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Title: Neurocognitive and psychosocial outcomes in survivors of childhood cancer treated in infancy compared those treated as older children or adolescents: a report from the Childhood Cancer Survivor Study (CCSS)

Background Infancy is a critical stage of development, attachment formation and milestone attainment. We hypothesized that survivors of childhood cancer diagnosed in infancy would be more vulnerable to impairment in neurocognitive and psychosocial outcomes compared to those diagnosed later in childhood.

Methods The CCSS was used to compare survivors diagnosed in infancy (<1 year old) to survivors diagnosed as toddlers (1-3 years), pre-school age (3-6), school age (6-11), early adolescence (11-15) and late adolescence (>15). Outcomes included neurocognitive function (CCSS Neurocognitive Questionnaire [task efficiency, emotional regulation, organization, memory]), emotional function (Brief Symptom Inventory-18 [depression, anxiety, somatization]), and health-related quality of life (HRQOL; Medical Outcomes SF-36 [4 mental and 4 physical scales]). Survivor reported chronic health conditions (CHC) using the Common Terminology Criteria for Adverse Events (v4.03) were grouped into none/low (grade 1 condition or less), medium (≥ 1 grade 2 and or 1 grade 3 condition)/high (≥ 2 grade 3 or 1 grade 4 and 1 grade 3 conditions) /severe (≥ 2 grade 4 or ≥ 2 grade 3 and 1 grade 4 conditions) accounting for frequency and grade of conditions. Unadjusted chi-square/exact chi-square tests evaluated comparison between age groups. Modified Poisson regression, adjusted for sex and current age, was used to assess outcome trends across diagnosis age groups and to conduct a subset analysis of the association between outcomes and CHC status.

Results Significant differences (p 's<0.001) were observed between diagnosis age group for all outcomes except emotional regulation ($P=0.75$). Survivors of infant cancer demonstrated the lowest frequency of impairment of all age groups in memory (15.3%), somatization (9.4%), general health (20.9%), physical functioning (10.1%), physical role functioning (14.1%), social role functioning (15.1%), vitality (18.8%) and pain (10.7%). There was an increasing deficit prevalence (P for trend <0.05) with increasing age at diagnosis for somatization (Relative risk[95%CI 1.11[1.07-1.51]), bodily pain (RR 1.10[1.07-1.13]) and similar results for all outcome measures except for task efficiency, emotional regulation, organization and anxiety. Medium/high/severe CHCs were prevalent across all age groups: infants 52.2%; toddler 57.7%; pre-school 56.4%; school age 63.2%; early adolescence 66.9%; late adolescence 72.4%. Survivors with medium/high/severe CHCs reported a greater degree of impairment for all outcome measures

compared to survivors with none/low CHCs across all age groups except infants in emotional regulation, depression, and anxiety outcomes.

Conclusions Infant cancer survivors have less neurocognitive impairment, emotional distress and superior HRQOL compared to older childhood cancer survivors. The presence of medium/high/severe chronic health conditions increased the prevalence of deficit in these domains across all age groups.