JACC: CARDIOONCOLOGY VOL. 6, NO. 4, 2024

EDITORIAL COMMENT

Time to Rethink Using Cardiovascular Risk Scores for Cancer Survivors

Katrina K. Poppe, PhD

Cardiovascular (CV) risk scores exist for a range of cardiac and vascular conditions and are likely to be applied to people regardless of their cancer history, but how accurate are they for cancer survivors? In a study reported in this issue of *JACC: CardioOncology*, McCracken et al,[1] building on the knowledge that many cancers are associated with increased risk for developing CV conditions,[2,3] investigated the accuracy of established CV risk scores for cancer survivors.

Using data from the UK Biobank, 31,534 cancer survivors were matched using a propensity score that included established CV risk factors to 126,136 control subjects who had never had cancer. This provided case and control groups with near identical risk factor profiles, thus isolating cancer history as the point of difference. The 7 established risk scores that were assessed included 4 predicting ischemic CV disease, 2 predicting stroke, 1 predicting heart failure, and 1 predicting the onset of atrial fibrillation (AF). Outcomes in the cohort were defined in the same way they are defined for each score, with the addition of a broad CV outcome (CVD2) that added heart failure, cardiomyopathy, AF, and valvular heart disease to the standard ischemic CV disease outcome, highlighting the nonischemic CV conditions to which cancer survivors are vulnerable. The scores for most outcomes performed poorly for people with Hodgkin or non-Hodgkin lymphomas and hematological, lung, and brain or central nervous system malignancies but less poorly for those with prior breast or prostate cancer (who together made up 41% of the cohort).

The work is thorough and thoughtful and shows good insight regarding the factors affecting CV risk models. Age represents the cumulative exposure to measured and unmeasured vascular risk factors, and as discussed by McCracken et al,[1] the contribution of standard vascular versus cancer-related risk factors to CV risk will differ depending on the patient's age. Known vascular risk factors will have a greater role in CV risk for older people and might explain the adequate performance of standard risk scores for people with prostate cancer. In contrast, cancer-related risk factors are more likely to drive the increased CV risk for younger people, contributing to the poor performance of standard risk scores for people with brain or central nervous system malignancies, for example. Vascular damage as a consequence of radiotherapy progresses more rapidly than damage due to atherosclerosis,[4] so "aging" can also happen at a different rate depending on type of treatment. It would be interesting to know if replacing the age at baseline assessment (here, the arbitrary age at which a person entered the UK Biobank) with age at cancer diagnosis would have led to even greater disparities in risk prediction for some cancer types. In practice, risk scores would be applied at the end of cancer treatment, so the age at which the cancer occurred is most relevant.

Most risk scores overpredicted risk in the UK Biobank cohort being studied (see Figure S5 in the paper[1]). This is expected, as the scores were derived in cohorts with different baseline risks from those in the UK Biobank, including from other countries and other periods in time, although it was surprising that the UK-derived QRISK and QStroke scores did not predict risk more accurately. The research was designed to assess the relative accuracy of risk prediction for cancer survivors compared with people who have not had cancer; however, some of the investigators' discussion and conclusions stray into describing "underestimation of risk in cancer survivors." All but the

From the University of Auckland, Auckland, New Zealand.
The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution 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.2024.07.006

JACC: CARDIOONCOLOGY, VOL. 6, NO. 4, 2024
AUGUST 2024:589–591

risk for developing AF is overestimated, in absolute terms, so it must be kept in mind that the underestimation being described is relative to the control group.

These comments do not detract from the key message that CV risk scores do not predict CV risk for people with histories of cancer as well as they do for people without cancer. But why do we expect them to be accurate? Why should scores designed to identify people at increased risk for developing CV conditions, using predictors routinely available in primary care, be relevant to people who have had a significant illness with systemic and CV effects from the cancer and/or treatment?

The 2022 European Society of Cardiology cardio-oncology guidelines provide recommendations about CV risk assessment at the end of cancer therapy.[4] Intended for assessment in the first year after cancer treatment, and differentiating people at high, medium, and low CV risk on the basis of the toxicity of treatment agents and pretreatment CV risk, the guidance is very specific to the type of treatment received. Cardiac biomarkers and echocardiography are recommended to assess ongoing CV risk. That is not in question, but these tests assess the impact of structural or myocardial damage, not broader vascular risk. The findings of McCracken et al's[1] study and others[2] suggest that limiting guidance to people who have received treatments that damage the myocardium underestimates the true effect of cancer on the CV system.

The question remains, therefore, of how to assess post-treatment CV risk. McCracken et al[1] suggest there is an "urgent need for development and validation of CV risk scores in cancer survivors." Deriving new CV scores means accommodating all permutations of cancer type and treatment and doing so again as new treatments become available. That alone is impractical, but the difficulty is compounded by the relatively small number of people available from whom to derive such scores. For example, of the 0.5 million people in the UK Biobank, 246 have prior lung cancer and no histories of CV disease. Of these, 20 experienced significant ischemic CV events, of which 7 were strokes, and 17 developed heart failure.[1] Such numbers are insufficient to derive stable, effective risk models, although cohorts could be combined to increase the data available. Another hurdle is that the large data sets required for derivation of risk scores might not contain the extent of information that would be expected in cancer-specific risk models, including stage and grade, cancer recurrence, and drugs dispensed in the hospital to mitigate chemotherapy-induced cardiotoxicities.[2] A pragmatic improvement is needed.

One approach may be to consider a history of some types of cancer as equivalent to already having CV disease, making people ineligible for the prediction of incident disease using standard risk equations. Significant renal impairment is considered such a "CV disease risk equivalent" in some scores.[5] That approach leaves cancer survivors without a risk score but reduces the chance that inaccurate risk estimation will negatively influence management decisions. Another approach might be to identify additional markers of increased CV risk that are available in people who have experienced cancer. Chest computed tomography (CT) is commonly used for staging of cancers. Coronary artery calcification is visible on CT and identifies people at increased CV risk.[6] Grading the extent of calcification might be beyond the remit of staging CT, but the presence of coronary calcium can signal someone at increased (ischemic) CV risk, regardless of cancer type or therapy.

Above all, messaging and clinical decision support tools need to make clear that survivors of certain cancers should not be assessed with routine CV risk equations. Long-term risk is typically managed in primary care, and this message needs to be heard clearly in that domain, as well as in cardiology and oncology.

These are not single-test solutions. But pausing to weigh the practicalities of deriving risk scores accommodating all permutations of cancer type and treatment against repurposing existing technologies and strategies might enable improvements in CV assessment for cancer survivors.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Poppe has received funding from the New Zealand Heart Foundation, the New Zealand Health Research Council, and the Pūtahi Manawa-Healthy Hearts for Aotearoa New Zealand Centre of Research Excellence.

ADDRESS FOR CORRESPONDENCE: Dr Katrina K. Poppe, Department of Medicine, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand. E-mail: k.poppe@auckland.ac.nz.

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KEY WORDS cardiovascular risk score, cardio-oncology