Mortality Risk of Second Malignancies in Childhood Cancer Survivors

BY CATLIN NALLEY

A team of researchers showed that long-term childhood cancer survivors who carry cancer-predisposing genetic variants are at an increased risk of mortality from subsequent malignant neoplasms. These findings, which were recently published in *The Lancet Oncology*, underscore the importance of genetic counseling and testing for these patients (2023; doi:10.1016/S1470-2045(23)00403-5).

"This is the first comprehensive study looking for the genetic reason for late mortality, specifically late mortality due to second cancers," said senior corresponding author Zhaoming Wang, PhD, Faculty at the St. Jude Department of Epidemiology and Cancer Control. "Now we know that cancer-predisposing variants contribute to the risk of death from second cancer."

These findings support the use of genetic counseling and clinical genetic testing for cancer predisposing variants to identify individuals at an increased risk, as well as the implementation of "early personalized cancer surveillance and prevention strategies" that could reduce the mortality burden associated with subsequent malignant neoplasms in this patient population, according to Wang and colleagues.

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"Our study pinpoints that clinical genetic testing to screen for and identify if survivors are carriers of these pathogenic variants could lead to early interventions for those at higher risk to develop deadly second cancers, potentially saving their lives," Wang emphasized. "Even before finishing childhood cancer treatment, clinicians can recommend a referral to genetic counseling so that survivors with these variants can seek cancer prevention strategies later on. Depending on the gene harboring the variant, survivors who are carriers may be able to implement prevention strategies to safeguard their long-term health."

Study Methodology

Subsequent cancers are the leading cause of late mortality (death beyond 5 years from childhood cancer diagnosis), according to Wang. "We previously reported the genetic risk for developing subsequent cancers and we wondered if the same genetic factors also confer the increased risk of subsequent cancer-related death."

Delving deeper in this area of study, the researchers initiated the current analysis, which included data from two retrospective cohort studies: St Jude Lifetime Cohort (SJLIFE; NCT00760656) and the Childhood Cancer Survivor Study (CCSS; NCT0112035). The researchers conducted prospective follow-up of long-term childhood cancer survivors who had corresponding germline whole-genome or whole-exome sequencing data.

An ongoing cohort study, SJLIFE enrolls patients who are alive at least 5 years following a childhood cancer diagnosis. Eligible patients were diagnosed and treated at St. Jude's Children's Research Hospital in Memphis, Tennessee, from 1962 to 2012. Participants undergo periodic comprehensive clinical assessments.

In CCSS, participants include childhood cancer survivors who are alive at least 5 years after diagnosis. The study involves two cohorts: patients diagnosed between 1970 and 1986 (the original CCSS cohort) and between 1987 and 1999 (the expansion CCSS cohort) at one of 31 participating institutions in the U.S. and Canada. Periodic self-reported outcomes are provided.

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To avoid data duplication, patients enrolled in both studies were excluded from the CCSS set in the current analysis. Demographic characteristics were assessed in both studies via self-report or proxy-report questionnaires, according to the investigators.

"Cancer predisposing variants affecting 60 genes associated with well-established autosomal-dominant cancer predisposition syndromes were characterized," stated Wang and colleagues. "Subsequent malignant neoplasms were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 with modifications.

"Cause-specific late mortality was based on linkage with the U.S. National Death Index and systematic cohort follow-up," they explained. "Fine-Gray subdistribution hazard models were used to estimate subsequent malignant neoplasm-related late mortality starting from the first biospecimen collection, treating non-subsequent malignant neoplasm-related deaths as a competing risk [and] adjusting for genetic ancestry, sex, age at diagnosis, and cancer treatment exposures."

Research Findings

The current study included 12,469 patients—6,172 male and 6,297 female. Of these, 4,402 were from the SJLIFE cohort with a median follow-up time of 7.4 years since the collection of the first biospecimen. There were 8,067 participants from the CCSS cohort and the median follow-up time since collection of the first biospecimen was 12.6 years.

Among patients in the SJLIFE group, 2,090 (47.5%) were female, 2,312 (52.3%) were male, 3,463 (78.7%) were non-Hispanic White, and 700 (15.9%) were non-Hispanic Black. Comparatively, the CCSS cohort included 4,207 (52.2%) female patients and 3,860 (47.8%) male patients. The majority of CCSS participants (85.2%) were non-Hispanic White.

Data revealed that 641 study participants (5.1%)—294 (6.7%) in the SJLIFE cohort and 347 (4.3%) in the CCSS cohort—carried cancer-predisposing variants, according to the study authors, who also reported that 1,157 participants developed subsequent malignant neoplasms (298 in SJLIFE and 859 in CCSS). Of those, 83 carried a cancer-predisposing variant.

"Cancer predisposing variant status was significantly associated with an increased severity of subsequent malignant neoplasms (CTCAE: Grade ≥4 vs. Grade <4; OR: 2.15; 95% CI: 1.18-4.19, p=0.0085) in the combined cohort, whereas there was no statistically significant difference in severity of subsequent malignant neoplasms between carriers and non-carriers when assessed within each cohort," Wang and colleagues outlined in their recent paper.

Breast (21.5%) and thyroid cancers (19.3%) were the most commonly diagnosed subsequent malignant neoplasms, according to the researchers, who also noted that "distribution of types of subsequent malignant neoplasm differed by cancer-predisposing variant carrier status in both SJLIFE and CCSS cohorts."

A total of 263 subsequent neoplasm-related deaths occurred. Of those, 44 were in the SJLIFE patient cohort and 219 in the CCSS group. "There was substantial variation in the types of subsequent malignant neoplasm associated with related deaths, with the most common type of subsequent malignant neoplasm resulting in death being CNS tumors (47 [17.9%] of 263 deaths)," Wang and team reported.

"Including 426 other-cause deaths (103 in SJLIFE and 323 in CCSS) and 76 unknown-cause deaths (27 in SJLIFE and 49 in CCSS), 174 par-

ticipants died in the SJLIFE cohort (median age at death: 44.9 years) and 591 participants died in the CCSS cohort (43.9 years)," they noted. "Although, notably, the duration of follow-up in SJLIFE was shorter and participants were younger at censoring than in CCSS."

Additionally, the analysis showed that the cumulative subsequent malignant neoplasm-related mortality at 10 years after the first biospecimen collection in carriers of cancer-predisposing variants was 3.7 percent in the SJLIFE cohort and 6.9 percent in CCSS patients. Comparatively, it was 1.5 percent and 2.1 percent among non-carriers in the SJLIFE and CCSS groups, respectively.

The investigators determined that the "same germline genetic risk factors (pathogenic or probable pathogenic genetic variants in 60 cancer-related genes) explained the increased risk of developing subsequent cancers also confer elevated risk for the subsequent cancer-related death," Wang said. "We found that carriers of genetic risk factors were more likely to develop severe or deadly subsequent cancer than non-carriers."

This research provides new insights about the contribution of genetic factors to survivors' future risk for cancer and cancer-related outcomes, specifically, the development of subsequent malignant cancers and death from subsequent malignant cancers, according to Wang.

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>
> *—Zhaoming Wang, PhD, at St. Jude Department of Epidemiology and Cancer Control*

"Our findings suggest that genetically driven cancers are likely to have poor prognosis for childhood cancer survivors and it remains to be validated/refuted by future studies to tell if it is a generalizable conclusion," he noted.

Potential Limitations

Wang and colleagues acknowledged this research does come with limitations. "First," they explained, "whole-genome sequencing and whole-exome sequencing data were available only for study participants who were alive at the first biospecimen collection, which can be variable with respect to follow-up length after cohort entry (5 years from childhood cancer diagnosis); [it] might not represent all participants who survived for 5 years and potentially impose bias; and cancer-predisposing variants associated with an increased risk of early mortality (e.g., relapse of a childhood cancer or subsequent acute myeloid leukemia) might be under-represented."

Additionally, while the post-hoc specific treatment-stratified analysis suggested there were different genetic effects within different treatment groups, the researchers were limited by the genetic heterogeneity and small sample size.

Lastly, the higher cumulative incidence of subsequent malignant neoplasm-related mortality among carriers in the CCSS cohort versus SJLIFE cohort could be explained, in part, by the older age of CCSS participants, according to Wang and colleagues.

Significance & Next Steps

The new knowledge gained from this study has the potential to enhance identification of subgroups with high-risk—intense monitoring and early intervention—or low-risk—reduced monitoring needs—for subsequent cancers among long-term survivors of childhood cancer, Wang told *Oncology Times*.

"We have combined all the available data sources to be able to statistically address the scientific question because: 1) only a small percentage of childhood cancer survivors who carry the pathogenic or probable pathogenic genetic variants, and 2) the total death events and particularly the subsequent cancer-related death events are small," he said. "There is no new data generation for this study, but we were able to achieve this major finding by combining existing data (more than 12,000 survivors). This is what I feel very proud of making a bold assumption and then taking action on the data analysis."

When discussing next steps, Wang noted, "We will expand to consider other important genes, for example, DNA repair genes. We will look into the genetic contributions to excess deaths due to other chronic health conditions, for example, cardiac outcomes, among survivors of childhood cancer." OT

Catlin Nalley is a contributing writer.

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to

1. Discuss the relationship between cancer predisposing genetic variants and the development of subsequent malignant neoplasms and associated late mortality among long-term childhood cancer survivors.

2. Analyze the significance of these study findings.

Disclosure: All authors, faculty, staff, and planners have no relevant financial relationships with any ineligible organizations regarding this educational activity.