

REPRODUCTIVE ENDOCRINOLOGY

Childhood cancer treatment decreases fertility

Women who were treated for cancer during childhood or adolescence have a decreased chance of ever becoming pregnant. New findings suggest the decrease in fertility is greatest among those who received high doses of ovarian or hypothalamic–pituitary radiation or large cumulative doses of alkylating agents.

The potential adverse effects of radiotherapy and chemotherapy on germ-cell survival and functioning of the hypothalamic–pituitary–gonadal axis are well known. Previous studies that examined fertility in adult survivors of childhood cancer did not, however, include adequate numbers of participants and did not have enough data on the patients' exposure to chemotherapeutic agents and radiation to establish quantitative dose–response relationships between fertility and specific exposures.

Green and co-workers performed a retrospective analysis of data on female 5-year survivors of cancer during childhood or adolescence ($n = 5,149$) and their randomly selected sisters ($n = 1,441$) who participated in the Childhood Cancer Survivor Study. The investigators excluded individuals who underwent

surgical sterilization and analyzed all first pregnancies in participants (regardless of their marital status), including pregnancies that were terminated. Data on pregnancy outcomes and various lifestyle factors were obtained from self-administered questionnaires.

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Compared with their sisters, childhood cancer survivors had a significantly reduced likelihood of pregnancy (relative risk 0.81, 95% CI 0.73–0.90, $P < 0.001$) even after the data were adjusted for age at diagnosis, marital status, education and smoking. The lowest likelihood of ever becoming pregnant was found among childhood cancer survivors who received hypothalamic–pituitary radiation at a dose of ≥ 30 Gy or ovarian–uterine radiation at a dose of > 5 Gy. High cumulative doses of alkylating agents and treatment with lomustine or cyclophosphamide also decreased fertility.

“Our findings could be employed for pretreatment counseling of the patients and their parents regarding options for fertility preservation,” says Daniel M. Green (St Jude Children's Research Hospital, Memphis, TN, USA), lead investigator of the study. In addition, these results have important implications for pediatric cancer treatment protocols. Future studies should assess whether therapies that use reduced cumulative doses of radiation or chemotherapeutic agents and thus have a less harmful effect on patients' fertility have similar efficacy to standard doses.

Several new drugs of interest, such as ifosfamide, were used infrequently in the participants of this study, who were all diagnosed and treated between 1970 and 1986. “The cohort is being expanded to include [patients] diagnosed between 1986 and 2000, a period during which the use of ifosfamide increased substantially, so that we will be able to evaluate its impact on fertility,” says Green.

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Original article Green, D. M. *et al.* Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. *J. Clin. Oncol.* 27, 2677–2685 (2009).