Both childhood and adult cancer survivors are keenly interested in understanding the potential battery of long-term health effects related to their disease and treatment. Unfortunately, the potential hazards are many. For example, large numbers of cancer survivors are left permanently infertile by therapy-induced gonadal failure (1), heart disease is among the serious sequelae of anthracycline treatment and mediastinal radiotherapy (2), and subsequent malignancies related to chemotherapy and radiotherapy can arise in several organ systems (3). In this issue of the Journal, Stahl et al. (4) tackle another pressing health question for cancer survivors—might they somehow pass along genetic damage capable of causing adverse outcomes in their children? Among the outcomes studied in this investigation, including preterm birth, low birth weight, and size for gestational age, only major congenital abnormalities emerged as a potential outcome associated with a paternal cancer diagnosis. With a prevalence of 3.7% among the children of male cancer survivors and 3.2% for men without a history of cancer, the children of cancer survivors had a modest 17% relative increase in major congenital abnormalities (adjusted relative risk 1.17, 95% confidence interval 1.05 to 1.31).

In this article, we see excellent use of the nationwide registries from Denmark and Sweden. The medical histories of the over 1.75 million children included in the analysis could be linked back not only to the cancer status of their father but also to their mothers for whom data such as maternal age, parity, and even smoking behavior during pregnancy were available. Nevertheless, there are inherent shortcomings to the use of these registries to address the study hypotheses. An important one in this case is the limited treatment data available for the cancer survivors, which prevented more than educated guesses about the types and doses of exposures that were applied (a daunting task given the nearly 50-year span since the start of the cancer registries, a time period during which cancer treatment practices evolved substantially). Thus, some of the investigator-defined groupings of cancers are unlikely to reflect homogeneous treatment exposures, and dose-response cannot be evaluated. But aside from these shortcomings, the analyses do not tell a cogent story. For example, why would a paternal history of skin cancer have among the strongest associations with future risk of major congenital abnormalities, where a paternal history of testicular cancer, a prime suspect, shows no association? Also, chromosomal abnormalities are among the only outcomes showing an inverse association with paternal cancer history, against expectation when looking for germline damage. Further telling, for the male cancer survivors who used assisted reproductive technologies, an equal proportion (4.4%) of children conceived with cryopreserved pretreatment sperm and with post-treatment sperm had a major congenital abnormality. This subanalysis is an important one, and the investigators deserve kudos for retrieving these data from the fertility clinics.

For the issues noted above, it is difficult for Stahl et al., and for us, to tie their results to any specific DNA-damaging treatment exposure. The interpretation of their findings is further complicated because, as the investigators acknowledge, an association between paternal history of cancer and major congenital abnormalities in the offspring (and its implication of transmissible germline damage) defies nearly all relevant epidemiological evidence to date. There is virtually no evidence among the offspring of childhood cancer survivors [reviewed in (1)], atomic bomb survivors (5–7), or radiation-exposed workers.
(8,9) for an excess of cytogenetic syndromes, single gene disorders, or malformations that would indicate heritable genetic mutations, at least those recognizable in live births.

The study by Stahl et al. is restricted to males, and this is an appreciably simpler situation than studying offspring effects among female cancer survivors, in which an array of internal and external influences on the early developing fetus in utero can lead to a congenital abnormality. For males, the effect presumably derives solely from the sperm. Sperm is in fact damaged by the mutagenic therapies used for many cancers, resulting in abnormal numbers of chromosomes (aneuploidy) that underlie certain types of genetic disorders, most too rare to be well enumerated even in this large group of male cancer survivors (10–13). Although sperm DNA damage has been shown to persist for as long as two years posttreatment (10), for the most part, the effect seems to be transient with no apparent lasting damage to the spermatogonial stem cells (10–14). However, any defined period of genetically compromised sperm could provide a basis for an increased risk of congenital abnormalities. Stahl et al. did find a somewhat stronger association with major congenital abnormalities for children born within 2 years of their father’s diagnosis compared with those born later (relative risks of 1.27 and 1.16, respectively; although these estimates were non-statistically significantly different).

If the prevalence of major congenital abnormalities is slightly elevated among the offspring of male cancer survivors in Denmark and Sweden, what are the possible explanations aside from treatment? One is heightened surveillance for health problems in these children whose parents have had serious, sometimes inherited, disease. Heightened surveillance may also be the reason for the slightly higher likelihood of detecting a major congenital abnormality in children born within 2 years of their father’s cancer diagnosis. Could an association with major congenital abnormalities be related to the father’s cancer itself? Are there shared genetic propensities for both the cancer and congenital abnormality? This is theoretically possible [note the link between cancer of the central nervous system and neurofibromatosis (15,16)], but there seems little reason why such a signal would not have been picked up previously in studies of cancer survivors (1).

Current cumulative evidence leans heavily away from the probability that cancer treatment is associated with deleterious genetic damage to the living offspring (1,17). For important and understandable reasons, however, it is still reasonable to investigate this issue, as these patients undergo DNA-damaging treatments specifically meant to interfere with molecular processes, and we still do not know conclusively how sensitive or tolerant the human germ cell is to these mutagenic insults (17,18). Against this backdrop, male cancer survivors should note that the new findings by Stahl et al. (4) are overall quite reassuring.

References


