# Childhood cancer survivor? What to expect when expecting

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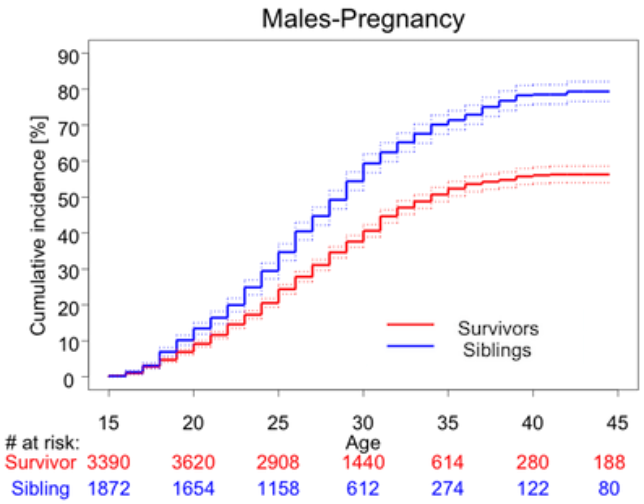


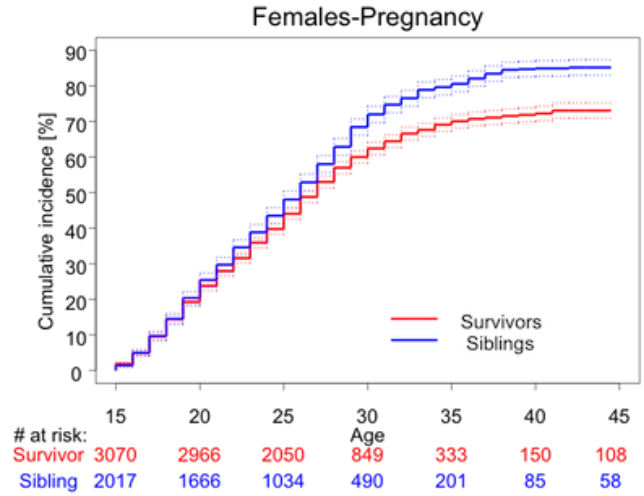


Cumulative incidence of first ever pregnancies in male and female cancer survivors and siblings. Incidence curves are shown with upper and lower 95% confidence intervals.

*Image provided by Dr. Eric Chow.*

The majority of children with cancer become long-term survivors. Among young adult survivors, questions about reproductive health poses as a leading concern. Previous studies have identified chemotherapeutic drugs, mainly alkylating drugs (e.g., cyclophosphamide), as being associated with reduced fertility in both sexes. However, little is known about the effects on reproductive outcomes from newer drugs, such as ifosfamide and similar DNA interstrand crosslinking drugs (e.g., cisplatin and carboplatin), in survivors of childhood cancer. To address this question Drs. Eric Chow, Wendy Leisenring, Kayla Stratton, and colleagues, aimed to establish the effects of contemporary

chemotherapy drugs on pregnancy in male and female survivors of childhood cancer not exposed to pelvic or cranial radiotherapy. The results from their study were recently published in *Lancet Oncology*.

Their analysis included data from a subset of the Childhood Cancer Survivor Study (CCSS) cohort, which followed 5-year survivors of the most common types of childhood cancer who were diagnosed before age 21 years and treated at 27 institutions in the USA and Canada between 1970 and 1999. They included 10,938 survivors and 3,949 siblings; siblings of survivors served as a comparison group. After a median follow-up of 8 years from cohort entry or at age 15 years, whichever was later, 4,149 (38%) survivors reported having or siring a pregnancy, of whom 3,453 (83%) individuals reported at least one live birth. After a median follow-up of 10 years, 2,445 (62%) siblings reported having or siring a pregnancy, of whom 2,201 (90%) individuals reported at least one live birth.

The investigators determined the doses of 14 alkylating and similar DNA interstrand crosslinking drugs from medical records. They then used sex-specific Cox models to establish the independent effects of each drug and the cumulative cyclophosphamide equivalent dose (CED, a dose devised to normalize alkylating agent exposure to units of a single drug) of all drugs in relation to pregnancies and live births occurring between ages 15 years and 44 years.

In both sexes, childhood survivors given chemotherapeutic drugs but not radiation therapy had a decreased likelihood of siring or having a pregnancy versus siblings (male survivors: hazard ratio [HR] 0.63, 95% CI 0.58– 0.68; female survivors: 0.87, 0.81– 0.94) or of having a live birth (male survivors: 0.63, 0.58– 0.69; female survivors: 0.82, 0.76– 0.89). In male survivors, reduced likelihood of siring a pregnancy was associated with higher doses of the following chemotherapy drugs: cyclophosphamide, ifosfamide, procarbazine, and cisplatin. CED in male survivors was significantly associated with a decreased likelihood of siring a pregnancy (per 5000 mg/m2 increments: HR 0.82, 0.79– 0.86). However, in female survivors, only busulfan and doses of lomustine equal to or greater than 411 mg/m2 were significantly associated with reduced pregnancy; CED was associated with risk only at the highest doses in analyses categorized by quartile (upper quartile vs. no exposure: HR 0.85, 0.74– 0.98. Results for live birth were similar to those for pregnancy.

"This is one of the largest studies on pregnancy and live birth among cancer survivors (of any age) who were not exposed to gonadal or cranial radiation." Dr. Chow elaborates, "importantly, it featured a broad range of chemotherapy agents in common use today, given at varying doses, which allowed us to establish more precise dose thresholds associated with reduced likelihood of pregnancy or live birth for male and female childhood cancer survivors. Our findings among male survivors included an association between risk and exposure to cisplatin, a finding not consistently reported among

childhood cancer survivors previously. We also found that female childhood cancer survivors who did not receive any radiotherapy to the pelvis or brain can be reassured that chemotherapy-specific effects generally appeared minimal in relation to these reproductive outcomes except when exposed to the highest cumulative doses."

Dr. Chow notes, "I think there is growing interest in this topic as a very important long-term quality of life issue for cancer survivors. In fact the Hutch just hosted a Pregnancy and Cancer symposium earlier this spring that was attended by multiple national experts in the field along with local researchers and patient/family advocates." As for future and ongoing research: "some of the work co-authors are engaged in include developing procedures for fertility preservation among prepubertal children (currently experimental), how to better disseminate fertility preservation practices relevant to pubertal and adult-aged patients at time of cancer diagnosis, and determining if there are superior biomarkers for ovarian reserve that can be used to better counsel women after cancer therapy regarding their family planning timeline. This is because as our research suggests, even if women treated with chemotherapy alone may have fairly good chances of achieving a pregnancy, their chances of doing so may diminish more quickly over time compared with their peers in the general population."

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Citation:

Chow EJ, Stratton KL, Leisenring WM, Oeffinger KC, Sklar CA, Donaldson SS, Ginsberg JP, Kenney LB, Levine JM, Robison LL, Shnorhavorian M, Stovall M, Armstrong GT, Green DM. 2016. Pregnancy after chemotherapy in male and female survivors of childhood cancer treated between 1970 and 1999: a report from the Childhood Cancer Survivor Study cohort. *Lancet Oncol*. 17(5):567-576.