Genetic Factors Contribute to Subsequent Neoplasms in Survivors of Childhood Cancer

“Implementation of appropriate cancer surveillance and risk-reducing strategies may improve health outcomes among variant carriers and provide important information regarding risk for family members.”

–Carmen L. Wilson, PhD

Recent studies have suggested that between 7.5% and 10% of survivors of childhood cancer carry a pathogenic or likely pathogenic genetic variant that predisposes them to subsequent neoplasms (SNs). However, the number of survivors of childhood cancer in the United States who are likely at risk, and the overall burden of heritable risk in this population, has never been firmly established.

In a new study published in Pediatric Blood & Cancer (2020;67:e28047. doi:10.1002/pbc.28047), investigators created a virtual cohort of 10-year survivors of childhood cancer using data regarding incidence and survival for various types of childhood cancer from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program. They combined this information with results from analysis to detect germline mutations of cancer predisposition genes performed as part of the St. Jude Lifetime Cohort study. “This study is important because our findings estimate the size of a high-risk population who may benefit from intensified cancer surveillance, and whose family members may benefit from [genetic] counseling,” says study co-author Carmen L. Wilson, PhD, an assistant member (faculty) in the department of epidemiology and cancer control and the St. Jude Children’s Research Hospital Graduate School of Biomedical Sciences in Memphis, Tennessee.

According to the results from the 2010 Childhood Cancer Survivor Study reported in the Journal of the National Cancer Institute (2010; 102:1083-1095. doi:10.1093/jnci/djq238), within 30 years after their original cancer diagnosis, approximately 8% of survivors of childhood cancer will develop at least 1 SN, and their cancer risk during this period is 6 times higher than that among the general population.

Although researchers acknowledge that some of these SN cases are the result of radiotherapy and/or chemotherapy administered to treat the first cancer, it has long been suspected that germline genetic mutations also contribute to the elevated risk of SNs among survivors of childhood cancer.

Study Details

According to Dr. Wilson, the objective of the study was to estimate the number of survivors of childhood cancer residing in the United States with pathogenic or likely pathogenic cancer-predisposing germline genetic variants. To accomplish this, researchers used data from the St. Jude Lifetime Cohort study to identify the percentage of 10-year survivors of childhood cancer who carry a pathogenic or likely pathogenic variant in 1 of 156 known cancer predisposition genes.

Their next step was to extract demographic and clinical information from SEER for subjects aged 15 years and younger who were diagnosed with cancer between 1960 and 2006 and were alive 10 years after their diagnosis.

By applying the overall frequency of pathogenic or likely pathogenic germline mutations from among 156 cancer predisposition genes from the St. Jude Lifetime Cohort study to this virtual cohort of 10-year survivors created from the SEER data, investigators estimated that approximately 21,800 individuals...
who survived at least 10 years from a diagnosis of childhood cancer with 1 or more pathogenic or likely pathogenic variants currently are living in the United States. The largest subsets at genetic risk were survivors of central nervous system tumors, acute lymphoblastic leukemia, and retinoblastoma.

Specifically, the highest estimated numbers of variant carriers appear to be among survivors of central nervous system tumors. These included 1800 survivors of astrocytoma and 1700 survivors of other gliomas. Researchers also found 4300 variant carriers among survivors of acute lymphoblastic leukemia and 3500 among survivors of retinoblastoma. The genes whose cancer predisposition variants were noted most frequently were \(RB1\) (3000 carriers), \(NF1\) (2300 carriers), and \(BRCA2\) (800 carriers).

The researchers were not surprised that the most frequently mutated genes noted among surviving childhood cancer patients included \(RB1\), \(NF1\), and \(TP53\) because these genes have well-established links with childhood cancers. “However, an important finding from this study is that \(BRCA2\) and \(BRCA1\), which are not generally considered to predispose to childhood cancer, were included among the most frequently mutated cancer predisposition genes,” says Dr. Wilson. “Although it remains unknown whether these unexpected variants are causal for the primary childhood cancer or a subsequent neoplasm, or simply incidental findings, knowledge of their status has important implications for cancer surveillance and preventive interventions for these individuals.”

### Study Implications

“Having estimates of the total number of survivors with a pathogenic or likely pathogenic variant provides an important context for consideration of the potential demands on health care providers and services relative to genetic counseling and surveillance, as well as the broader public health perspective,” Dr. Wilson says. “Implementation of appropriate cancer surveillance and risk-reducing strategies may improve health outcomes among variant carriers and provide important information regarding risk for family members.”

Emily Tonorezos, MD, MPH, a general internist at Memorial Sloan Kettering Cancer Center in New York City, who was not involved in the study, agrees that it is important to realize that a heritable predisposition to cancer is common among survivors of childhood cancer for several reasons. “Most importantly, quantification of the absolute burden of cancer predisposition for childhood cancer survivors informs policy, research, and health care delivery,” she says. “This should be a crucial part of decision making [for legislators and organizations that fund cancer research].”

Dr. Tonorezos, an associate member in the Memorial Sloan Kettering Cancer Center program for the care of adult survivors of childhood cancer, recommends that clinicians prioritize the early detection of SNs for these patients, incorporate knowledge of a cancer predisposition variant when choosing treatments for patients with SNs, and offer preventive measures. “Also, siblings and other family members may be offered counseling and testing for the identified variant,” she says.

Dr. Wilson notes that further studies are needed to assess the feasibility and usefulness of genetic counseling and testing programs to improve the identification of survivors who are variant carriers, as well as the effects of appropriate cancer surveillance and risk-reducing strategies on health outcomes among this high-risk population. “It will be important to develop and fund interventions to promote genetic counseling and testing, to detect and prevent subsequent neoplasms, and to help childhood cancer survivors achieve wellness.”

For clinicians looking for guidance, Dr. Tonorezos suggests identifying an established clinical genetics service that offers counseling and testing for survivors of childhood cancer. “Typically, untrained providers should not initiate genetics services.”

doi: 10.3322/caac.21603