No Risk of Genetic Disease in Childhood Cancer Survivors’ Offspring Found

Two recent publications suggest that childhood exposure to potentially mutagenic radiation and chemotherapy agents does not significantly increase the risk of congenital anomalies or genetic disease in the offspring of these patients.

The Childhood Cancer Survivor Study
Lisa Signorello, ScD, associate professor of medicine at Vanderbilt University Medical Center in Nashville, Tennessee; senior epidemiologist at the International Epidemiology Institute in Rockville, Maryland; and lead author of one of the studies said cancer survivors are often concerned about birth defects in their children and these results provide reassuring evidence that can be cited by clinicians.

The Childhood Cancer Survivor Study included 2755 participants aged younger than 21 years at their initial cancer diagnosis (J Clin Oncol [published online ahead of print December 12, 2011]. doi: 10.1200/JCO.2011.37.2938). The most common cancer diagnoses were leukemia or lymphoma, together accounting for 57% of cases. The data were collected from a baseline questionnaire and periodic follow-up questionnaires that included questions regarding pregnancy history and medical conditions of the participants’ children. The participants’ medical records were reviewed for complete details of their cancer treatment. The final analysis included 4699 children of 1128 male and 1627 female childhood cancer survivors. Congenital anomalies were defined as cytogenetic abnormalities such as Down syndrome, single-gene defects such as achondroplasia, and congenital malformations such as cleft lip.

Approximately 60% of participants had been exposed to radiotherapy and 47% had exposure to alkylating agents. No association between exposure to radiation or alkylating agents and the risk of congenital anomalies among the children was found. When comparing women exposed to radiation or alkylating agents with those exposed to neither, the prevalence of congenital anomalies was 3% versus 3.5% (P = .51) and in men the result was 1.9% versus 1.7% (P = .79). Further analysis revealed no association between congenital anomalies and radiation doses specifically to the ovaries or testes. Similarly, a higher dose of an alkylating agent was not associated with an increased risk of congenital anomalies.

The Danish Registry of Childhood Cancer Study
A second study identified 4676 childhood cancer survivors through the Danish Cancer Registry (J Clin Oncol [published online ahead of print November 28, 2011]. doi: 10.1200/JCO.2011.35.0504). Researchers used the Central Population Register and Medical Birth Register to identify all liveborn offspring and stillbirths. Among the 4676 survivors, 1474 had 2767 pregnancies that resulted in a liveborn singleton or stillbirth. From this fertility cohort, a sample of 472 survivors who had 1037 pregnancies that resulted in a live birth or stillbirth were included in the final analysis. The 472 survivors included a cohort of 100 survivors with affected children and 372 randomly selected survivors. Of the 372 randomly selected survivors, 327 did not have affected children and comprised the noncase subcohort. Forty-five of the randomly selected survivors did have affected children and were thus both case and subcohort members. Medical records of survivors were reviewed for details of cancer treatment. The cancer registry data were linked with national health databases for genetic diseases (defined as chromosomal abnormalities, congenital malformations, stillbirths, and neonatal deaths). Cancer was not considered a genetic disease, but information on cancer diagnosis before the age of 20 years in offspring was also collected.

Lisa Signorello, ScD, said cancer survivors are often concerned about birth defects in their children and these results provide reassuring evidence that can be cited by clinicians.
The risk of genetic disease in offspring was similar between irradiated and nonirradiated survivors. Also, no increased risk was seen among the offspring of survivors who had received alkylating agents versus those not receiving any chemotherapy or versus those not receiving chemotherapy or radiation; however, the numbers were small, as only 17 survivors in the analysis received alkylators.

There was a suggestion of an increased risk of genetic abnormalities in the offspring of mothers with higher radiation doses to the uterus; those with the highest uterine doses had a relative risk of 2.3, but this was not statistically significant. Furthermore, no association between ovarian or testicular radiation and genetic abnormalities was observed. Nine nonhereditary cancers (no cases of leukemia) were found in the offspring of 9 survivors; these cases showed no cancer pattern.

“Hopefully, the conclusion of these 2 studies will meet some of the reproductive concerns of childhood cancer survivors, geneticists, and pediatric oncologists. Our hope is that this information will be used by physicians in counseling childhood cancer survivors who desire and are able to have children,” says lead author, Jeanette Falck Winther, MD, head of research on childhood cancer survivorship at the Danish Cancer Society Research Center in Copenhagen, Denmark.

**Clinical Implications and Further Studies**

Melissa Hudson, MD, director of the cancer survivorship division at St. Jude Children’s Research Hospital in Memphis, Tennessee, says these studies are clinically relevant, as survivors are often concerned about the potential impact of cancer treatment on both their ability to have children and on their children’s health. “Study results indicate no increased risk of genetic diseases or congenital anomalies in offspring born to survivors of childhood cancer treated with mutagenic chemotherapy and gonadal radiation therapy,” she says.

An editorial accompanying the Danish study (*J Clin Oncol* [published online ahead of print November 28, 2011]. doi: 10.1200/JCO.2011.38.3877) noted that since about 70% of young people with cancer are still alive at 10 years after diagnosis, these studies are very relevant to the oncology team. “For survivors of cancer in childhood and adolescence, 2 important questions are frequently raised. First, will I be fertile, and second, if I have children will they be at increased risk for cancer themselves?” write the authors, W. Hamish B. Wallace of the Royal Hospital for Sick Children, Edinburgh, United Kingdom, and Hilary O. D. Critchley and Richard A. Anderson of the Queen’s Medical Research Institute at the University of Edinburgh.

Dr. Winther says the 2 studies overcame the major limitations of earlier studies by including larger cohorts and more detailed cancer treatment information such as gonadal radiation doses and drug treatments and dosage. “These studies were able to interpret the epidemiologic results for the selected outcomes in light of dose-response evaluations and concluded that preconception cancer treatment in childhood did not lead to transgenerational germ cell mutations that resulted in disease in the next generation,” she says.

Researchers from both studies are involved in the ongoing Genetic Consequences of Cancer Treatment study, which will include about 15,000 survivors of childhood and young adult cancer and evaluate rates of clinical genetic disease in their offspring. In addition, a subset of the population will have blood samples taken to identify specific abnormalities such as defects in DNA damage-response and repair genes and the potential for these to be inherited.

“Ongoing work from this research group involves sequencing the DNA of cancer families (parents and their offspring) to see if there is any evidence of treatment-induced damage on the molecular scale, even if no abnormalities are observed in the children,” Dr. Winther says. (More information on this study can be found at www.gcct.org.)

According to Dr. Signorello, even in the absence of a birth defect, inherited genetic damage could have implications for a child’s future health.

Dr. Hudson agrees. “It is possible that mutagenic therapy causes inherited mutations that are not at this point clinically recognized. Advances in genomic technologies will permit ongoing studies to directly evaluate the presence of genetic damage in germ cells that can be transmitted to offspring, but for now, these results are very reassuring for survivors who are considering family planning.”