

Premature Menopause in Survivors of Childhood Cancer

Female childhood cancer survivors (CCS) who retain ovarian function after completing cancer treatment are at increased risk of developing premature menopause, defined as cessation of menses before age 40 years. However, the data regarding premature menopause in female CCS are scanty, although particular attention should be also paid to other endocrine alterations, and neurocognitive and neurobehavioral problems.

Sklar and colleagues assessed the incidence of and risk factors for premature menopause in 2819 CCS females older than 18 years of age who continued to menstruate for at least 5 years after their cancer diagnosis. The group was composed of control participants in the multicenter Childhood Cancer Survivor Study (CCSS), including 1065 female siblings of participants in the CCSS. Female CCS patients who received more than 30 Gy of radiation to the brain and/or had a primary tumor in the region of the hypothalamus-pituitary gland (known to cause hypogonadotropic hypogonadism) were excluded. Of 2819 subjects, 1025 had leukemia, 404 Hodgkin's lymphomas, 324 bone tumors, 297 kidney tumors, 271 sarcomas, 207 neuroblastomas, 154 non-Hodgkin's lymphomas, and 137 brain tumors. The comparison group was 1065 female siblings of participants in the CCSS. A total of 126 CCS and 32 control siblings developed nonsurgical premature menopause. The cumulative incidence of nonsurgical premature menopause was higher for CCS than control siblings (8% vs 0.8%; RR=13.21, 95% CI=3.26 to 53.51; $P<0.001$). A multiple Poisson regression model showed that risk factors for nonsurgical premature menopause included attained age, exposure to increasing dose of radiation to the ovaries, increasing alkylating agent score (based on number of alkylating agents and cumulative dose), and a diagnosis of Hodgkin's lymphoma. For female CCS subjects who were treated with alkylating agents plus abdominopelvic radiation, the cumulative incidence of nonsurgical menopause approached 30%. The results of this study will facilitate counseling current female CCS about their future risk of premature menopause and aid in designing new regimens that seek to diminish late ovarian toxicity.

Sklar CA, Mertens AC, Mitby P, et al. Premature menopause in survivors of childhood cancer: a report from the childhood cancer survivor study. *J Natl Cancer Inst.* 2006;98:890-6.

Editor's Comment: *This is a very interesting observational study which provides important information for physicians who care for female CCS patients. Because survival rates of cancer patients have improved markedly in recent years, the long-term complications and late effects, such as endocrine impairments and neuropsychological problems, have become increasingly important even after many years following the conclusion of treatment. The interest in the late effects of ovarian function, especially of acute ovarian failure, premature menopause and fertility,*

has increased over time.

Acute ovarian failure (AOF), defined as never menstruating or premature menopause within 5 years of diagnosis of childhood cancer, is known to develop in female CCS. Chemaitilly et al¹ studied AOF in 3390 eligible female CCS in the CCSS. In this group, 215 patients (6.3%) developed AOF. Survivors who received cranial irradiation at doses of more than 30 Gy, those with hypothalamic/pituitary tumors, and survivors who underwent bilateral oophorectomy were excluded. Survivors with AOF were older at diagnosis and more likely to have been diagnosed with Hodgkin's lymphoma or to have received abdominal or pelvic radiotherapy than survivors without AOF. Among survivors with AOF, 116 (54%) had received at least 10 Gy ovarian irradiation. In a multivariable logistic regression model, increasing doses of ovarian irradiation, exposure to procarbazine, and exposure to cyclophosphamide at ages 13 to 20 years were independent risk factors for AOF.

Concerning premature menopause in CCS, Sklar and colleagues studied a total of 2819 subjects. Median age at cancer diagnosis was 7 years (range 0 to 20), and median age at study was 29 years (range 18 to 50), 69% of survivors had reached age 25 years, 47% reached age 30 years, 26% attained age 35 years, 10% were age 40 years, and 8% were older than 40 years of age. The results of their study indicated that the risk of developing nonsurgical premature menopause was 13-fold higher than that of siblings, with cumulative incidence of 8% by 40 years of age. The risk factors for nonsurgical premature menopause are: attained age, diagnosis of Hodgkin's lymphoma, and exposure to increasing doses of both alkylating agents and radiation to the ovaries.

Premature menopause and AOF leads to the early and often unexpected loss of reproduction potential as well as the cessation of ovarian sex hormone production. Thus, survivors who experience AOF or premature menopause are at increased risk of developing a variety of adverse health outcomes, including osteoporosis, cardiovascular disease, and psychosexual dysfunction.

Their results have confirmed that treatment of female childhood cancer is associated with a considerable risk of developing AOF and premature menopause. Therefore, it is necessary to inform young adult female CCS patients who are still menstruating, about the risk factors of premature menopause (ie, attained age, Hodgkin's lymphoma, chemotherapy with alkylating agents, and radiation to the ovaries) to facilitate family planning and timing of future pregnancies. It is also necessary for physicians as well as patients and family members to know that premature menopause can occur even after several years following childhood cancer treatment.

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Reference

1. Chemaitilly W, Mertens AC, Mitby P, et al. *J Clin Endocrinol Metab.* 2006;91:1723-8.