JACC: CARDIOONCOLOGY VOL. 3, NO. 1, 2021

EDITORIAL COMMENT

Predicting Risk of Hypertension Among Childhood Cancer Survivors

A Polygenic Score to the Rescue?*

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Childhood cancer survivors suffer from substantially increased risk of cardiovascular disease as they transition into adulthood, in part due to their increased rates of hypertension (1). Observational studies have indicated that: 1) childhood cancer survivors are diagnosed with hypertension at rates 2- to 3-fold higher than the general population; 2) hypertension is a leading risk factor for cardiovascular disease among childhood cancer survivors, associated with an up to 10-fold increased risk; and 3) cardiovascular risk associated with radiotherapy is amplified in the presence of hypertension (1,2).

Despite substantially increased rates, not all childhood cancer survivors go on to develop hypertension. Because blood pressure is known to have an important inherited component, one hypothesis is that childhood cancer therapies selectively unmask hypertension in those patients with a genetic predisposition. Such gene-environment interactions have recently been demonstrated across a range of disease conditions, including alcohol intake preferentially leading to cardiomyopathy or cirrhosis in individuals with the highest inherited risk (3,4) and COVID-19 infection leading to critical illness in those with certain genetic risk profiles (5).

In this issue of *JACC: CardioOncology*, Sapkota et al. (6) study 7,995 participants from 3 childhood cancer survivor cohorts to test: 1) whether rates of hypertension vary according to genetic risk; and 2) whether this risk is amplified in the context of 2 known risk factors—obesity and cancer therapy.

To quantify genetic risk of hypertension in each participant, Sapkota et al. (6) used a previously published "polygenic score," a quantitative tool that captures the cumulative effects of common DNA variants on disease risk (7,8). A prior paper studied the relationship of 7.1 million common variants with blood pressure traits in up to 757,601 individuals using a "genome-wide association study" approach, identifying 901 DNA variants that impact blood pressure (9). Importantly, none of the associated variants individually accounted for a significant proportion of the observed variability, with effect sizes ranging from 0.05 to 1.10 mm Hg. Obtaining meaningful ability to predict the risk of hypertension thus requires aggregating information into a single score, where the numbers of risk-increasing variants in each person are counted and weighted by their impact on blood pressure. This score was previously validated to predict both blood pressure and risk of hypertension in participants of the U.K. Biobank prospective cohort study, with an average systolic blood pressure ranging from 134 to 147 mm Hg and a more than 3-fold gradient in odds of hypertension noted across deciles of the polygenic score (9).

In the present study, Sapkota et al. (6) investigated the relationship of the polygenic score with the risk of hypertension in 3 cohorts of childhood cancer survivors, with trajectories of hypertension occurrence studied into young adulthood (median age at last

*Editorials published in *JACC: CardioOncology* reflect the views of the author and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

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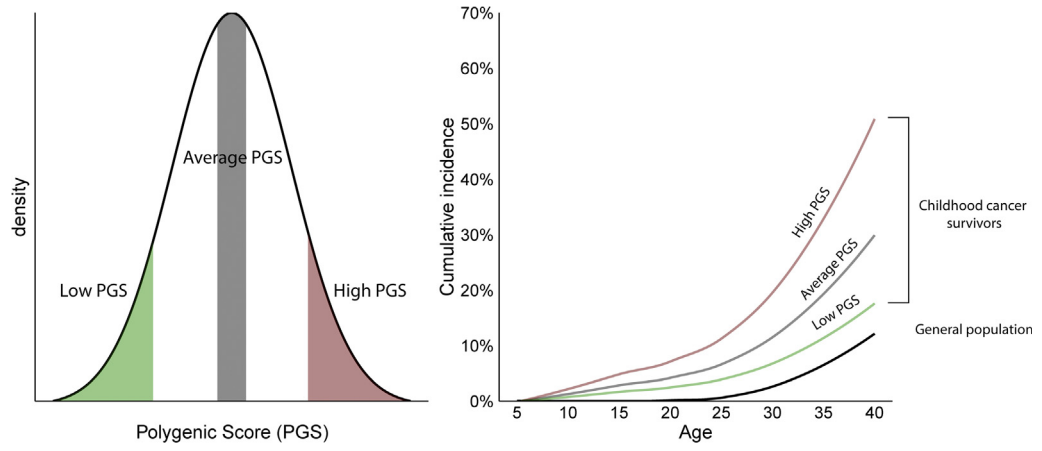
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2021.02.002

FIGURE 1 PGS to Stratify Risk of Hypertension in Childhood Cancer Survivors



(Left) A density plot for a polygenic score (PGS) in a population. The top decile **(red),** bottom decile **(green),** and middle 2 deciles **(gray)** of the polygenic score are shaded. **(Right)** Simulated cumulative prevalence curves using the prevalence of hypertension in childhood cancer survivors from SJLIFE (St. Jude Lifetime Cohort Study) (1) and assuming a hazard ratio per SD of the polygenic score as the odds ratio reported in this study.

follow-up ranged from 30 to 42 years across studies). Prevalence of hypertension ranged from 8% to 29% across the 3 studies, in each case approximately 3 times higher than would be expected for this age group in the general population. Sapkota et al. (6) confirmed a considerable and consistent gradient in risk of hypertension according to decile of the polygenic score within each study: odds ratios for top versus bottom decile of 2.63, 3.03, and 2.60 in the 3 cohorts, respectively. These findings suggest that the genetic drivers of hypertension in childhood cancer survivors are comparable to those in the general population.

Recognizing that genetics is only 1 factor contributing to the risk of hypertension, Sapkota et al. (6) then explored whether the risk associated with the polygenic score varies according to 2 nongenetic risk factors: obesity and cancer therapy. Interestingly, Sapkota et al. (6) observed a significantly increased risk gradient for the polygenic score in individuals who were overweight or obese, as well as those who underwent hypothalamic-pituitary radiation. This observation suggests that, even among those persons with similar genetic risk, environmental exposures can variably unmask this predisposition, analogous to the "2-hit" model often described for cancers.

These observations provide proof of principle for a potentially new paradigm of cardiovascular risk surveillance and mitigation among childhood cancer survivors. Given the high absolute rates of hypertension and the magnitude of the gradient across score deciles, one might imagine a future effort to develop a simple risk predictor for future risk of hypertension that includes a polygenic score. As an illustrative example, we use estimates provided in this paper by Sapkota et al. (6) to simulate the risk of a given childhood cancer survivor manifesting hypertension (**Figure 1**). For a 35-year-old cancer survivor with a polygenic score in the lowest decile, we estimate a risk of about 11%, only modestly higher than a risk of about 7% for a given individual in the general population. By contrast, for a cancer survivor with a polygenic score in the highest decile, the risk may be up to 32%.

The conclusions of this paper by Sapkota et al. (6), although interesting and important, should be interpreted in the context of several limitations. First, the polygenic score used to quantify inherited risk could have been improved. We and others have shown that use of a genome-wide set of common variants, including 1 with up to 6.6 million variants, substantially increases predictive power for complex diseases over scores with only a few hundred variants, as used here (8). Second, Sapkota et al. (6) chose to exclude individuals of non-European ancestry from their analysis, even though the polygenic score had been shown to associate with a risk of hypertension in patients of other ancestries (albeit with an attenuated effect size) (9). Moving forward, sharing results across all available ancestries should be prioritized, if only

to emphasize the importance of ongoing efforts—both from a data aggregation and a method development standpoint—that seek to mitigate transancestral disparities in polygenic score performance (10–12). Third, Sapkota et al. (6) did not extend the relationship of the polygenic predictor with hypertension to cardiovascular events of greater clinical relevance, such as incident myocardial infarction, stroke, or heart failure, although one might reasonably assume that such a relationship would be present.

Genetic predictors show promise as a tool to identify high-risk individuals currently "flying under the radar" within our clinical practice. For example, we are already offering polygenic assessment for coronary artery disease as a clinical test in our own institution and, alongside investigators across the country, are studying the impact of returning high polygenic scores for several diseases in more than 25,000 individuals as part of the National Institutes of Health–organized Electronic Medical Records and Genomics (eMERGE) Network (13,14). The findings of Sapkota et al. (6) suggest that, in childhood cancer survivors, a polygenic score for hypertension may prove similarly useful in identifying a subset of individuals at particularly high risk. This result points to a promising future, where well-validated models, integrating inborn predisposition, cancer therapies received, and time-updated clinical risk factor variables, could enable tailored cardiovascular surveillance and prevention efforts to mitigate the significant disease burden among childhood cancer survivors.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Mr. Agrawal has received funding support from the Sarnoff Cardiovascular Research Foundation Fellowship. Dr. Khera has received grant 1K08HG010155 from the National Human Genome Research Institute; has received a Hassenfeld Scholar Award from Massachusetts General Hospital; has received a Merkin Institute Fellowship from the Broad Institute of Massachusetts Institute of Technology and Harvard University; has served as a scientific advisor to Sanofi, The Medicines Company, Maze Therapeutics, Navitor Pharmaceuticals, Verve Therapeutics, Amgen, Color, and Columbia University (National Institutes of Health); has received speaking fees from Illumina, MedGenome, Amgen, and the Novartis Institute for Biomedical Research; has received sponsored research agreements from the Novartis Institute for Biomedical Research and IBM Research, and reports a patent related to a genetic risk predictor (20190017119).

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KEY WORDS cancer survivors, gene-environment interaction, hypertension, polygenic score