The Impact of Sex and Associations With Treatment Exposures on Neurocognitive Impairment in Pediatric Cancer Survivors: A report from the Childhood Cancer Survivor Study

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Abstract

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Objective. Sexual dimorphism in human brain structure and behavior is influenced by exposure to sex hormones during critical developmental periods. In children, cancer and cancer treatments may alter hormone activity and brain development, impacting neurocognitive functions.

Participants and Methods. Five-year survivors of childhood cancer (N=15,560) diagnosed at <21 years from 1970 to 1999, and 3,206 siblings from the Childhood Cancer Survivor Study completed the Neurocognitive Questionnaire (NCQ), a measure of self-reported task efficiency (TE), emotion regulation (ER), Organization, and working memory (WM). We compared rates of cognitive impairment (i.e., NCQ scores >90th percentile) in survivors and same-sex siblings, and sex differences in risk factors for cognitive impairment (i.e., treatment exposures, chronic health conditions (CHCs), cancer diagnosis, age at diagnosis) using modified Poisson regressions.

Results. Survivors were more likely to report cognitive impairment than same-sex siblings (Males: TE OR=2.3, p<.001; ER OR=1.7, p=.008; Organization OR=1.5, p=.04; WM OR=2.3, p<.001. Females: TE OR=2.6, p<.001; ER OR=1.9, p<.001; Organization OR=1.5, p=.02; WM OR=2.6, p<.001). Within survivors, females were more likely than males to report impairment in TE (OR=1.2, p=.001), ER (OR=1.5, p<.001), and WM (OR=1.2, p<.001). There were no sex differences in symptom severity in siblings (all ps>.05). Risk factors for cognitive impairment in survivors included cranial radiation dose (TE <20Gy OR=1.5, p=.008, ≥20Gy OR=2.5, p<.001; ER OR=1.5, p<.001; Organization <20 Gy OR=1.4, p<.001; < WM 20 Gy OR=1.8, p<.001, ≥20Gy OR=2.7, p<.001), presence of moderate to severe CHCs (TE 1 CHC OR=1.9, p<.001, >1 CHC OR=3.6, p<.001; ER 1 CHC OR=1.7, p<.001, >1 CHC OR=2.2, p<.001; Organization 1 CHC OR=1.5, p=.001, >1 CHC OR=2.5, p<.001; WM 1 CHC OR=1.8, p<.001, >1 CHC OR=4.1, p<.001). There were sex differences in cognitive impairment risk factors in survivors. In females, cranial radiation dose (<20 Gy TE OR=1.6, p=.02; ≥20Gy TE OR=1.4, p=.01), leukemia diagnosis (TE OR=1.4, p=.02), or diagnosis age between 3-5 years (WM OR=1.4, p=.02) conferred higher risk for cognitive impairment compared to males with the same history. Females diagnosed with Hodgkin's lymphoma (Organization OR=0.61, p=.05) or non-Hodgkin's

lymphoma (Organization OR=0.55, p=.03) were at lower risk for cognitive impairment compared to males.

Conclusions. We found sex-specific differences in rates of, and risk factors for, neurocognitive impairment, suggesting a sex vulnerability. Future studies examining interactions between sex hormones and treatment exposures during brain development will enable tailoring treatments follow-up interventions to ensure that quality of life is maximized.