

Clinically Meaningful Symptoms in Adult Survivors of Childhood Cancer: A Comparison with the U.S. General Population Using the Modified Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

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Background: Symptom assessment for cancer survivors should prioritize prevalent and clinically meaningful symptoms. This study compared the prevalence of 140 symptoms between adult survivors of childhood cancer and the U.S. general population and identified those symptoms that healthcare providers (HCPs) considered clinically meaningful.

Methods: This cross-sectional study included 1,208 5-year adult survivors of childhood cancer from the Childhood Cancer Survivor Study, sampled to reflect SEER distributions by age, sex, and cancer diagnosis, and 1,356 community controls from the Slice panel, sampled to reflect National Health Interview Survey distributions by age, sex, and race/ethnicity. A total of 140 symptoms across 12 domains (cardiovascular, digestive, head/neck, musculoskeletal, sexual, cognitive/psychological, respiratory, neurological, urinary, metabolic, skin, general) were assessed, including 62 original and 18 modified from the PRO-CTCAE and 60 newly created via qualitative interviews with survivors. Survivors and controls were propensity-score-matched on personal socio-demographics (age at survey, sex, race/ethnicity, education, marital status, income, insurance, employment, living arrangement, smoking) and neighborhood adversity per the Social Vulnerability Index. Symptom prevalence was compared using multivariable logistic regression on the matched sample. In addition, 232 international HCPs (oncologists, primary care physicians, nurses) from 21 countries caring for childhood cancer survivors rated each symptom across three dimensions of clinical significance (survivorship relevance, clinical manageability, assessment importance). Each symptom was clinically meaningful if $\geq 50\%$ of HCPs endorsed it as highly (vs. slightly/moderately) relevant, manageable, and/or important.

Results: The mean $\pm$ SD attained age was 40.8 $\pm$ 10.3 years in survivors and 54.7 $\pm$ 15.7 years in controls; the mean $\pm$ SD time since diagnosis was 33.6 $\pm$ 8.0 years. Females comprised 57.0% of survivors and 54.1% of controls. Survivors reported a significantly higher prevalence of 26 symptoms vs. controls (odds ratios [ORs] range: 2.1-6.3; all $p < 0.05$). Of these symptoms, 12 were newly identified via qualitative interviews. The most prevalent symptoms spanned multiple domains, with prominence in cognitive/psychological, skin, and general domains. In addition, 55 symptoms were rated as clinically meaningful by HCPs, including 26 newly identified. Sixteen symptoms were both more prevalent in survivors and HCP-rated as clinically meaningful (e.g.,

pain, memory problems, hearing loss). Psychological symptoms that were more prevalent in survivors vs. controls and clinically meaningful included slow thinking (OR=6.1, 95%CI=3.0-12.7) and memory problems (OR=3.5, 95%CI=1.7-7.4); physical symptoms more prevalent in survivors included blurry vision (OR=3.3, 95%CI=1.5-7.1), hearing loss (OR=3.8, 95%CI=1.3-10.7), and hematuria (OR=5.8, 95%CI=1.4-23.6).

Conclusions: Adult survivors of childhood cancer experience a high prevalence of multidomain symptoms, many of which clinicians consider clinically meaningful but are not captured by standard tools such as the PRO-CTCAE (e.g., hematuria, slow thinking). This concordance between survivor reports and clinician ratings reveals important gaps in current symptom surveillance and underscores the need for a survivor-specific symptom assessment framework to enhance symptom detection and support person-centered survivorship care.