Identifying survivors at high risk of secondary cancers

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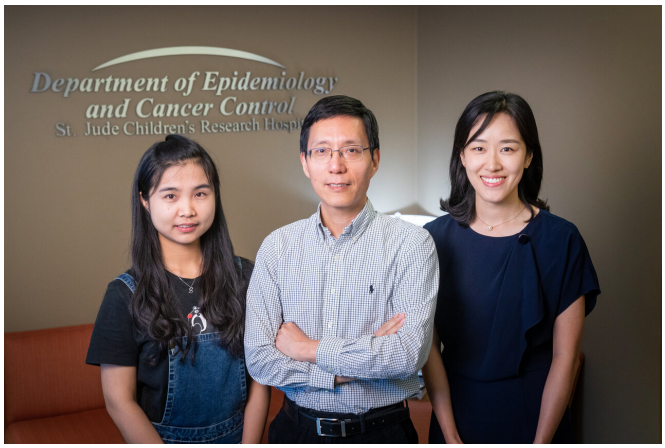

Left to right: Nan Qi, PhD, Zhaoming Wang, Ph.D., of St. Jude, and Nan Song, Ph.D., of the St. Jude Department of Epidemiology and Cancer Control. Credit: St. Jude

Scientists at St. Jude Children's Research Hospital are studying the combined effect of cancer treatments and inherited mutations in DNA-repair genes. Their results may help predict which survivors are at increased risk of another cancer. The work appears as an advance online publication today in the *Journal of Clinical Oncology*.

Childhood cancer survivors experience a substantial burden of long-term chronic health conditions, including a high rate of secondary cancers. The development of secondary cancers among survivors can be therapy-related, but inherited mutations can also play a role.

"Our study is one of the largest and most in-depth looking at the combined effects of therapy and inherited genetics," said corresponding author Zhaoming Wang, Ph.D., of the St. Jude departments of Epidemiology and Cancer Control and Computational Biology. "We were particularly interested in mutations involved in DNA repair, which play a role in how the body responds to and remediates DNA damage caused by cancer treatments."

Clues in the data

The team performed whole genome sequencing on DNA from blood samples to evaluate 127 genes from six DNA-repair pathways. The data were compared to clinical records detailing the cumulative doses of chemotherapy and maximum dose of region-specific radiotherapy given to the patients.

"We identified mutations affecting specific types of DNA-repair mechanisms, which combined with certain intensities of therapies, could dramatically increase the risk of developing subsequent cancers like breast cancer, sarcoma and thyroid cancer," said co-first author Na Qin, Ph.D., of St. Jude Epidemiology and Cancer Control.

The team looked at the records of 4,402 pediatric cancer survivors. Of those survivors, 495 individuals developed 1,269 secondary cancers. The team identified 538 germline mutations in 98 DNA-repair genes including POLG, MUTYH, ERCC2 and BRCA2.

"These data truly reflect how inherited mutations in DNA-repair genes and cancer therapy can have a combined effect, increasing significantly the risk of developing another cancer later in life," said co-senior author Yutaka Yasui, Ph.D., of St. Jude Epidemiology and Cancer Control.

Protecting the health of childhood cancer survivors

The work relied on whole genome sequencing of DNA from blood samples gathered through the St. Jude Lifetime Cohort study (St. Jude LIFE). The team in St. Jude LIFE brings long-term childhood cancer survivors back to the hospital for regular

health screenings throughout their adult lives.

Findings from St. Jude LIFE help childhood cancer survivors learn more about their health needs, while providing novel insights into the late effects of childhood cancer treatment.

"A more precise ability to identify survivors at high risk of subsequent cancers may help facilitate access to genetic counseling and testing, which can inform personalized cancer surveillance and prevention strategies," said co-senior author Leslie Robison, Ph.D., St. Jude Department of Epidemiology and Cancer Control chair.

The genomic data generated through St. Jude LIFE is freely available to researchers on the St. Jude Cloud platform, a data-sharing resource available to the research community worldwide.

"St. Jude Cloud is one of the world's largest repositories of pediatric genomics data and offers a suite of unique analysis tools and visualizations," said co-senior author Jinghui Zhang, Ph.D., St. Jude Department of Computational Biology chair. "By making these tools available to researchers around the world, we hope to accelerate the pace of research into pediatric cancer."

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