms of chemobrain in breast cancer patients are not fully understood. However, increasing research evidence indicates that the etiology of chemobrain is strongly influenced by genetic effects. The GSK3β gene was closely associated with cognitive dysfunction, and it was clear that a possible association between GSK3β polymorphism and chemobrain needs to be tested in the population. Therefore, this study aimed to evaluate the correlation between GSK3β gene polymorphisms and chemobrain in breast cancer survivors, which were combined with bioinformatics analysis technology, taking breast cancer patients and healthy controls as research objects.

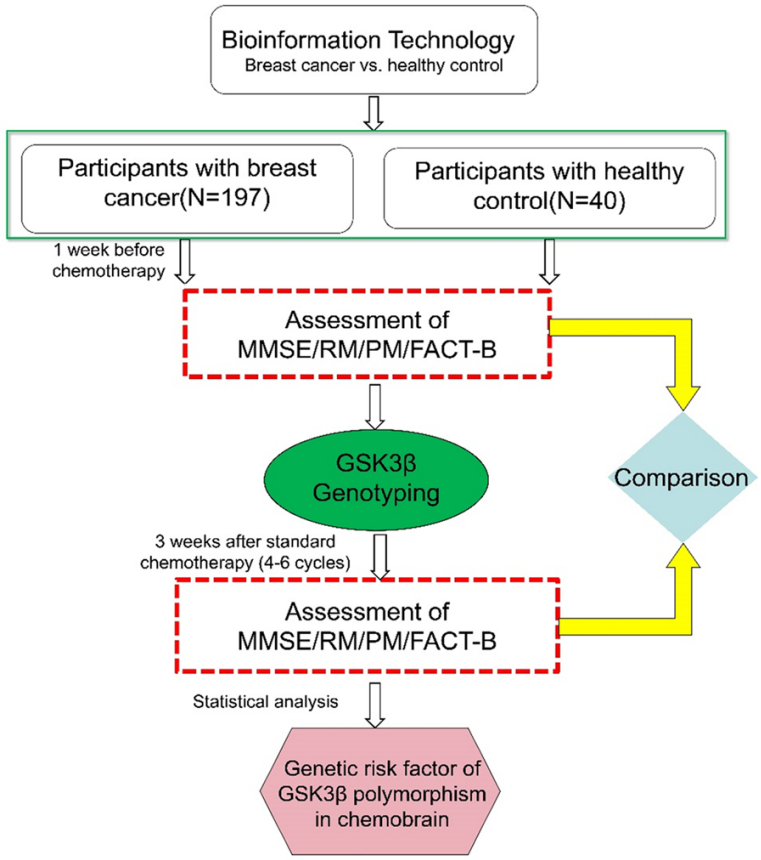


Figure 1. Flowchart of the study. Bioinformatics analysis and clinical data verification were performed in this study, and a total of 197 breast cancer patients and 40 healthy controls were enrolled.

Materials and methods

Bioinformatics analysis

We analyzed the expression of the GSK3β gene in breast cancer tissues and healthy controls through the Cancer Genome Atlas (TCGA) database (https://www.cancer.gov/) [30]. Inside, 1093 cases of breast cancer and 112 healthy controls were included in this analysis. The free online database TIMER2.0 (http://timer.cistrome.org/) was applied for differential analysis of the GSK3β gene across cancers.

Participants

A total of 197 breast cancer survivors and 40 healthy controls with matched age and education were enrolled as research objects from August 2017 to March 2022. The controls were mainly recruited from relatives of the breast cancer patients. All breast cancer patients received chemotherapy based on paclitaxel and doxorubicin for at least 4-6 courses. At the same time, the following participants were excluded: 1) those with a history of central nervous system radiotherapy, 2) those with a history of Alzheimer's disease and dementia, 3) those who did not follow the doctor's instructions, 4) those with abnormal brain structure or function, and 5) those who were users of antipsychotic drugs. This study was approved by the Research Ethics Committee of the Second Affiliated Hospital of Anhui Medical University, China (Number of Ethics: 20180033). The informed consent form was obtained from each participant.

Procedures

First, the differential expression of the GSK3β polymorphism between breast cancer and healthy control tissues was determined through bioinformatics analysis. Second, clinical data validation was carried out. Overall cognitive function (MMSE), memory scale (RM, PM), and quality of life (QOL) were assessed twice in all enrolled breast cancer patients: one week before standard chemotherapy (T1) and three weeks after the completion of four to six courses of chemotherapy (T2). In the healthy control group, only one cognitive test was needed. During this time, 5 ml of participants' peripheral blood was taken for GSK3β polymorphism testing. The baseline information and chemotherapy regimens for all participants could be obtained from the electronic medical system and interviews. All participants provided informed consent. Finally, statistical analysis was performed to evaluate the genetic risk factors for GSK3β polymorphism in chemobrain. The specific process is shown in **Figure 1**.

Neuropsychological tests

The Mini-Mental State Examination (MMSE) was used to check total cognitive function. The evaluation criteria for cognitive impairment

were MMSE scores below 26 points. All participants were tested with a prospective and retrospective memory questionnaire (PRMQ) to evaluate memory function [31]. The content of this scale could be quantified, and the score was reliable. The PRMQ included 16 questions, each with 4 different situations (never, occasionally, often, always). This questionnaire was divided equally into PM and RM subscales. PM scores ranged from 0 to 32, and RM scores ranged from 0 to 32, with higher scores often indicating greater damage to the corresponding memory.

The Functional Assessment of Cancer Therapy-Breast (FACT-B) scale was used to assess quality of life (QOL) in patients with breast cancer [32]. The scale included five components: physical status, social/family status, emotional status, functional status and additional attention. Each component had 6-7 questions. Each question was divided into five levels: never (0 points), little (1 point), some (2 points), equal (3 points), and very (4 points). Forward scoring: the social/family and functional areas were scored, and the rest were scored in reverse. A higher score indicated a better QOL.

Genotyping

Peripheral venous blood (5 ml) was taken from all participants during cognitive function testing. This blood was used to extract genomic DNA. Five SNP loci (rs3107669, rs1154597, rs334543, rs334558 and rs3755557) of the GSK3β gene were selected to analyze the genetic risk through insulting a large number of studies [25, 27, 29]. Genotyping was performed by Shanghai Genesky Biotechnology Co., Ltd. to identify SNP alleles with high specificity using the improved multiple ligase detection reaction (iMLDR). The online Primer3 software (http://bioinfo.ut.ee/primer3-0.4.0/) was applied to design primers for each gene locus.

The sequences were as follows: rs310766-9F: TTATCTGCATGGGGGAAGCTGT; rs310766-9R: TGAATTGCCAAAGTGTGTGCTGT; rs115459-7F: GGACCCTGCAATCACCCTCTTA; rs115459-7R: atgatTGGTCCTAGGGAAAACTGTCAA; rs33-4543F: ACCTCAGTGCAGGGTTTGTTCC; rs33-4543R: CCTACCAAATTAGGACTCCCTCTCATAC; rs334558F: GGCACAAGCCCGCATTC; rs3345-58R: CGCAGACAGCGCTCCTCA; rs3755557F: ACCAGCGTCCATTGTTCTACCA; and rs37555-57R: CTTCATCAGTGTTTCAAAGCAAGAGC. Some samples were randomly selected for PCR amplification. The amplified products were sequenced by ABI3730XL. Finally, GeneMapper 5.0 software (Applied Biosystems, USA) was used to analyze the raw data.

Statistical analysis

The clinical baseline characteristics of all participants were analyzed by the independent-sample t test or the Mann-Whitney U test for normally distributed or nonnormally distributed data. One-way ANOVA was applied to evaluate the cognitive function between the before chemotherapy (BC), after chemotherapy (AC) and healthy control (HC) groups. Bioinformatic analyses (Timer2.0 database (http://timer.compgenomics.org/), TCGA database, and R language) were used to assess differences in the expression levels of the GSK3β gene between breast cancer patients and healthy controls. Binary logistic regression analysis was used to evaluate the genetic risk of GSK3β gene polymorphisms in breast cancer patients and healthy controls. To further analyze the correlation between the GSK3β rs3107669 polymorphism and cognitive impairment in breast cancer survivors, multiple linear regression was applied. Then, the differences between two groups containing genotype carriers (C/C vs. C/A+A/A) for cognitive tasks were used to further clarify this correlation. All statistical data were double-tailed, and $P<0.05$ was considered statistically significant. SPSS software (version 22.0, Chicago, IL, USA) was used for statistical analysis. The forest maps and histograms were drawn with GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA).

Results

Participant characteristics

The baseline information is presented in **Table 1**. There was no significant difference in average age (50.22±9.56 vs. 53.13±11.91) or years of education (9.82±3.33 vs. 9.33±2.88) between the breast cancer and healthy control groups ($P>0.05$). Most breast cancer patients (65.4%) presented only mild symptoms (Karnofsky performance status scale (KPS) ≥90). Approximately half of the patients (47.2%) were identified as having luminal B breast cancer, and approximately 11.2% had triple-negative

Table 1. The background characteristics of participants

Variable	Groups	
	Breast cancer (n=197)	Healthy control (n=40)
Age (Mean ± SD, year)	50.22±9.56	53.13±11.91
Y of Education (Mean ± SD)	9.82±3.33	9.33±2.88
KPS		
90-100	129 (65.4%)	-
70-80	68 (34.6%)	-
Molecular typing		
Luminal A	28 (14.2%)	
Luminal A	93 (47.2%)	
HER-2 overexpression	54 (27.4%)	
TNBC	22 (11.2%)	
Stages (%)		
I	22 (11.3%)	-
II	63 (32.3%)	-
III	36 (18.5%)	-
IV	74 (37.9%)	-

Note: KPS, karnofsky performance status scale; TNBC, triple negative breast cancer.

breast cancer (TNBC). Approximately 62.1% of the breast cancer patients were stage 1-III.

The expression of GSK-3β from bioinformation analysis

Compared with that in normal tissue, the expression of GSK-3β in breast cancer increased significantly in the TIMER 2.0 pancancer data (**Figure 2A**). Statistical differences were found in the sequencing results of single GSK-3β gene expression in the TCGA database and R language analysis method (**Figure 2B**). GSK-3β was correlated with phagocytosis, recognition, cell recognition, and synaptic membrane from gene ontology functional enrichment analysis (**Figure 2C**). The KEGG results indicated that the neuroactive ligand-receptor interaction pathway and synaptic vesicle cycle pathway were significantly enriched (**Figure 2D**).

Cognitive tasks in breast cancer patients and healthy controls

The results for cognitive tasks between breast cancer patients and healthy controls are shown in **Table 2** and **Figure 3**. Significant differences were found in the MMSE (F=49.655, P<0.0001), RM (F=17.673, P<0.0001), PM (F=23.163, P<0.0001) and FACT-B (F=136.348, P<0.0001) scores between the before chemotherapy (BC), after chemotherapy (AC) and healthy control (HC) groups. Among them, cognitive decline and memory impairment were present in breast cancer patients after chemotherapy. MMSE (27.39±1.53 vs. 25.37±2.85, P<0.0001), RM (14.69±4.25 vs. 16.94±5.08, P<0.0001), PM (14.39±4.53 vs. 16.91±4.58, P<0.0001) and FACT-B (78.52±18.67 vs. 51.79±14.38, P<0.0001) scores were performed between the BC and AC groups. Similarly, the cognitive function of breast cancer patients after chemotherapy was significantly lower than that of healthy controls. MMSE (25.37±2.85 vs. 28.00±1.60, P<0.0001), RM (16.94±5.08 vs. 13.33±2.60, P<0.0001), PM (16.91±4.58 vs. 12.83±3.27, P<0.0001) and FACT-B (51.79±14.38 vs. 78.88±18.37, P<0.0001) scores were performed between the AC and HC groups. No significant difference was mentioned in MMSE, RM, PM and FACT-B scores between the BC and HC groups (P>0.05). This result indicated that no difference was found between breast cancer patients before chemotherapy and healthy controls.

Genotyping analysis

Table 3 indicates that the allelic distribution of GSK3β rs3107669 was significantly different between the breast cancer and healthy control groups (*P*=0.014). Five SNP loci (rs3107669, rs1154597, rs334543, rs334558 and rs3755557) of the GSK3β gene were in Hardy-Weinberg equilibrium (HWE) in all participants (P>0.05). **Table 4** shows that the genotypic frequency distribution of rs3107669 was confirmed to be significantly different (codominant model: χ^2=7.522, *P*=0.023; dominant model: χ^2=7.147, P=0.008). Furthermore, the genetic risk of GSK3β rs3107669 was found between breast cancer and healthy controls (adjusted, OR=0.382, 95% CI=0.186-0.786, *P*=0.009) (**Figure 4A**).

Correlation between the GSK3β rs3107669 polymorphism and cognitive impairment

Breast cancer survivors with the GSK3β rs3107669 (C/A+A/A) genotype had higher

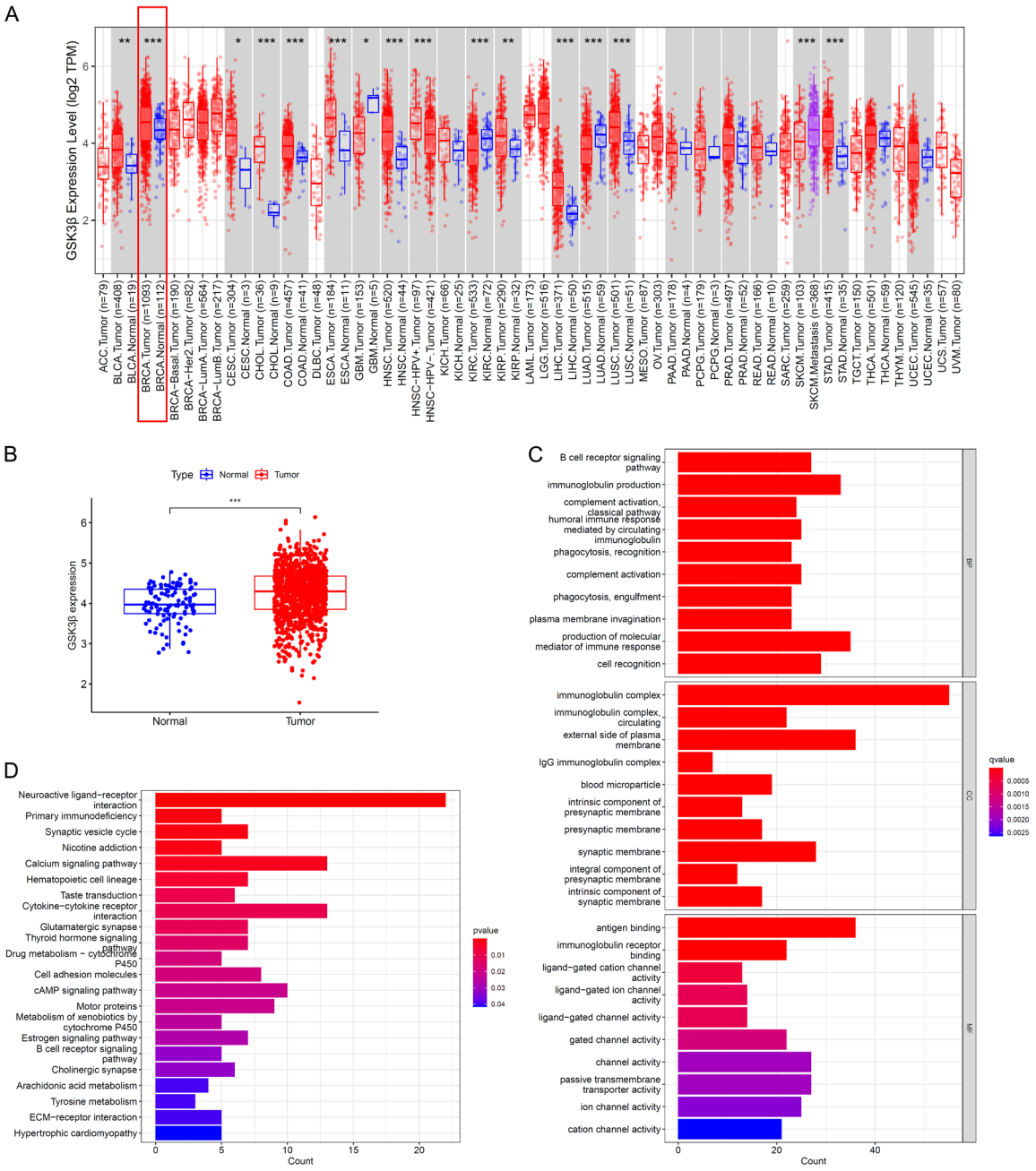


Figure 2. The results of bioinformatics analysis. A, B. Significant difference in GSK-3β gene expression between breast cancer patients and healthy controls from TIMER 2.0 pancancer and TCGA data. C, D. Gene ontology functional enrichment and KEGG pathway enrichment analysis of the GSK-3β gene in breast cancer. The number of enriched genes and *p* values are represented by the length and color of the bars, respectively. TCGA, The Cancer Genome Atlas; KEGG, Kyoto Encyclopedia of Genes and Genomes.

MMSE (Beta=0.412; 95% CI=2.001~3.818; P<0.0001) and lower RM test scores (Beta= -0.306; 95% CI=-5.556~-2.145; P<0.0001) than the survivors with GSK3β (C/C) from multiple linear regression (**Table 5** and **Figure 4B**). Higher RM scores were related to poorer memory. We found that a lower risk of retrospective memory impairment was found in GSK3β rs3107669 (C/A+A/A) survivors. This indicated that the GSK3β polymorphism was a risk factor for chemotherapy-associated memory impairments in breast cancer survivors.

Table 2. Cognitive task in breast cancer and healthy controls group

	BC group	AC group	HC group	F	P
MMSE	27.39±1.53	25.37±2.85	28.00±1.60	49.655	0.000****
RM	14.69±4.25	16.94±5.08	13.33±2.60	17.673	0.000****
PM	14.39±4.53	16.91±4.58	12.83±3.27	23.163	0.000****
FACT-B	78.52±18.67	51.79±14.38	78.88±18.37	136.348	0.000****

Note: ****P<0.0001; MMSE, the mini-mental state examination; RM, retrospective memory; PM, prospective memory; FACT-B, Functional Assessment of Cancer Therapy-Breast; BC, before chemotherapy; AC, after chemotherapy; HC, heathy control.

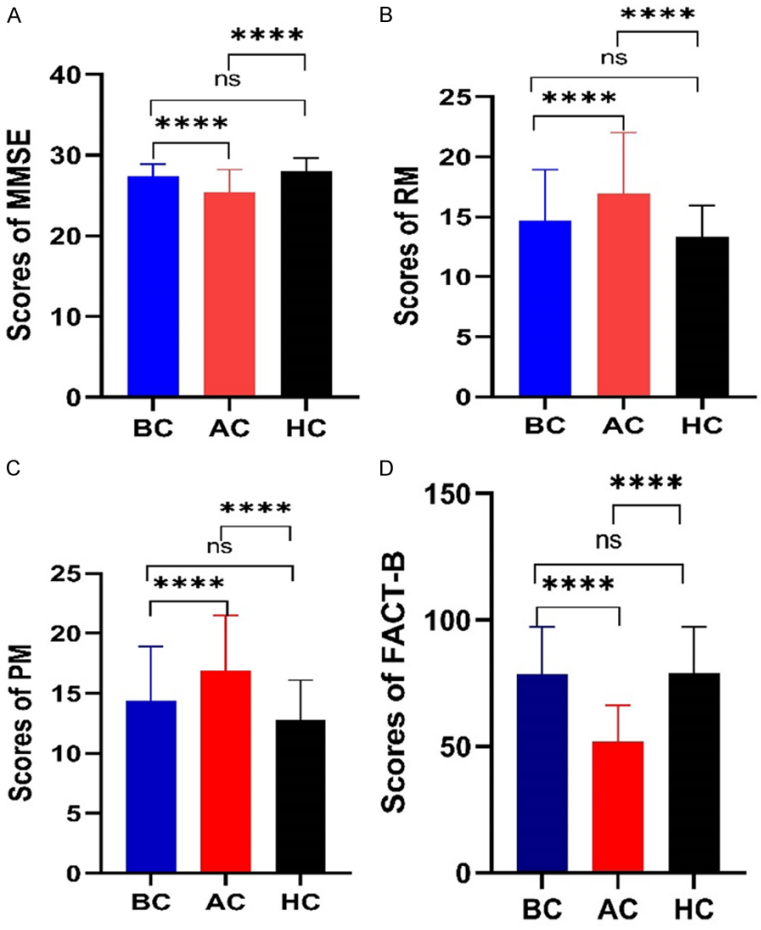


Figure 3. Cognitive test in all enrolled participants. A-D. The scores of the MMSE, RM, PM and FACT-B in the BC, AC and HC groups. Note: ****P<0.0001. MMSE, the mini-mental state examination; RM, retrospective memory; PM, prospective memory; FACT-B, Functional Assessment of Cancer Therapy-Breast; BC, before chemotherapy; AC, after chemotherapy; HC, healthy control.

Cognitive tasks before and after chemotherapy: C/C group vs. C/A+A/A group

No significant difference was found in MMSE, RM, PM and FACT-B scores between the C/C and C/A+A/A groups before chemotherapy in breast cancer survivors (P>0.05). Furthermore, the MMSE (23.03±2.85 vs. 25.97±2.53, P<0.0001) score was significantly decreased in the C/C genotype carriers of GSK3β rs3107669 compared with C/A+A/A carriers after chemotherapy. The RM (20.00±5.81 vs. 16.17±4.58, P<0.0001) scores were significantly increased in the C/C group after chemotherapy. This indicated that GSK3β rs3107669 C/C genotype carriers more easily developed chemotherapy-associated retrospective memory deficits (**Table 6** and **Figure 5**).

Discussion

In this study, we investigated the possible association between GSK3β gene polymorphism and chemobrain in breast cancer survivors. Our analysis showed that 1) significant differences were found in GSK3β gene expression between breast cancer patients and healthy controls, and the GSK3β gene was a genetic risk factor; 2) remarkable PM and RM impairment were observed in breast cancer survivors after chemotherapy, and their quality of life decreased significantly; and 3) notably, the GSK 3β rs3107669 C/C/genotype was found to exacerbate chemotherapy-induced RM defects. Our study was the first to provide genetic evidence of GSK 3β gene polymorphisms involved in chemotherapy-associated RM impairment.

The same was true of chemobrain, and an increasing number of observational studies

Table 3. Informaition about five SNPs locis of GSK3β gene in breast cancer and healthy controls

SNP	GSK3β				
	rs3107669	rs1154597	rs334543	rs334558	rs3755557
Chr. Position	119567101	119736833	119832621	119813282	119814957
Alleles	C/A	A/G	C/A	A/G	T/A
MAF	0.475	0.063	0.378	0.465	0.122
P for HWE	0.438	0.607	0.491	0.240	0.241
*P**	0.014*	0.703	0.957	0.291	0.321

Note: *P<0.05; SNP, Single nucleotide polymorphism; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium; **p*-value for alleles frequency differences between breast cancer and healthy controls.

Table 4. Genetic risk of GSK3β (rs3107669, rs1154597, rs334543, rs334558, rs3755557) in breast cancer and healthy controls

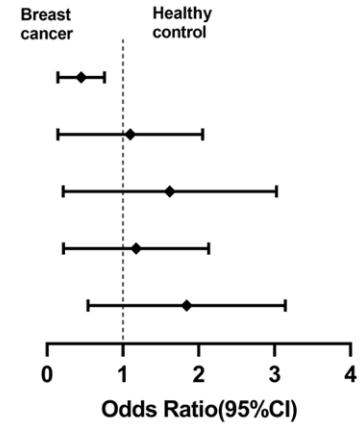
SNP	Model	Genotype	Breast cancer	Healthy control	χ^2	P[a]	Binary Logistic regression	
							OR (95% CI)	P[b]
rs3107669	Co-dominant	C/C	40	16	7.522	0.023*		
		C/A	107	18			3.333 (1.194-9.302)	0.021*
		A/A	50	6			1.402 (0.525-3.747)	0.501
	Dominant	C/A+A/A	157	24	7.147	0.008**	0.382 (0.186-0.786)	0.009**
		C/C	40	16				
rs1154597	Co-dominant	G/G	0	0	0.156	0.693		
		G/A	25	6			0.824 (0.314-2.160)	0.693
		A/A	172	34				
	Dominant	-	-	-	-	-	-	-
rs334543	Co-dominant	C/C	25	6	0.398	0.819		
		C/A	99	18			1.095 (0.386-3.105)	0.865
		A/A	73	16			0.830 (0.397-1.736)	0.620
	Dominant	C/A+A/A	172	34	0.156	0.693	1.214 (0.463-3.183)	0.693
		C/C	25	6				
rs334558	Co-dominant	A/A	37	7	2.301	0.316		
		A/G	109	18			0.643 (0.239-1.735)	0.383
		G/G	51	15			0.561 (0.262-1.203)	0.137
	Dominant	A/G+G/G	160	33	0.037	0.848	0.917 (0.376-2.235)	0.849
		A/A	37	7				
rs3755557	Co-dominant	T/T	154	28	1.373	0.503		
		T/A	38	11			0.909 (0.102-80.78)	0.932
		A/A	5	1			1.447 (0.153-13.725)	0.747
	Dominant	T/A+A/A	43	12	1.246	0.264	1.535 (0.721-3.269)	0.267
		T/T	154	28				

Note: **P*<0.05; **P<0.01; a, The χ^2 test of *P* values for SNP polymorphisms genotype frequencies between breast cancer and healthy control group; b, *P* value for logistic regression analysis; odds ratio (the OR); 95% confidence interval (95% CI).

have confirmed its significant heterogeneity. Koppelmans et al. [33] found that the effects of chemotherapy on cognition were long-term, and verbal memory, processing speed and executive function were significantly decreased in breast cancer patients after chemotherapy. Ng et al. [34] found that approximately 30% of breast cancer patients showed significant cognitive deficits after chemotherapy, of whom 16% had acute cognitive changes and 11% had persistent cognitive impairment. Bilenduke et al. [35] determined that breast cancer patients showed more pronounced cognitive dysfunction and negative depressive emotions

A

SNP	Genotype	No. of patients	No. of Controls	Odds Ratio (95%CI)	P
rs3107669	C/A+A/A	157	24	0.382(0.186-0.786)	**0.009****
	C/C	40	16		
rs1154597	G/A	25	6	0.824(0.314-2.160)	0.693
	A/A	172	34		
rs334543	C/A+A/A	172	34	1.214(0.463-3.183)	0.693
	C/C	25	6		
rs334558	A/G+G/G	160	33	0.917(0.376-2.235)	0.849
	A/A	37	7		
rs3755557	T/A+A/A	43	12	1.535(0.721-3.269)	0.267
	T/T	154	28		



B

Cognitive test	GSK3β rs3107669	Coef. (95%CI)	P value
MMSE	C/C	Ref.	-
	C/A+A/A	0.412(2.001~3.818)	**0.000****
RM	C/C	Ref.	-
	C/A+A/A	-0.306(-5.556~-2.145)	**0.000****
PM	C/C	Ref.	-
	C/A+A/A	0.004(-1.575~1.655)	0.961
FACT-B	C/C	Ref.	-
	C/A+A/A	-0.057(-6.978~2.916)	0.419

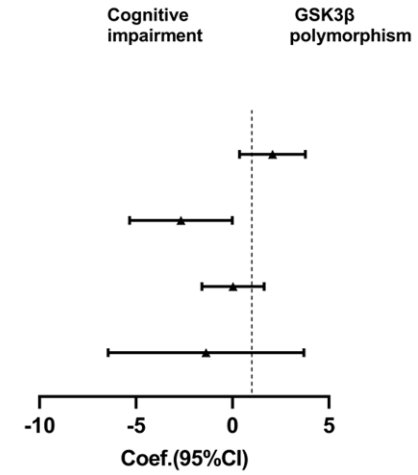


Figure 4. The forest plot for all enrolled participants. A. The genetic risk of GSK3β rs3107669 between breast cancer and healthy controls; B. The correlation between GSK3β rs3107669 polymorphism and MMSE, RM, PM and FACT-B tasks. Note: **P<0.01. ****P<0.0001. MMSE, the mini-mental state examination; RM, retrospective memory; PM, prospective memory; FACT-B, Functional Assessment of Cancer Therapy-Breast.

after chemotherapy than healthy controls. Surprisingly, the results of this study once again confirmed that memory impairment was present in breast cancer patients after chemotherapy, which seriously hampered their quality of life.

What was the mechanism of chemobrain? The current evidence indicates that chemobrain is complex and influenced by multiple factors, including oxidative stress and inflammation, cytokine dysregulation, DNA damage and telomere shortening, genetic polymorphisms, and more [5, 36]. To this end, our group has conducted much exploratory research. We found that cytokines (IL-1β, TNF-α and IL-4) were involved in the development of breast cancer chemobrain [37]. Similarly, a genetic polymorphism (COMT) was closely associated with chemotherapy-related cognitive deficits in breast cancer patients, and for the first time, molecular typing (ER/PR, HER2, Ki-67) and COMT polymorphisms were identified as risk factors for chemobrain in breast cancer patients [38-40]. Therefore, to further improve the study of genetic risk factors and supplement the results of gene polymorphism (GSK 3β) was the breakthrough point of chemobrain in breast cancer.

GSK 3β plays an important role in nerve growth and synaptic plasticity and is a key regulator of various intracellular signaling pathways [41]. GSK3β could affect learning and memory by participating in neuroplasticity in the dentate gyrus of the hippocampus [42]. GSK3β could regulate memory by participating in hippocampal cell proliferation [43]. GSK3β overexpression in a mouse model reproduced abnormalities in the nervous system of Alzheimer's disease patients and was accompanied by mor-

Table 5. Multiple linear regression between GSK3β rs3107669 polymorphism and cognitive impairment in breast cancer patients with chemotherapy

Cognitive test	Influencing Factor	Beta	95% CI	t	*P* value
MMSE	Genotype				
	C/C	Ref.	-	-	-
	C/A+A/A	0.412	2.001~3.818	6.316	0.000****
	Years of Age				
	≥50	Ref.			
	<50	0.095	-0.237~1.324	1.373	0.171
	Years of education				
	HSDIP or above	Ref.			
	JHSDIP or below	0.049	-0.507~1.063	0.700	0.485
RM	Genotype				
	C/C	Ref.	-	-	-
	C/A+A/A	-0.306	-5.556~-2.145	-4.453	0.000****
	Years of Age				
	≥50	Ref.			
	<50	0.035	-1.108~1.823	0.481	0.631
	Years of education				
	HSDIP or above	Ref.			
	JHSDIP or below	0.008	-1.393~1.554	0.108	0.914
PM	Genotype				
	C/C	Ref.	-	-	-
	C/A+A/A	0.004	-1.575~1.655	0.049	0.961
	Years of Age				
	≥50	Ref.			
	<50	0.036	-1.060~1.715	0.465	0.643
	Years of education				
	HSDIP or above	Ref.			
	JHSDIP or below	-0.004	-1.436~1.354	-0.058	0.954
FACT-B	Genotype				
	C/C	Ref.	-	-	-
	C/A+A/A	-0.057	-6.978~2.916	-0.810	0.419
	Years of Age				
	≥50	Ref.			
	<50	-0.097	-7.049~1.452	-1.299	0.196
	Years of education				
	HSDIP or above	Ref.			
	JHSDIP or below	0.163	0.444~8.991	2.177	0.031*

Note: *P<0.05; ****P<0.0001; HSDIP, High School Diploma; JHSDIP, Junior high school Diploma; MMSE, the mini-mental state examination; RM, retrospective memory; PM, prospective memory; FACT-B, Functional Assessment of Cancer Therapy-Breast. *P* value for multiple linear regression; Standardized Coefficient (the Beta); 95% confidence interval (95% CI).

phological changes in granulosa neurons [44]. GSK3β was considered to be a risk gene for schizophrenia, and cognitive deficits were stable in those patients [45, 46]. GSK3β dysfunction has been linked to bipolar disorder, depression, and Alzheimer's disease [47, 48]. The clinical manifestation of chemobrain was the same as that of mental diseases such as Alzheimer's disease, which could show reduced memory and executive ability [49]. Therefore, we hypothesized that the GSK3β gene polymorphism was closely related to chemobrain. At present, few groups have deepened our understanding of the relationship between

Table 6. Comparison of cognitive function in breast cancer patients with different GSK3β rs3107669 genotypes

	N	MMSE	RM	PM	FACT-B
rs3107669					
Before Chemotherapy					
C/C group	40	27.28±1.57	15.03±4.69	14.55±4.76	80.75±17.56
C/A+A/A group	157	27.41±1.53	14.61±4.14	14.34±4.49	77.95±18.96
t/z		-0.480	-0.437	-0.031	-0.712
p		0.631	0.662	0.975	0.476
After Chemotherapy					
C/C group	40	23.03±2.85	20.00±5.81	16.88±4.95	53.28±16.72
C/A+A/A group	157	25.97±2.53	16.17±4.58	16.92±4.49	51.41±13.76
t/z		-5.598	-4.302	-0.115	-0.177
p		0.000****	0.000****	0.908	0.859

Note: ****P<0.0001; MMSE, the mini-mental state examination; RM, retrospective memory; PM, prospective memory; FACT-B, Functional Assessment of Cancer Therapy-Breast; BC, before chemotherapy; AC, after chemotherapy; HC, heathy control.

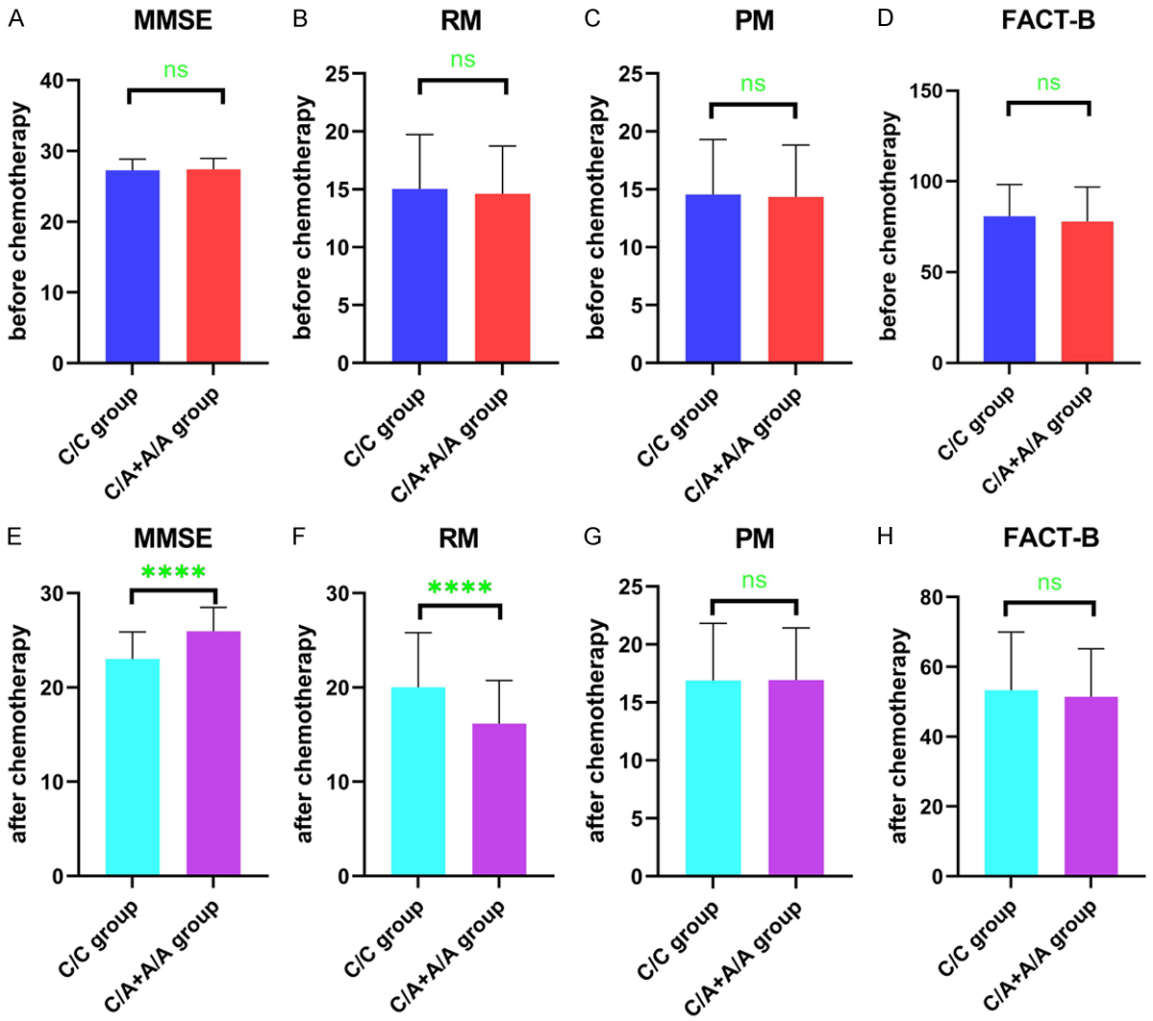


Figure 5. Cognitive tests before and after chemotherapy in the C/C and C/A+A/A groups. A-D. The scores of the MMSE, RM, PM and FACT-B between the C/C and C/A+A/A groups before chemotherapy. E-H. The MMSE, RM, PM and FACT-B scores between the C/C and C/A+A/A groups after chemotherapy. Note: ****P<0.0001. MMSE, the mini-mental state examination; RM, retrospective memory; PM, prospective memory; FACT-B, Functional Assessment of Cancer Therapy-Breast.

GSK3β gene polymorphisms and chemobrain, both at home and abroad. The results of this study were the first to confirm the effect of this gene on chemotherapy-associated cognitive deficits in breast cancer, further complementing the genetic risk factors for chemobrain.

GSK3β gene polymorphism was closely associated with cognitive function. Inkster et al. [50] found that the GSK3β A/A genotype was related to reduced gray matter volume in the right hippocampus and bilateral temporal gyrus in patients with depression. Individuals who carry the GSK-3β rs334558 A allele have a significantly increased risk of depression [51]. The risk allele A on the GSK-3β promoter has been reported to be associated with schizophrenia susceptibility in Han Chinese individuals [52]. GSK-3β gene polymorphism was involved in cognitive decline in Alzheimer's disease, and amyloid Aβ42 was its biomarker [27, 53].

The association between GSK-3β gene polymorphism and cognitive dysfunction reinforced the hypothesis that heterogeneity was present in chemobrain for breast cancer. Our findings indicated that the GSK-3β rs3107669 polymorphism was strongly associated with RM impairment in breast cancer patients after chemotherapy, while the C/C genotype increased the risk of memory deficits. We speculated that, first, the activity of the GSK-3β enzyme in patients with the C/C genotype was more inhibited than before, which led to a decline in the function of hippocampal neurons. Ochs et al. [54] showed that the loss of GSK-3β in hippocampal neurons in adult mice might lead to decreased dendrite spine density. Banach et al. [55] found that GSK-3β could cause synaptic dysfunction, which was accompanied by changes in the morphology of dendritic spines of granulosa cells in the dentate gyrus. Therefore, we hypothesized that the rs3107669 polymorphism may affect hippocampal synaptic plasticity to cause cognitive dysfunction in breast cancer patients. Of course, further animal experiments are needed to confirm this hypothesis. Second, the GSK-3β rs3107669 polymorphism could directly affect the proliferation of brain neurons. Dobson-Stone et al. [56] found that GSK-3β polymorphism could contribute to decreased proliferation of neuronal precursors and decreased brain volume by affecting the expression of enzyme activity in the brain. Similarly, Sunada et al. [57] found that the GSK-3β polymorphism could affect the hippocampal volume of patients with major depression. Third, GSK-3β polymorphism directly affected the transmission of multiple signaling pathways. GSK-3β is involved in the Wnt/β-catenin, PI3K/PTEN/AKT and Notch signaling pathways, and these pathways play a key role in neurodegenerative diseases [58, 59]. GSK-3β was the key node factor of the above signaling pathways. This indicated that GSK-3β may act as a vital link in chemobrain genesis and treatment.

Some limitations should be noted in this study. First, this study was a single-center cross-sectional study from a teaching hospital, and the longitudinal follow-up records were vague. Second, only five SNPs of the GSK3β gene were explored, which included many other types of polymorphisms. The role of these sites in chemobrain was unclear. Third, it was necessary to supplement the animal model of chemobrain for breast cancer. This needs to be confirmed in future exploration.

Conclusion

In conclusion, our group was the first to present the genetic effect between the GSK-3β rs3107669 polymorphism and chemotherapy-associated retrospective memory impairments in breast cancer survivors. The preliminary understanding of the role of this gene was performed in chemobrain.

Our findings not only complement the heterogeneity of chemobrain for breast cancer but also be able to identify those populations at greatest risk of cognitive impairment.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (Nos. 81372487, 81872504).

Disclosure of conflict of interest

None.

Address correspondence to: Huaidong Cheng, Department of Oncology, Shenzhen Hospital of Southern Medical University, Shenzhen 518000, Guangdong, P. R. China; Department of Oncology,

The Second Hospital of Anhui Medical University, Hefei 230601, Anhui, P. R. China. Tel: +86-13955112735; E-mail: chd1975ay@126.com

References

[1] Siegel RL, Miller KD, Wagle NS and Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023; 73: 17-48.

[2] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.

[3] DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, Jemal A and Siegel RL. Breast cancer statistics, 2019. CA Cancer J Clin 2019; 69: 438-451.

[4] Di Nardo P, Lisanti C, Garutti M, Buriolla S, Alberti M, Mazzeo R and Puglisi F. Chemotherapy in patients with early breast cancer: clinical overview and management of long-term side effects. Expert Opin Drug Saf 2022; 21: 1341-1355.

[5] Janelsins MC, Kesler SR, Ahles TA and Morrow GR. Prevalence, mechanisms, and management of cancer-related cognitive impairment. Int Rev Psychiatry 2014; 26: 102-113.

[6] Ossorio-Salazar VA and D'Hooge R. Methodological shortcomings of preclinical research on chemotherapy-induced cognitive impairment. Neurosci Biobehav Rev 2023; 150: 105198.

[7] Saita K, Amano S, Kaneko F and Okamura H. A scoping review of cognitive assessment tools and domains for chemotherapy-induced cognitive impairments in cancer survivors. Front Hum Neurosci 2023; 17: 1063674.

[8] Janelsins MC, Heckler CE, Peppone LJ, Kamen C, Mustian KM, Mohile SG, Magnuson A, Kleckner IR, Guido JJ, Young KL, Conlin AK, Weiselberg LR, Mitchell JW, Ambrosone CA, Ahles TA and Morrow GR. Cognitive complaints in survivors of breast cancer after chemotherapy compared with age-matched controls: an analysis from a nationwide, multicenter, prospective longitudinal study. J Clin Oncol 2017; 35: 506-514.

[9] Koevoets EW, Schagen SB, de Ruiter MB, Geerlings MI, Witlox L, van der Wall E, Stuiver MM, Sonke GS, Velthuis MJ, Jobsen JJ, Menke-Pluijmers MBE, Goker E, van der Pol CC, Bos MEMM, Tick LW, van Holsteijn NA, van der Palen J, May AM and Monninkhof EM; PAM study group. Effect of physical exercise on cognitive function after chemotherapy in patients with breast cancer: a randomized controlled trial (PAM study). Breast Cancer Res 2022; 24: 36.

[10] Henry JD. Prospective memory impairment in neurological disorders: implications and management. Nat Rev Neurol 2021; 17: 297-307.

[11] Wang Y, Deng Y, Cao L, Zhang J and Yang L. Retrospective memory integration accompanies reconfiguration of neural cell assemblies. Hippocampus 2022; 32: 179-192.

[12] Ganz PA, Kwan L, Castellon SA, Oppenheim A, Bower JE, Silverman DH, Cole SW, Irwin MR, Ancoli-Israel S and Belin TR. Cognitive complaints after breast cancer treatments: examining the relationship with neuropsychological test performance. J Natl Cancer Inst 2013; 105: 791-801.

[13] Andryszak P, Wilkosc M, Zurawski B and Izdebski P. Verbal memory in breast cancer patients treated with chemotherapy with doxorubicin and cyclophosphamide. Eur J Cancer Care (Engl) 2018; 27.

[14] Luijendijk MJ, Bekele BM, Schagen SB, Douw L and de Ruiter MB. Temporal dynamics of resting-state functional networks and cognitive functioning following systemic treatment for breast cancer. Brain Imaging Behav 2022; 16: 1927-1937.

[15] Cheng H, Yang Z, Dong B, Chen C, Zhang M, Huang Z, Chen Z and Wang K. Chemotherapy-induced prospective memory impairment in patients with breast cancer. Psychooncology 2013; 22: 2391-2395.

[16] Li W, Gan C, Lv Y, Wang S and Cheng H. Chemotherapy-induced prospective memory impairment in breast cancer patients with different hormone receptor expression. Medicine (Baltimore) 2017; 96: e6514.

[17] Ahles TA and Saykin AJ. Candidate mechanisms for chemotherapy-induced cognitive changes. Nat Rev Cancer 2007; 7: 192-201.

[18] Small BJ, Rawson KS, Walsh E, Jim HS, Hughes TF, Iser L, Andrykowski MA and Jacobsen PB. Catechol-O-methyltransferase genotype modulates cancer treatment-related cognitive deficits in breast cancer survivors. Cancer 2011; 117: 1369-1376.

[19] Serrano-Pozo A, Das S and Hyman BT. APOE and Alzheimer's disease: advances in genetics, pathophysiology, and therapeutic approaches. Lancet Neurol 2021; 20: 68-80.

[20] Koleck TA, Bender CM, Sereika SM, Ahrendt G, Jankowitz RC, McGuire KP, Ryan CM and Conley YP. Apolipoprotein E genotype and cognitive function in postmenopausal women with early-stage breast cancer. Oncol Nurs Forum 2014; 41: E313-E325.

[21] Ahles TA, Orlow I, Schofield E, Li Y, Ryan E, Root JC, Patel SK, McNeal K, Gaynor A, Tan H, Katheria V, Vazquez J, Corrales-Guerrero S, Sadeghi

K, Traina T and Hurria A. The impact of APOE and smoking history on cognitive function in older, long-term breast cancer survivors. J Cancer Surviv 2022; [Epub ahead of print].
[22] Cheng H, Li W, Gan C, Zhang B, Jia Q and Wang K. The COMT (rs165599) gene polymorphism contributes to chemotherapy-induced cognitive impairment in breast cancer patients. Am J Transl Res 2016; 8: 5087-5097.
[23] Hooper C, Killick R and Lovestone S. The GSK3 hypothesis of Alzheimer's disease. J Neurochem 2008; 104: 1433-1439.
[24] Lauretti E, Dincer O and Pratico D. Glycogen synthase kinase-3 signaling in Alzheimer's disease. Biochim Biophys Acta Mol Cell Res 2020; 1867: 118664.
[25] Chen Y, Hua S, Wang W, Fan W, Tang W, Zhang Y and Zhang C. A comprehensive analysis of GSK3B variation for schizophrenia in Han Chinese individuals. Asian J Psychiatr 2020; 47: 101832.
[26] Mateo I, Infante J, Llorca J, Rodriguez E, Berciano J and Combarros O. Association between glycogen synthase kinase-3beta genetic polymorphism and late-onset Alzheimer's disease. Dement Geriatr Cogn Disord 2006; 21: 228-232.
[27] Kettunen P, Larsson S, Holmgren S, Olsson S, Minthon L, Zetterberg H, Blennow K, Nilsson S and Sjolander A. Genetic variants of GSK3B are associated with biomarkers for Alzheimer's disease and cognitive function. J Alzheimers Dis 2015; 44: 1313-1322.
[28] Bai F, Shi Y, Yuan Y, Yue C, Zhuang L, Xu X, Liu X and Zhang Z. Association of a GSK-3beta polymorphism with brain resting-state function in amnestic-type mild cognitive impairment. J Alzheimers Dis 2012; 32: 387-396.
[29] Hohman TJ, Chibnik L, Bush WS, Jefferson AL, De Jaeger PL, Thornton-Wells TA, Bennett DA and Schneider JA. GSK3beta interactions with amyloid genes: an autopsy verification and extension. Neurotox Res 2015; 28: 232-238.
[30] Filippi A and Mocanu MM. Mining TCGA database for genes with prognostic value in breast cancer. Int J Mol Sci 2023; 24: 1622.
[31] Ronnlund M, Mantyla T and Nilsson LG. The Prospective and Retrospective Memory Questionnaire (PRMQ): factorial structure, relations to global subjective memory ratings, and Swedish norms. Scand J Psychol 2008; 49: 11-18.
[32] Matthies LM, Taran FA, Keilmann L, Schneeweiss A, Simoes E, Hartkopf AD, Sokolov AN, Walter CB, Sickenberger N, Wallwiener S, Feisst M, Gass P, Lux MP, Schuetz F, Fasching PA, Sohn C, Brucker SY, Graf J and Wallwiener M. An electronic patient-reported outcome tool for the FACT-B (functional assessment of cancer therapy-breast) questionnaire for measuring the health-related quality of life in patients with breast cancer: reliability study. J Med Internet Res 2019; 21: e10004.
[33] Koppelmans V, Breteler MM, Boogerd W, Seynaeve C, Gundy C and Schagen SB. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. J Clin Oncol 2012; 30: 1080-1086.
[34] Ng T, Dorajoo SR, Cheung YT, Lam YC, Yeo HL, Shwe M, Gan YX, Foo KM, Loh WK, Koo SL, Jain A, Lee GE, Dent R, Yap YS, Ng R and Chan A. Distinct and heterogeneous trajectories of self-perceived cognitive impairment among Asian breast cancer survivors. Psychooncology 2018; 27: 1185-1192.
[35] Bilenduke E, Sterrett JD, Ranby KW, Borges VF, Grigsby J, Carr AL, Kilbourn K and Lowry CA. Impacts of breast cancer and chemotherapy on gut microbiome, cognitive functioning, and mood relative to healthy controls. Sci Rep 2022; 12: 19547.
[36] Loh KP, Janelsins MC, Mohile SG, Holmes HM, Hsu T, Inouye SK, Karuturi MS, Kimmick GG, Lichtman SM, Magnuson A, Whitehead MI, Wong ML and Ahles TA. Chemotherapy-related cognitive impairment in older patients with cancer. J Geriatr Oncol 2016; 7: 270-280.
[37] Zhao J, Zuo H, Ding K, Zhang X, Bi Z and Cheng H. Changes in plasma IL-1beta, TNF-alpha and IL-4 levels are involved in chemotherapy-related cognitive impairment in early-stage breast cancer patients. Am J Transl Res 2020; 12: 3046-3056.
[38] Li W, Yu S, Duan X, Yao S, Tang L and Cheng H. COMT rs737865 mediates chemobrain in breast cancer patients with various levels of Ki-67. Am J Cancer Res 2022; 12: 3185-3197.
[39] Li W, Zhang Q, Cai Y, Chen T and Cheng H. The COMT genetic factor regulates chemotherapy-related prospective memory impairment in survivors with HER2-/+ breast cancer. Front Oncol 2022; 12: 816923.
[40] Li W, Zhao J, Ding K, Chao HH, Li CR, Cheng H and Shen L. Catechol-O-methyltransferase gene polymorphisms and the risk of chemotherapy-induced prospective memory impairment in breast cancer patients with varying tumor hormonal receptor expression. Med Sci Monit 2020; 26: e923567.
[41] Grimes CA and Jope RS. The multifaceted roles of glycogen synthase kinase 3beta in cellular signaling. Prog Neurobiol 2001; 65: 391-426.
[42] Hooper C, Markevich V, Plattner F, Killick R, Schofield E, Engel T, Hernandez F, Anderton B, Rosenblum K, Bliss T, Cooke SF, Avila J, Lucas JJ, Giese KP, Stephenson J and Lovestone S. Glycogen synthase kinase-3 inhibition is inte-

gral to long-term potentiation. Eur J Neurosci 2007; 25: 81-86.
[43] Pardo M, Abrial E, Jope RS and Beurel E. GSK-3beta isoform-selective regulation of depression, memory and hippocampal cell proliferation. Genes Brain Behav 2016; 15: 348-355.
[44] Pallas-Bazarra N, Kastanauskaite A, Avila J, DeFelipe J and Llorens-Martin M. GSK-3beta overexpression alters the dendritic spines of developmentally generated granule neurons in the mouse hippocampal dentate gyrus. Front Neuroanat 2017; 11: 18.
[45] Chen J, Wang M, Waheed Khan RA, He K, Wang Q, Li Z, Shen J, Song Z, Li W, Wen Z, Jiang Y, Xu Y, Shi Y and Ji W. The GSK3B gene confers risk for both major depressive disorder and schizophrenia in the Han Chinese population. J Affect Disord 2015; 185: 149-155.
[46] Fang X, Chen Y, Wang Y and Zhang C. Identification of risk factors for suicidal ideation in patients with schizophrenia. Psychiatry Res 2019; 271: 195-199.
[47] Niciu MJ, Ionescu DF, Mathews DC, Richards EM and Zarate CA Jr. Second messenger/signal transduction pathways in major mood disorders: moving from membrane to mechanism of action, part II: bipolar disorder. CNS Spectr 2013; 18: 242-251.
[48] Simayi J, Bayinsang, Nuermaimaiti M, Hailati S, Han M, Reheman Z, Wumaier A and Zhou W. A network pharmacology-based study on the mechanism of dibutyl phthalate of ocimum basilicum L. against Alzheimer's disease through the AKT/GSK-3beta pathway. Biomed Res Int 2022; 2022: 9494548.
[49] Tyagi K, Masoom M, Majid H, Garg A, Bhurani D, Agarwal NB and Khan MA. Role of cytokines in chemotherapy-related cognitive impairment of breast cancer patients: a systematic review. Curr Rev Clin Exp Pharmacol 2023; 18: 110-119.
[50] Inkster B, Nichols TE, Saemann PG, Auer DP, Holsboer F, Muglia P and Matthews PM. Association of GSK3beta polymorphisms with brain structural changes in major depressive disorder. Arch Gen Psychiatry 2009; 66: 721-728.
[51] Yang J, Ke S, Qiao Z, Yang X, Qiu X, Song X, Zhao E, Zhou J, Zhao M, Yang Y, Fang D and Cao D. Interactions between glycogen synthase kinase-3beta gene polymorphisms, negative life events, and susceptibility to major depressive disorder in a Chinese population. Front Psychiatry 2021; 11: 503477.
[52] Yan P, Qiao X, Wu H, Yin F, Zhang J, Ji Y, Wei S and Lai J. An association study between genetic polymorphisms in functional regions of five genes and the risk of schizophrenia. J Mol Neurosci 2016; 59: 366-375.
[53] Zhang N, Yu JT, Yang Y, Yang J, Zhang W and Tan L. Association analysis of GSK3B and MAPT polymorphisms with Alzheimer's disease in Han Chinese. Brain Res 2011; 1391: 147-153.
[54] Ochs SM, Dorostkar MM, Aramuni G, Schon C, Filser S, Poschl J, Kremer A, Van Leuven F, Ovsepian SV and Herms J. Loss of neuronal GSK3beta reduces dendritic spine stability and attenuates excitatory synaptic transmission via beta-catenin. Mol Psychiatry 2015; 20: 482-489.
[55] Banach E, Jaworski T and Urban-Ciecko J. Early synaptic deficits in GSK-3beta overexpressing mice. Neurosci Lett 2022; 784: 136744.
[56] Dobson-Stone C, Polly P, Korgaonkar MS, Williams LM, Gordon E, Schofield PR, Mather K, Armstrong NJ, Wen W, Sachdev PS and Kwok JB. GSK3B and MAPT polymorphisms are associated with grey matter and intracranial volume in healthy individuals. PLoS One 2013; 8: e71750.
[57] Sunada N, Takekita Y, Nonen S, Wakeno M, Koshikawa Y, Ogata H, Kinoshita T and Kato M. Brain volume-related polymorphisms of the glycogen synthase kinase-3beta gene and their effect on antidepressant treatment in major depressive disorder. Neuropsychobiology 2019; 78: 136-144.
[58] Lin J, Song T, Li C and Mao W. GSK-3beta in DNA repair, apoptosis, and resistance of chemotherapy, radiotherapy of cancer. Biochim Biophys Acta Mol Cell Res 2020; 1867: 118659.
[59] Yang W, Liu Y, Xu QQ, Xian YF and Lin ZX. Sulforaphene ameliorates neuroinflammation and hyperphosphorylated Tau protein via regulating the PI3K/Akt/GSK-3beta pathway in experimental models of Alzheimer's disease. Oxid Med Cell Longev 2020; 2020: 4754195.