

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

Myeong-ga Cho, MSN, RN, Susan M. Sereika, PhD, Meredith H. Cummings, BSN, RN, OCN®, Kirk I. Erickson, PhD, Catherine M. Bender, PhD, RN, FAAN, and Yvette P. Conley, FAAN, PhD

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