Predicting Future Heart Failure in Survivors of Childhood Cancer

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JM Kocarnik

There are more than 400,000 childhood cancer survivors living in the United States today. Cardiovascular disease is one of the main contributors to morbidity and mortality in this population, as survivors are at a significantly increased risk of cardiomyopathy leading to congestive heart failure (CHF). Risk scores which predict individual risk of future cardiovascular disease could help identify those at highest risk, and steer those individuals towards earlier screening and treatment. While such scores have been created for older adults, they have not been developed for this high-risk group. In a recent report in the *Journal of Clinical Oncology*, Drs. Eric Chow and Norman Breslow in the Public Health Sciences and Clinical Research Divisions developed a model that can predict the risk of subsequent heart failure among childhood cancer survivors.

To build these risk models, the authors utilized data from the Childhood Cancer Survivor Study, which follows childhood cancer survivors over time to identify any long term outcomes that might result from their cancer or treatment history. For this study they observed over 13,000 survivors through the age of 40 years for the development of heart failure, defined as heart failure leading to death or requiring medications or heart transplantation. 4,000 siblings of the cancer survivors were also followed over time, which helped establish the baseline population risk of heart failure for comparison. "We took readily available clinical information such as age, sex, and exposure to radiation and certain chemotherapy agents that one should have recorded as elements of a standard cancer survivor treatment summary/care plan," said lead author Dr. Chow. Together, this data provided a rich resource for building a risk prediction model from historical records.

The authors developed their risk score by evaluating the relationship between CHF and various selected exposures. Age at diagnosis, sex, chemotherapy (anthracycline), and radiotherapy were significantly associated with CHF. Regression estimates from these variables were converted into integer values that could then be added together and assigned to low, moderate, high, and very high risk group categories. These risk groups separated individuals into groups with substantially different risks of CHF by age 40 (see figure). For the group predicted at low risk, the cumulative incidence of CHF was not significantly elevated compared to that of the siblings (0.5 vs. 0.3 percent by age 40), while the cumulative incidence of CHF was considerably higher for the "very high" risk group (greater than 20 percent by age 40).

The risk model showed good performance when applied to the Childhood Cancer Survivor Study data, with an area under the curve of 0.74, and was then tested in other studies to validate its performance. "Obtaining the collaboration of multiple investigators from other large childhood cancer survivor cohorts was critical in helping us validate our prediction models," said Dr. Chow. "These included other investigators from the Hutch (i.e. Norm Breslow of the National Wilms Tumor Study), and those from St. Jude Children's Research Hospital and from the Netherlands." The risk models showed generally similar prediction ability in these independent validation studies (areas under the curve of 0.68 to 0.82), demonstrating the broader applicability of the model.

To make the risk score easily accessible, the authors created a website form (link below) that easily calculates an individual risk. This form requires entering only a few pieces of information, each of which should be readily available to clinicians soon after completion of childhood cancer therapy. This risk assessment can then be utilized for personalizing future screening strategies and interventions. Such an assessment could be useful not only for pinpointing those at high risk who may benefit from earlier detection and intervention, but also for identifying those at low risk who might only require standard surveillance.

Moving forward, the authors are working to make the model even more robust. "While the paper's risk score of around 0.75 is reasonably good, it can still be improved," explains Dr. Chow. "We are more deeply examining the influence and utility of incorporating conventional risk factors such as hypertension, dyslipidemia, and diabetes into the model. We are also developing similar models to predict risk of ischemic heart disease and stroke after childhood cancer as well."

Link to online risk calculator: ccss.stjude.org/chfcalc

Chow EJ, Chen Y, Kremer LC, Breslow NE, Hudson MM, Armstrong GT, Border WL, Feijen EA, Green DM, Meacham LR, Meeske KA, Mulrooney DA, Ness KK, Oeffinger KC, Sklar CA, Stovall M, van der Pal HJ, Weathers RE, Robison LL, Yasui Y. 2014. Individual prediction of heart failure among childhood cancer survivors. *J Clin Oncol*. pii: JCO.2014.56.1373. [Epub ahead of print]

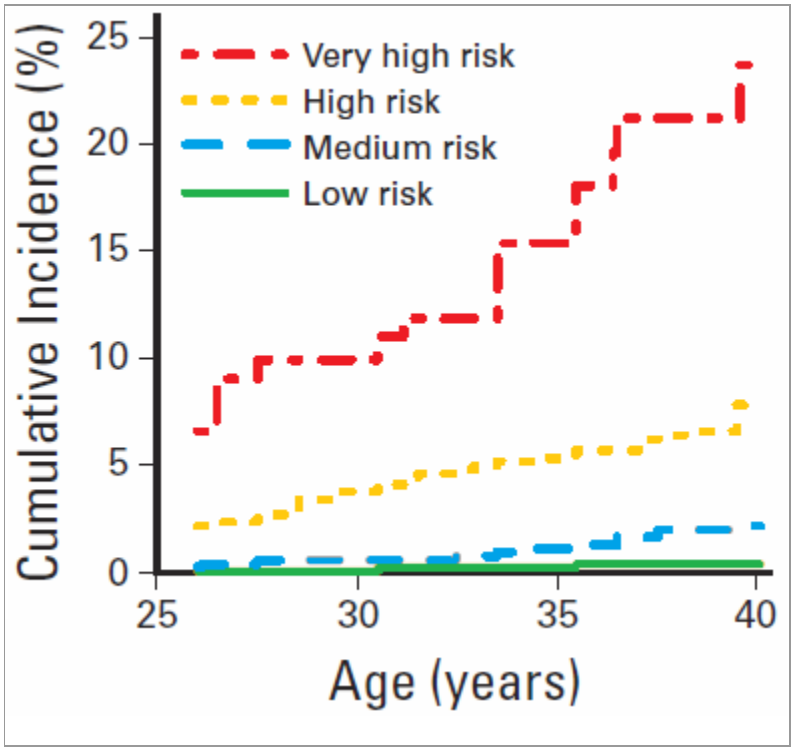

Image provided by Dr. Eric Chow

Cumulative incidence of congestive heart failure among childhood cancer survivors, grouped by a risk score accounting for sex, age at cancer diagnosis, chemotherapy (anthracycline) dose, and chest radiotherapy dose.