DNA Methylation of *BDNF* and *RASA2* Genes Is Associated With Cognitive Function in Postmenopausal Women With Breast Cancer

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OBJECTIVES: To determine associations among DNA methylation of brain-derived neurotrophic factor (*BDNF*) and RAS p21 protein activator 2 (*RASA2*) genes with processing speed and perceived cognitive function.

SAMPLE & SETTING: This was a cross-sectional, secondary analysis of baseline data from a randomized controlled trial, the Exercise Program in Cancer and Cognition Study.

METHODS & VARIABLES: Data included M values for DNA methylation of the *BDNF* and *RASA2* genes; processing speed, objectively measured using the Grooved Pegboard and Digit Vigilance Test scores; and perceived cognitive function, self-reported using the Patient Assessment of Own Functioning Inventory. Regression analysis was conducted.

RESULTS: Greater methylation of cg21291635 of the *BDNF* gene ($p = 0.01$) and cg20247102 of the *RASA2* gene ($p = 0.013$) were associated with poorer processing speed, whereas greater methylation of cg20108357 of the *BDNF* gene ($p < 0.001$) and cg00567892 of the *RASA2* gene ($p = 0.019$) were associated with better perceived cognitive function.

IMPLICATIONS FOR NURSING: Gene methylation variations were demonstrated, suggesting the genes' potential roles and two possible distinct mechanisms of cognitive function in cancer.

KEYWORDS DNA methylation; cognition; processing speed; perceived cognitive function; breast cancer

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Breast cancer is the most prevalent cancer type among women in the United States (American Cancer Society, 2023). About 75% of primary breast cancer cases are postmenopausal at diagnosis (Borch et al., 2015; Key et al., 2001), and more than 80% of postmenopausal women diagnosed with breast cancer receive endocrine therapy (Burstein et al., 2019; Lao et al., 2021). As many as 75% of women with breast cancer go through cancer-related cognitive decline (CRCD) (Cerulla Torrente et al., 2020). CRCD has profound negative effects on occupational functioning (Munir et al., 2010), self-confidence, social relationships (Von Ah et al., 2013), and quality of life by influencing interpersonal relationships, leisure activities, anxiety, and depression (Goretti et al., 2010; Hill et al., 2017; Mitchell et al., 2010). Processing speed is the speed at which an individual perceives a given stimulus, interprets the information from that stimulus, and produces a response (Kraft & Woods, 2021). It is among the most frequent cognitive domains to decline in patients with cancer (Pendergrass et al., 2018) and one of the most sensitive cognitive domains contributing to a decline in cerebral functions (Lezak et al., 2012).

Depending on the type of cancer and cancer treatment, the manifestations of CRCD vary widely in timing, severity, and the affected cognitive domains (Collins et al., 2009). CRCD frequently occurs during cancer treatment, but compared to women without breast cancer, 20%–30% of patients with breast cancer experience worsened cognitive function before the initiation of any systematic treatment (Cerulla Torrente et al., 2020). CRCD persists after adjuvant treatment in 49% of women with breast cancer who are aged 65 years

or older (Lange et al., 2016). Patients with breast cancer who received chemotherapy reported poorer processing speed compared to individuals without breast cancer (Bernstein et al., 2017). In addition, women who received chemotherapy and adjuvant endocrine therapy showed a greater decline in processing speed within one year of completing chemotherapy compared to those receiving chemotherapy alone (Collins et al., 2009). Cognitive function among patients with cancer has been measured with self-reported questionnaires and objective neuropsychologic tests, and the inconsequential link between self-reported and objectively measured cognitive function has been widely and consistently reported (Bray et al., 2018). One plausible explanation for this discrepancy is that some individuals may feel their cognitive functions are declining because they are exerting more effort to accomplish tasks, which could result in increased brain activity not detected by standard objective measures (Campbell et al., 2018). However, little biobehavioral evidence is known to explain the variability of cognitive function among women with breast cancer.

DNA methylation is a plausible biomarker to explain this variability. According to the accelerated aging theory, the presence of cancer and its treatments possibly accelerate the normal aging process, leading to alterations in brain structures and cognition, as well as death (Mandelblatt et al., 2013). DNA methylation is a notable and promising tool for guiding care in cancer survivorship because of its reversible nature and the fact that it is measured using blood samples (Guida et al., 2019; Mandelblatt et al., 2021). DNA methylation is an epigenetic modification that affects gene expression. Methylation patterns vary at interindividual and tissue levels by adding or removing methyl groups over cytosine-phosphate-guanine (CpG) sites (Issa, 1999). Given their stability and regulation by genetic and lifestyle factors, DNA methylation patterns have the potential to serve as peripheral biomarkers for tracking cognitive aging variabilities at the population level (Conole et al., 2021). Despite limited research in patients with cancer, there is growing evidence linking declined cognitive function with DNA methylation patterns in genes that are critical for neural function or signaling (Yang et al., 2020).

Several plausible genes are associated with processing speed in humans; among them are the brain-derived neurotrophic factor (*BDNF*) and RAS p21 protein activator 2 (*RASA2*) genes. *BDNF* plays a role in neural cell creation, protection, and regulation, as well as synaptic plasticity, and is associated with memory in aging (Erickson et al., 2010). DNA methylation at the *BDNF* promoter is associated with reduced synthesis of *BDNF* in neurons (Martinowich et al., 2003). *RASA2* codes RAS proteins that control the mechanisms regulating cellular signaling, and is expressed in the brain, particularly in the cerebellum and hypothalamus (Rajalingam et al., 2007). *BDNF* and *RASA2* genes are implicated in cognitive dysfunction in Alzheimer disease and schizophrenia (Knowles et al., 2019). Considering their roles, a higher level of methylation is hypothesized to be related to a lower expression level, potentially leading to poorer cognitive function. However, very little is known about DNA methylation patterns in relation to cognitive function in the context of breast cancer and its treatments.

The authors found no previous studies exploring the associations of cognitive function with DNA methylation of *BDNF* and *RASA2* genes in postmenopausal women with early-stage breast cancer who have been prescribed adjuvant therapy. In this hypothesis-generating exploratory study guided by accelerated aging theory, the aim was to investigate the DNA methylation of the *BDNF* and *RASA2* genes in association with processing speed and perceived cognitive function in this population.

Methods

Design

This study was a secondary analysis of a cross-sectional design using existing baseline phenotypic and epigenomic data from a randomized controlled trial, the Exercise Program in Cancer and Cognition Study, which aimed to examine whether six-month aerobic exercise improves cognitive function in postmenopausal women with early-stage breast cancer receiving endocrine therapy (R01CA196762). An ancillary study investigated the role of epigenomics in the Exercise Program in Cancer and Cognition Study (R01CA221882). This study was approved by the institutional review boards of the University of Pittsburgh (PRO15120433), St. Clair Hospital (PRO1712001), and Carnegie Mellon University (study2016_00000197). The parent study met all ethical guidelines, including confidentiality, and all participants provided informed consent. The analyses used deidentified baseline data and were exempt from additional review by the institutional review board.

Participants

Enrollment criteria for both parent studies were identical and included women who were postmenopausal; aged younger than 80 years; diagnosed with stage 0, I,

II, or IIIa breast cancer; were eligible to receive endocrine therapy; spoke English; and had a minimum of eight years of education. Exclusion criteria included the following: a diagnosis of any type of cancer before breast cancer (excluding some skin cancers), clinical evidence of distant metastases, a self-reported hospitalization for psychiatric illness within the past two years, a history of neurologic illness, complications with breast cancer surgery, or reconstructive surgery within the study period. Because of the COVID-19 pandemic, the inclusion criteria were later expanded to include women who were within two years of completing primary therapy (surgery and/or chemotherapy). More detailed information can be found in the protocol

TABLE 1. Sample Characteristics (N = 153)

	Included (N = 102)		Not Included (N = 51)		
Characteristic	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**	**p**
Age (years)	62.7	7.99	62.2	9.1	0.744
Body mass index (kg/m^2)	31.1	6.53	30.1	6.91	0.415
Education (years)	16.3	2.46	15.5	2.9	0.11
Processing speed					
Score	0.1	0.71	–0.2	1.03	0.029*
PAOFI score					
Total	21.1	17.14	22.6	17.73	0.61
Sensorimotor	2.9	3.15	2.1	2.36	0.084
Memory	8.6	6.36	9.7	6.62	0.309
Language and communication	5.8	5.37	5.8	5.54	0.995
Higher-level cognitive and intellectual functions	3.8	4.58	4.9	6.22	0.214
Characteristic	**n**	**%**	**n**	**%**	**p**
Breast cancer stage					0.838
Ductal carcinoma in situ	14	14	10	20	
I	64	63	32	63	
IIa	15	15	6	12	
IIb	5	5	2	4	
IIIa	4	4	1	2	
Chemotherapy					0.767
No	84	82	41	80	
Yes	18	18	10	20	
Endocrine therapy					0.126
Yes	96	94	45	88	
No or unknown	6	6	6	12	
Race					0.318
Black or African American	8	8	1	2	
White	90	88	48	94	
Other[a]	4	4	2	4	

* Correlation is significant at the 0.05 level (two-tailed).
[a] Defined as American Indian, Asian, Native American, or more than 1 race
PAOFI—Patient's Assessment of Own Functioning Inventory
Note. Included were cases with DNA methylation data; not included were cases without DNA methylation data. For missing PAOFI scores, imputation using regression with auxiliary variables (e.g., age, year of education, verbal IQ score computed with the National Adult Reading Test) was conducted.
Note. Because of rounding, percentages may not total 100.

articles (Bender et al., 2024; Gentry et al., 2018). For this study, participants with cognitive function and DNA methylation data at prerandomization were eligible.

Measures

The original data were collected before randomization and six months after random group assignment from a total of 153 participants. Because the participants were randomly assigned to the exercise group (n = 77) or the usual care group (n = 76), and to exclude the influence of exercise on DNA methylation of *BDNF* (Gómez-Pinilla et al., 2002; Szuhany et al., 2015; Walsh & Tschakovsky, 2018), the data used were exclusively from prerandomization for this study.

DNA methylation data of the *BDNF* and *RASA2* genes were collected with the Illumina© Infinium™ MethylationEPIC, version 1.0, BeadChip, using DNA extracted from peripheral blood. Using minfi and ENmix R packages, quality control was performed, and low-quality probes were detected and removed. A total of 88 CpG sites in the *BDNF* gene and 37 CpG sites in the *RASA2* gene from 102 participants were retained after quality control. Methylation M values, the log of the ratio of the methylated and unmethylated intensities, were used. When M values are positive, the methylated signal is higher and indicates hypermethylation. When M values are negative, the unmethylated signal is higher and indicates hypomethylation. M values close to 0 imply similar signals between being methylated and unmethylated.

A processing speed factor was computed using scores from the Grooved Pegboard and Digit Vigilance tests (Lewis & Rennick, 1979). The scores for the Grooved Pegboard Test (Lewis & Rennick, 1979) are the times it takes participants to insert pegs into randomly positioned holes on a pegboard with their dominant and nondominant hands. For the Digit Vigilance Test (Lewis & Rennick, 1979), participants need to find and cross out all sixes and nines found on two pages of 59 lines of randomly appearing single-digit numbers. The scores are the time to complete a task and the number of errors committed. The individual neuropsychologic tests were selected because of their sensitivity to alterations in processing speed in women with breast cancer (Bender et al., 2015). The processing speed factor was derived by exploratory factor analysis. A mean Z score from the Z scores generated from the test values was computed as the final processing speed factor score. Overall, higher values indicate better processing speed.

Perceived cognitive function was measured with the Patient's Assessment of Own Functioning Inventory (PAOFI) (Chelune et al., 1986), a self-report measure of perceived cognitive problems that yields a total and five subscale scores in the following categories: memory (nine items), language and communication (nine items), use of hands (two items), sensory-perceptual (three items), and higher-level cognitive and intellectual functions (nine items). The use of hands and sensory-perceptual subscales are combined as another more generalizable subscale, the sensorimotor subscale (five items), which is negatively associated with quality of life among women with breast cancer (Bell et al., 2013). This exploratory study used total scores as well as sensorimotor, memory, language and communication,

TABLE 2. Associations Among Processing Speed and PAOFI Total and Subscale Scores (N = 102)

		PAOFI[a]				
Category	Processing Speed[b]	Total	Sensorimotor	Memory	Language and Communication	HLCIF
Processing speed[b]	1	0.043	0.098	0.018	0.051	–0.09
Total	–	1	0.654*	0.9*	0.887*	–0.852*
Sensorimotor	–	–	1	0.411*	0.436*	0.534*
Memory	–	–	–	1	0.767*	0.697*
Language and communication	–	–	–	–	1	0.755*
HLCIF	–	–	–	–	–	1

* Correlation is significant at the 0.05 level (two-tailed).
[a] Square-root transformed
[b] Reflected and $\log_{10}$ transformed
HLCIF—higher-level cognitive and intellectual functions; PAOFI—Patient's Assessment of Own Functioning Inventory

and higher-level cognitive and intellectual functions subscale scores. The scores are the sums of items on which participants rate the frequency of cognitive problems on a six-point Likert-type scale ranging from 0 (almost never) to 5 (almost always). The total score ranges from 0 to 160, with higher scores indicating poorer perceived cognitive functioning. In women with breast cancer, the construct validity and reliability are supported (Bell et al., 2013).

Potential covariates included demographic information (age [years], education [years]), body mass index (kg/m^2), and disease and treatment information (cancer stage [ductal carcinoma in situ, I, IIa, IIb, or III], endocrine therapy [yes or no], chemotherapy [yes or no]). Patients with sufficient variability were adjusted in the analysis.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics, version 28.0. Data were first screened for abnormalities (e.g., missing values, outliers). To describe the characteristics of the sample, descriptive analysis was conducted. Underlying statistical assumptions were checked with scatterplots and residual analysis. For Pearson correlation and linear regression analyses, DNA methylation M values that were not normally distributed were reflected and $\log_{10}$ transformed. The processing speed score was reflected and square-root transformed to accommodate the violation of normality. To explore the associations of processing speed and perceived cognitive function, and to identify potential covariates and significantly associated CpG sites with processing speed and perceived cognitive function, Pearson correlation analyses were conducted. The level of significance was set at $p < 0.05$ (two-tailed). Among the significantly associated CpG sites within each gene, multicollinearity was assessed with the variance inflation factor. To investigate the associations between DNA methylation of identified CpG sites as the predictor variable and processing speed and perceived cognitive function as the outcome variables, multiple linear regression was performed with adjustment for covariates, including age, years of education, cancer stage, and body mass index. To summarize the association between the outcome and the predictor, standardized coefficients (β) were reported.

Results

Sample Characteristics

Of the 153 participants in the parent study, 51 (33%) lacked DNA methylation data and were not included in this study. The characteristics of included and not included participants are summarized and reported in Table 1. The included participants (N = 102) were aged an average of 62.7 (SD = 7.99) years, and most were White (n = 90, 88%), diagnosed with stage I breast cancer (n = 64, 63%), and prescribed endocrine therapy (n = 96, 94%) but not chemotherapy (n = 84, 82%). They were highly educated, with a mean education of 16.3 (SD = 2.46) years, and had an average body mass index of 31.1 kg/m^2 (SD = 6.53). Participants' mean PAOFI total ($\bar{X}$ = 21.1, SD = 17.14) and subscale scores were calculated (sensorimotor: $\bar{X}$ = 2.9, SD = 3.15; memory: $\bar{X}$ = 8.6, SD = 6.36; language and communication: $\bar{X}$ = 5.8, SD = 5.37; and higher-level cognitive and intellectual functions: $\bar{X}$ = 3.8, SD = 4.58). Except for processing speed, which was higher ($p = 0.029$) in the included participants ($\bar{X}$ = 0.1, SD = 0.71), no other significant differences were detected between included and not included participants. Processing speed was not associated with the PAOFI total or subscale scores (see Table 2).

DNA Methylation Patterns, Processing Speed, and Perceived Cognitive Function Associations

The M values of CpG sites in the *BDNF* and *RASA2* genes and their associations with processing speed and PAOFI scores are reported online in Supplemental Tables 1 and 2. Except for cg10635145 of *BDNF* ($\bar{X}$ = 0.04, SD = 0.51, p = 0.477) and cg15870109 of *RASA2* ($\bar{X}$ = –0.01, SD = 0.18, p = 0.51), the mean M values of all CpG sites were different from zero, indicating that they were hypomethylated or hypermethylated.

The overall M value of *BDNF* was not associated with processing speed (r = 0.027, p = 0.784) or with the PAOFI total (r = 0.139, p = 0.16) and subscale scores (sensorimotor: r = 0.062, p = 0.539; memory: r = 0.13, p = 0.194; language and communication: r = 0.11, p = 0.271; higher-level cognitive and intellectual functions: r = 0.13, p = 0.192). Of 88 CpG sites of the *BDNF* gene, only cg21291635 was positively associated with processing speed (r = 0.251, p = 0.011), indicating that greater methylation of cg21291635 was associated with poorer processing speed. Cg20108357 (r = –0.356, p < 0.001) showed the largest association with the PAOFI total score, indicating that greater methylation of cg20108357 was associated with better perceived cognitive function.

The overall M value of the *RASA2* gene was not associated with processing speed (r = –0.031, p = 0.756) or PAOFI total (r = –0.057, p = 0.568) or subscale scores (sensorimotor: r = –0.161, p = 0.106; memory: r = –0.049, p = 0.623; language and communication: r = 0.019, p = 0.854; higher-level cognitive and intellectual

TABLE 3. Associations of M Values of Identified CpG Sites in *BDNF* and *RASA2* Genes With Processing Speed and PAOFI Total and Subscale Scores (N = 102)

CpG Site	B	95% CI	β	p	R^2	Adjusted R^2
Processing speed[a]						
BDNF						
cg21291635	0.349	[0.086, 0.612]	0.234*	0.01	0.262	0.224
RASA2						
cg20247102	0.408	[0.088, 0.728]	0.223*	0.013	0.259	0.22
PAOFI[b] total						
BDNF						
cg20108357	−1.246	[−1.954, −0.539]	−0.328**	< 0.001	0.171	0.128
cg06260077	1.063	[0.101, 2.026]	0.213*	0.031	0.11	0.064
cg23619332	0.932	[0.094, 1.77]	0.215*	0.03	0.111	0.064
cg03984780	0.672	[−0.061, 1.404]	0.182	0.072	0.097	0.05
cg15710245	1.266	[0.094, 2.438]	0.207*	0.035	0.108	0.062
cg25412831	1.251	[0.274, 2.228]	0.245*	0.013	0.124	0.079
cg22288103	0.845	[0.027, 1.662]	0.199*	0.043	0.105	0.058
RASA2						
cg04444195	0.95	[−0.439, 2.339]	0.143	0.178	0.083	0.035
cg00567892	−1.774	[−3.247, −0.3]	−0.23*	0.019	0.118	0.072
cg25221719	−1.207	[−2.929, 0.515]	−0.142	0.167	0.084	0.036
PAOFI[b] subscale: higher-level cognitive and intellectual functions						
BDNF						
cg20108357	−0.687	[−1.184, −0.191]	−0.258**	0.007	0.173	0.13
cg23619332	0.638	[0.062, 1.213]	0.209*	0.03	0.151	0.107
cg03984780	0.623	[0.127, 1.119]	0.241*	0.014	0.163	0.119
cg00298481	0.789	[0.025, 1.554]	0.198*	0.043	0.146	0.101
RASA2						
cg00567892	−1.13	[−2.146, −0.114]	−0.208*	0.03	0.152	0.107
PAOFI[b] subscale: language and communication						
BDNF						
cg20108357	−0.687	[−1.165, −0.209]	−0.276**	0.005	0.118	0.072
cg03984780	0.446	[−0.039, 0.932]	0.185	0.071	0.075	0.027
cg15462887	0.579	[−0.014, 1.173]	0.171	0.056	0.079	0.031
cg25156688	0.634	[0.145, 1.123]	0.255*	0.012	0.105	0.058
RASA2						
cg15870109	1.296	[−0.075, 2.666]	0.187	0.064	0.077	0.029
PAOFI[b] subscale: memory						
BDNF						
cg20108357	−0.833	[−1.286, −0.381]	−0.343**	< 0.001	0.174	0.131
cg06260077	0.776	[0.162, 1.39]	0.243*	0.014	0.117	0.071
cg25412831	0.972	[0.354, 1.59]	0.297**	0.002	0.145	0.101
cg06991510	−0.819	[−1.567, −0.07]	−0.211*	0.032	0.103	0.056

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TABLE 3. Associations of M Values of Identified CpG Sites in *BDNF* and *RASA2* Genes With Processing Speed and PAOFI Total and Subscale Scores (N = 102) *(Continued)*

CpG Site	B	95% CI	β	p	R^2	Adjusted R^2
PAOFI[b] subscale: memory *(continued)*						
BDNF (continued)						
cg15462887	0.596	[0.022, 1.17]	0.201*	0.042	0.099	0.052
cg06046431	0.799	[−0.114, 1.711]	0.178	0.086	0.087	0.04
RASA2						
cg00567892	−1.048	[−1.999, −0.096]	−0.212*	0.031	0.103	0.057
PAOFI[b] subscale: sensorimotor						
BDNF						
cg20108357	−0.417	[−0.828, −0.006]	−0.202*	0.047	0.057	0.008
cg23143371	−0.747	[−1.355, −0.139]	−0.242*	0.017	0.075	0.026
RASA2						
cg04444195	0.786	[0.019, 1.553]	0.217*	0.045	0.058	0.009
cg00567892	−0.853	[−1.682, −0.023]	−0.203*	0.044	0.058	0.009
cg21492365	−0.87	[−1.708, −0.033]	−0.207*	0.042	0.059	0.01
cg12254248	−0.876	[−1.613, −0.138]	−0.235*	0.02	0.071	0.023

* Correlation is significant at the 0.05 level (two-tailed); ** correlation is significant at the 0.01 level (two-tailed).
[a] Composite score; reflected and square-root transformed
[b] Square-root transformed
B—unstandardized coefficient; *BDNF*—brain-derived neurotrophic factor; CI—confidence interval; CpG—cytosine-phosphate-guanine; PAOFI—Patient's Assessment of Own Functioning Inventory; *RASA2*—RAS p21 protein activator 2
Note. Transformed variables were used for regression analysis.
Note. Adjusted for age, years of education, cancer stage, and body mass index

functions: r = −0.004, p = 0.968). Of the 37 CpG sites in the *RASA2* gene, only cg20247102 was positively associated with processing speed (r = 0.23, p = 0.02), indicating that greater methylation of cg20247102 was associated with poorer processing speed. Cg00567892 was negatively associated with all PAOFI scores except for the language and communication domain, indicating that greater methylation of cg00567892 was associated with better perceived cognitive function except in the language and communication subscale. Exploration of the DNA methylation levels of the identified CpG sites in the *BDNF* and *RASA2* genes for processing speed and PAOFI revealed no notable intraindividual multicollinearity.

CpG Site-Specific Regression Analysis

Multiple linear regression analysis for the associations of M values of the identified CpG sites in each gene with processing speed and PAOFI scores was performed, adjusting for age, years of education, cancer stage, and body mass index. The standardized regression coefficients (β) and variance explained (R^2) can be found in Table 3. For processing speed, significant associations were found with M values of cg21291635 in the *BDNF* gene (β = 0.234, p = 0.01, adjusted R^2 = 0.224) and of cg20247102 in the *RASA2* gene (β = 0.223, p = 0.013, adjusted R^2 = 0.22) in the full regression model controlling for covariates. Among the identified CpG sites in the *BDNF* gene, M values of cg20108357 remained significantly and negatively associated with the PAOFI total and all subscale scores with moderate to large effect sizes after covariate adjustment. Among the identified CpG sites in the *RASA2* gene, M values of cg00567892 remained significantly and negatively associated with the PAOFI total and all subscale scores except for the language and communication subscale score with moderate effect sizes after covariate adjustment. The full regression model explained a maximum of 12.8% of the variance in predicting the PAOFI total score and subscale scores.

Discussion

These findings suggest that some CpG sites for the *BDNF* and *RASA2* genes were associated with cognitive

function, but the direction of their association varied in postmenopausal women with early-stage breast cancer who were prescribed endocrine therapy. Although the levels of serum BDNF and RAS proteins have been associated with cognitive function (Cesarini et al., 2009; Chan et al., 2019), these findings further contribute to knowledge of its mechanism by demonstrating associations of DNA methylation patterns of the *BDNF* and *RASA2* genes with processing speed and perceived cognitive function. This exploratory study is one of the first to explore the DNA methylation of individual CpG sites of the two genes in the breast cancer context. This study suggests that different mechanisms may exist for processing speed and perceived cognitive function, potentially because of the expression of methylated CpG sites in different brain regions depending on the specific domains of cognitive function. In addition, different demographic, socioeconomic, or psychological confounding factors may influence the relationships of DNA methylation patterns with processing speed and perceived cognitive function.

BDNF is involved in neural cell creation, protection, and regulation, as well as synaptic plasticity (Erickson et al., 2010), and a higher plasma BDNF level was associated with better cognitive function (Komulainen et al., 2008; Lu et al., 2014), implicating its protective effects against cognitive decline. The current study indicates that greater methylation at cg21291635, which is potentially associated with lower *BDNF* expression, may correlate with poorer processing speed. This finding aligns with previous studies in patients with major depressive disorder (Ferrer et al., 2019), but this is the first it has been reported in a cancer context. Conversely, these findings linking greater methylation at cg20108357, which is possibly associated with lower *BDNF* expression, to better perceived cognitive function have not been reported in any population and require further exploration to provide broader insights into their effects.

RASA2 is involved in regulating cellular signaling, encompassing cell growth, migration, adhesion, structural maintenance, survival, and differentiation, through the RAS proteins (Rajalingam et al., 2007). RAS proteins are small guanosine triphosphatases that act as molecular switches, toggling between an active guanosine triphosphate–bound state and an inactive guanosine diphosphate–bound state, which triggers a series of intracellular events (Carnevale et al., 2022). The activation of RAS signaling is strictly regulated, and the RASA2 protein, a RAS guanosine triphosphate phosphatase–activating protein, is an inhibitory factor of RAS signaling (Rajalingam et al., 2007). Alteration of *RASA2* gene expression in the brain could influence cognition and the normal function of the *RASA2* gene. Greater methylation of cg20247102, likely associated with lower *RASA2* expression, may correlate with poorer processing speed; conversely, the more cg00567892 is methylated, likely associated with lower *RASA2* expression, the better the perceived cognitive function except for language and communication. These findings highlight the potential role of DNA methylation of the *RASA2* gene on cognitive function, an unexplored aspect of the gene in any other population, including patients with cancer.

Gene expression differs depending on where methylation occurs within the gene. Increased gene expression has been related to hypomethylation in promoter areas and hypermethylation in gene–body regions (Ball et al., 2009). Although the intron in the gene body is not directly involved in the synthesis of proteins, the methylation level of introns could affect gene expression. Hypomethylation of introns could enhance gene expression by stimulating alternative promoters to transcribe and reveal muted regulatory elements that may be easily detected (Lakshminarasimhan & Liang, 2016). In human tissues, hypermethylation of the first intron was related to a decrease in gene expression, likely because of its unique properties, such as closer distance to the transcription start site and enriched active chromatin marks (Anastasiadi et al., 2018).

Because *BDNF* protects against cognitive decline (Komulainen et al., 2008; Lu et al., 2014) and *RASA2* depletion may worsen it (Knowles et al., 2019), greater expression with hypomethylation of both genes may benefit cognitive function. Support for this relationship was found with lower methylation levels' correlation with better processing speed; however, additional interpretation is limited because of the lack of data for protein levels. The relationship was not found for self-reported cognitive functions, indicating that DNA methylation patterns may influence objectively measured and self-reported cognitive functions through likely distinct epigenetic mechanisms. This exploratory study highlights the role of epigenetic markers in understanding cognitive function, particularly in patients with cancer.

These findings bring new insight into the intricate associations between DNA methylation and cognitive function, which should be interpreted by taking potential confounding factors into account to discuss broader implications. These implications include the influence of cancer and cancer treatments, the

inherent complexity and temporal variabilities of methylation processes, and psychosocial factors such as fatigue, anxiety, and depression. In addition, the distinct constructs of perceived and objectively measured cognitive functions (Middleton et al., 2006) add another layer of complexity, potentially influencing the observed associations.

Cancer and its treatments may accelerate the normal aging process by altering DNA methylation patterns (Mandelblatt et al., 2013). Because DNA methylation is dynamic and can influence cognition or be influenced by the decline of cerebral function (Treble-Barna et al., 2023), additional research is required to determine the predictive role of DNA methylation on cognition. In addition, according to Middleton et al. (2006), perceived cognitive function is influenced more by emotional states including depression, anxiety, and fatigue (Middleton et al., 2006), whereas emotional states' effects on objective cognition are relatively lower or nonsignificant. The emotional states as predictors of perceived cognition have been consistently reported among patients with cancer (Almeria et al., 2020; Lycke et al., 2017; Srisurapanont et al., 2017). Age, education (Srisurapanont et al., 2017), lifetime cognitive activity, and physical activity (Wirth et al., 2014) were reported as predictors of objective cognition. DNA methylation patterns may influence cognition, but cancer, cancer treatments, emotional states, age, education, and lifestyle factors may moderate the influence. Because of the absence of universally accepted, clinically meaningful criteria for the extent of DNA methylation and cognitive change, this study's findings are inconclusive but suggest that the DNA methylation pattern is promising as a clinically predictive and prognostic biomarker for CRCD.

Limitations

This exploratory study has several limitations. First, the sample size for this analysis was limited to data that were available from the parent study, thus limiting the generalizability of the findings. Second, because of the cross-sectional design, it is not possible to draw causal inferences about the relationships between DNA methylation and cognitive function. Future studies with longitudinal designs are required to inform the detailed description of the relationship over time. Third, because this was an exploratory study with a hypothesis-generating purpose, no correction for multiple testing was performed, which could potentially inflate the risk of type I error. Additional studies with larger sample sizes are required to validate these findings and assess their reproducibility. In addition, one-third of the participants recruited for the parent study were not eligible, which could contribute to selection bias or limit the generalizability of these findings.

KNOWLEDGE TRANSLATION

- Cytosine-phosphate-guanine sites associated with objectively measured and self-reported cognitive function and the directions of association varied, potentially indicating two distinct epigenetic mechanisms.
- Within each gene, different methylation patterns of cytosine-phosphate-guanine sites were associated with different domains of perceived cognitive function.
- DNA methylation of the brain-derived neurotrophic factor and RAS p21 protein activator 2 genes may take potential roles in cognitive function in a cancer context.

Implications for Nursing

Understanding epigenetic mechanisms is crucial for oncology nurses because it directly affects their ability to manage and anticipate cognitive decline in patients. This knowledge not only aids in the early detection of patients at risk for CRCD but also enhances the development of personalized nursing interventions. As genomic data and biospecimens become increasingly accessible, it is important for nursing practices to incorporate this information to address specific symptoms associated with cancer treatments. This study highlights how epigenetic modifications, particularly DNA methylation, can influence cognitive function. Although not all methylation changes are reversible, nurses can advocate for and implement lifestyle interventions such as dietary improvements and exercise. These interventions may modify the epigenetic changes associated with alterations in these markers. Such proactive strategies are vital in managing CRCD, providing a strong foundation for nurses to apply this evolving science in everyday clinical settings and ultimately improving patient care outcomes.

Conclusion

To the authors' knowledge, this exploratory, hypothesis-generating study is among the first to explore the associations among DNA methylation of the *BDNF* and *RASA2* genes, processing speed, and perceived cognitive function in postmenopausal women with early-stage breast cancer who have been prescribed endocrine therapy. These findings underscore the variability in the associations between DNA

methylation and cognitive function and illuminate the possibility of distinct epigenetic mechanisms of processing speed and perceived cognitive function. They provide initial evidence linking these DNA methylation patterns to cognitive function. Additional longitudinal research with larger and more diverse samples is required to understand these associations and to identify individuals at higher risk for cognitive decline, guiding precision symptom management. In addition, given the complex and multidimensional nature of cognitive function and its various phenotypic manifestations, more comprehensive and targeted research is required to better understand the complex associations between DNA methylation and cognitive functions. These preliminary findings suggest that this strategy might identify patients at risk for cognitive decline in earlier stages and guide the development of targeted nursing interventions for CRCD.

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