

# Association Between Genes in the Nuclear Factor E2–Related Factor 2 Antioxidative Response Elements Pathway and Cancer-Related Fatigue in Women With Early-Stage Breast Cancer

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**OBJECTIVES:** To explore genes in the nuclear factor E2–related factor 2 antioxidative response elements (Nrf2-ARE) signaling pathway using a multiomics approach for associations with variability of cancer-related fatigue (CRF) in postmenopausal women with early-stage hormone receptor-positive breast cancer.

**SAMPLE & SETTING:** Postmenopausal women (N = 116) with early-stage hormone receptor-positive breast cancer were recruited from western Pennsylvania.

**METHODS & VARIABLES:** Candidate genes from the Nrf2-ARE pathway were investigated for associations with CRF occurrence and severity. Associations were evaluated using logistic regression for occurrence and linear regression for severity.

**RESULTS:** The rs2706110 TT genotype in *NFE2L2* was associated with a 3.5-fold increase in odds of CRF occurrence. The cytosine-phosphate-guanine (CpG) site cg22820568 in *PRDX1* was associated with CRF occurrence and severity.

**IMPLICATIONS FOR NURSING:** Biomarkers based on Nrf2-ARE genes may help to identify women at increased risk for more severe CRF and to develop targeted interventions.

**KEYWORDS** antioxidants; breast neoplasms; DNA methylation; fatigue; polymorphism

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More than 3.8 million women in the United States are breast cancer survivors (Giaquinto et al., 2022). Cancer-related fatigue (CRF) is among the most common symptoms associated with breast cancer and its treatments (Berger et al., 2012; Mao et al., 2018; Sanft et al., 2023). One in four women with breast cancer will experience CRF at some point (Maass et al., 2021). The National Comprehensive Cancer Network defines CRF as “a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning” (Sanft et al., 2023, p. 797). CRF is different from general fatigue because it is not likely to improve with adequate rest, may be more severe, and is more likely to cause interference in daily activities (Berger et al., 2015). Patients with breast tumors report among the highest prevalence of moderate to severe CRF (Kang et al., 2023). A growing body of evidence suggests that early identification and treatment of CRF across the trajectory of cancer treatment may decrease its occurrence and severity (Bower et al., 2019). The burden associated with CRF includes interference with activity and physical functioning, inability to work (Schmidt et al., 2019) and socialize, greater financial stress, and increased healthcare utilization (Behringer et al., 2016). These effects result in decrements in quality of life (Bower et al., 2000). In addition, CRF is associated with worse disease trajectories and reductions in survival (Groenvold et al., 2007).