

**PREMATURE MENOPAUSE IN SURVIVORS OF CHILDHOOD AND ADOLESCENT
CANCER: DATA FROM THE CHILDHOOD CANCER SURVIVOR STUDY (CCSS)**

Charles Sklar, MD¹, Ann Mertens, PHD², Pauline Mitby, MS², John Whitton MS³, Marilyn Stovall, PHD⁴, Jean Mulder, MD⁵, Daniel Green, MD⁶, Stacy Nicholson, MD⁷, Yutaka Yasui, PHD³ and Leslie Robison, PHD². ¹Pediatrics, Memorial Sloan-Kettering Cancer Center, New York, NY; ²Pediatrics, University of Minnesota, Mpls, MN; ³Cancer Prevention Research Program, Fred Hutchinson Cancer Research Center, Seattle, Washington; ⁴Radiation Physics, University of Texas M.D. Anderson Cancer Center, Houston, TX; ⁵Medicine, Massachusetts General Hospital, Boston, MA; ⁶Pediatrics, Roswell Park Cancer Institute, Buffalo, NY and ⁷Pediatrics, Oregon Health Sciences University, Portland, OR.

Background: Female survivors of pediatric cancer are at low risk of developing ovarian (ov) failure during or immediately after cancer therapy. Nonetheless, female survivors are at increased risk for a premature menopause (PM) later in life. Data concerning the risk factors for a PM are limited.

Objective: To determine, in a large cohort of young adult survivors of pediatric cancer, the incidence of and risk factors for a PM.

Design/Methods: We determined menstrual status, age at menopause and cause of menopause (surgical vs non-surgical) in female participants in the CCSS (age \geq 18 yrs), a multi-site retrospective study of 5-yr survivors of childhood cancer. 2823 survivors were eligible. We excluded survivors with cessation of menses $<$ 5 yrs after diagnosis and hypothalamic-pituitary radiation (RT) $>$ 3000 cGy. Controls were 1074 siblings. PM defined as age $<$ 40 yrs at menopause

Results: Survivors were a median of 7 yrs (0-20) at diagnosis and a median of 29 yrs (18-50) at study. Non-surgical PM developed in 71 survivors a median of 31 yrs (19-39). The risk of menopause by age 40 yrs was 8%. Compared to siblings, the relative risk (RR) of PM in survivors was 14.5 (95% Confidence Interval [CI] 3.6-58.7, $p<$ 0.01). In a multivariate Poisson-regression model increasing age at follow-up, higher alkylating agent score, and increasing dose of ov RT were independent risk factors for PM.

Survivors treated with 1-99 cGy ov RT had a RR of PM of 3.5 (95% CI 1.5-9.6, $p<$ 0.01) and those treated with \geq 1000 cGy ov RT had a RR of PM of 16.7 (95% CI 5.6-52.7, $p<$ 0.001) compared to those treated with no ov RT. There was an interaction between a diagnosis of Hodgkin's disease (HD) and ov RT; HD survivors who did not receive ov RT had a RR of PM 7.6 (95% CI 1.0-40.7, $p=$ 0.022). Risk of surgical PM was similar between survivors and siblings (RR 0.8, 95% CI 0.5-1.3)

Conclusions: The data from this study provide important information that will facilitate counseling current survivors about their risk of PM over time.

Supported by NIH grants U24-CA55727 and R01 CA79024