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EDITORIAL COMMENT

Genomics for Improving Heart Failure Risk Assessment in Cancer Patients

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In 2022, the European Society of Cardiology published their cardio-oncology guidelines, providing a milestone in cardiovascular (CV) surveillance and care for cancer patients,[1] with a major focus on baseline CV risk assessment to guide the type, intensity, and duration of CV surveillance during and after cancer treatment.[2] The guidelines provide a checklist for baseline CV risk assessment and stratification that incorporates cancer history and treatment; CV history and risk factors; and electrocardiography, echocardiography, and cardiac biomarker measurement.[1] However, because of a paucity of research, currently there are no recommendations on genomic risk assessment.

Genetic variation can predispose to disease through monogenic variants in which a single variant has a large impact on the structure and function of a protein that is sufficient to cause or significantly increase the risk of disease. For example, titin-truncating variants lead to the production of an abnormal titin protein, which can lead to dilated cardiomyopathy. Genome-wide association studies (GWAS) have also identified many common genetic variants associated with CV diseases. Individually, these variants only have a small effect on disease risk, but carrying a high burden of these risk variants can significantly increase disease risk. The combined effect of these common risk variants is called a polygenic risk score (PRS) and provides an estimate of an individual's genetic liability to disease.[3] A coronary artery disease (CAD) PRS predicts CAD independently of traditional CV risk factors, including family history.[4] PRS integration into CV risk calculators for population screening is already being trialed,[5] but few studies have investigated PRS for CV risk stratification in cancer patients. A PRS for CAD has previously been shown to be associated with incident CAD in a cohort of female breast cancer cases[6] as well as in childhood cancer survivors.[7]

In this issue of *JACC: CardioOncology*, Soh et al[8] evaluate for the first time a PRS for heart failure (HF) for predicting HF incidence in a cancer compared to a noncancer population in the UK Biobank.[9] Although the PRS was significantly associated with HF incidence in both the cancer and noncancer populations, it did not improve prediction over and above the ARIC (Atherosclerosis Risk In Communities) heart failure risk score, which includes multiple conventional CV risk factors. In addition, the ARIC heart failure score performed much better in the noncancer cohort compared to the cancer cohort, implying additional risk factors unique to cancer patients. The authors conclude that the genetic factors contributing to HF occurrence are not as important compared to clinical factors. However, there are several important points for consideration when interpreting the study results.

First, HF is a complex syndrome, with monogenic, polygenic, and environmental contribution to disease risk. In terms of genomic risk, the current study only investigated polygenic risk. A recent study that retrospectively tested cancer patients with a history of anthracycline-induced cardiac dysfunction found 7% carried a likely pathogenic variant within known cardiomyopathy genes, as opposed to none found in a matched cohort of patients without cardiac disease.[10] This highlights the importance of assessing the full spectrum of genetic risk variants for risk stratification.

An important environmental risk factor for HF incidence that is specific to cancer patients is exposure to cardiotoxic cancer treatments. However, a lack of treatment data in the UK Biobank

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meant Soh et al[8] were unable to include cardiotoxic treatment exposure as a risk factor or test for a genetic by environment interaction. In addition, adverse CV effects can vary by cancer treatment. For example, anthracycline treatment can cause cardiomyopathy but is not commonly associated with vascular disease,[11] and a cardiomyopathy-specific PRS may be a better predictor to assess than a PRS for all-cause HF.

When investigating PRS, it is important to understand what factors determine the predictive power of a PRS. The first is the proportion of variance in the phenotype that is explained by all common risk variants, known as single-nucleotide polymorphism-based heritability (SNV-based h^2). If a disease has a SNV-based h^2 of 1, this would indicate that common variants explain 100% of the variance in disease, and, theoretically, if we can identify all the risk variants and accurately estimate their effect on disease risk using a GWAS, the resulting PRS should have almost perfect discriminatory power. However, common complex diseases tend to have low to moderate SNV-based h^2 estimates, reflecting low to moderate contribution of common genetic variants. To put things into context, SNV-based h^2 for CAD is around 50%,[12] but it is only 5% for HF.[13] The SNV-based h^2 estimate also provides the upper bound for how much of the disease variance is captured by a PRS, which in turn is dependent on the power of a GWAS to identify all contributing common disease variants and accurately estimate their effect size. Despite the availability of very large GWASs of common disease, these are still not sufficiently powered to identify all risk variants, which is reflected in the proportion of disease variance explained by current PRSs being much lower than the SNV-based h^2 estimates. Despite a SNV-based h^2 of around 50% for CAD, the PRS based on a GWAS of >250,000 CAD cases and >900,000 controls only captures around 20% of disease variance.[12] The first large-scale GWAS of HF (>45,000 HF cases) identified only 10 genetic risk loci,[14] whereas the most recent and largest GWAS of HF (>150,000 HF cases)[15] has identified over 50 risk loci and for the first time variants in the *ERBB2* gene, which encodes HER2, the target for trastuzumab, demonstrating the need for sufficiently-powered GWASs for PRS generation. Despite large sample sizes, the HF PRS explains only around 1% of disease variance.[13]

Another important factor that impacts the power of a GWAS and a PRS is heterogeneity in the underlying disease etiology. HF is a complex, clinical syndrome that can result from different pathobiology. GWASs of HF subtypes suggest different genetic architectures and distinct genetic association profiles between HF with reduced and with preserved ejection fraction.[16] GWASs of nonischemic HF subtypes showed a much higher heritability of 12% for nonischemic HF with reduced ejection fraction compared to only 1.8% for nonischemic HF with preserved ejection fraction, suggesting varying contributions of common genetic variants to different HF subtypes.[15] Therefore, the genomic contribution may vary across HF subtypes, and understanding which are most relevant in cancer patients may help guide the development of risk models. Given that an individual's PRS is fixed from birth, there is an opportunity for improved risk stratification in younger cancer patients and in those without traditional CV risk factors. It is important to note that just as a single biomarker for CV disease risk cannot be used as stand-alone diagnostic tests neither can a PRS.

Looking into the future, larger GWASs of HF subtypes may provide more powerful PRSs for improved genomic prediction. Studies should evaluate the contribution of both monogenic and polygenic risk and the interaction with cardiotoxic treatment exposure. Large cancer cohorts with whole genome sequence data and longitudinal life course clinical data such as the Cancer Programme of the 100,000 Genomes Project, which aims to provide whole genome sequencing for cancer patients to inform precision cancer care, should also be leveraged for improved CV risk prediction in cancer patients.

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