Cardiovascular risk assessment in cancer survivors: addressing an unmet clinical need

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Comment

Risk assessment have become pivotal in the prevention of cardiovascular disease (CVD). Risk prediction tools are meant to estimate prognosis in an unbiased and reliable way, and to provide objective outcome probabilities.[1] Even though their use is recommended by European and American clinical practice guidelines, they are not adequately implemented in clinical practice.[2,3] In New Zealand (NZ), CVD risk assessment for people aged 30 to 74 years without prior CVD is now based on the 5-year CVD risk prediction equations derived from the NZ cohort of the PREDICT study.[4] This risk tool has been embedded in the decision support software across primary care settings. In addition to provide probabilities of fatal and non-datal outcomes, its use also provides guidance for management (i.e., patients should be managed differently according to their risk category).

Cancer survivors are at an increased risk of CVD. Not only because of the exposure to cardiotoxic therapies, but also because of the presence of concomitant cardiometabolic risk factors (insulin resistance, obesity, or tobacco exposure are associated with both the cancer and CVD pathways), advancing age (cancer is largely a disease of aging), and a decrease in adherence to medications for non-cancer conditions by patients on or soon following active cancer therapy (e.g., statins). Most of these factors are directly or indirectly included in risk calculators for the general population. Nevertheless, the validity of traditional risk prediction tools in cancer survivors was not robustly validated yet. To date, some evidence was provided by small studies on certain specific cancer type.[5] The paucity of research in CVD risk prediction tools among cancer survivors has not yet met the clinical need.

In this issue of *The Lancet*, Essa Tawfiq and colleagues present an open cohort study to assess the performance of cardiovascular disease risk prediction equations in a large NZ population of cancer survivors is reported.[7] The aim was to validate the existing prediction model for primary care patients in a sub-cohort (cancer patients) of the original cohort. In a large population of 14,263 cancer survivors (57% women), with broad age representation

(mean age 60·5 years (SD 8·5) the model had moderate discrimination (c-statistics were 0·67 and 0·73 for men and women, respectively), and relatively good calibration according to three clinical risk groups of 5-year risk (< 5%, 5-14·9%, and ≥15%). The three clinical risk groups were produced based on clinically meaningful cut-offs. If risk is <5%, only lifestyle advice is recommended, whereas if 5-year risk is ≥15%, both medication and lifestyle advice are strongly recommended. For those with 5-year risk 5-14·9%, initiation of CVD medication management can also be considered on top of lifestyle advice.

This study fills a gap of evidence by showing a reasonably good model performance in a population of patients that had been somehow neglected when it comes to predict their CVD outcomes.[8] Importantly, the tool provides sex-specific assessment. Moreover, the broad implementation of the risk equation, and its implications on the clinical decision-making are other strong points of the study. Such a great effort to cover this unmet clinical need also require to be presented in the light of their two main weaknesses. First, discrimination performance is moderate at best. The Harrell's c-index for men and women suggest that that there is a great overlapping between scores (predicted probabilities) in patients with and without the outcome. In the ideal situation (c-index of 1), all participants with the outcome would have a higher score than any given patient without the outcome. In this study, a higher scoring punctuation does not necessarily translate into a higher risk of events (particularly for men, c-index=0·67). The obvious reason for this suboptimal performance is the inherently nature of the predicted outcome. While death is an unambiguous event which not very often occurs randomly, non-fatal events (e.g., hospitalization) happen more at random, and are therefore less easy to predict than death.[9] The other main limitation of the study is the failure to account for competing risks of death, which is of course very relevant for cancer survivors. A competing risk may prevent the event of interest from taking place (e.g., a person who dies of cancer is no longer at risk of cardiovascular death).[10] Although the 5-year CVD risk prediction equations was developed for a general population in which competing mortality risks were not

a major issue,[10] it should be acknowledged that cancer survivors are known to have an increased mortality risk compared with other primary care patients without history of cancer.

Other less relevant limitations of the study might be the long recruitment period (between 1996 and 2016 for cancer diagnosis, and between 2002 and 2018 for CVD risk assessment), and the lack of cancer-specific predictors.[11] The long recruitment period is relevant because considerable advances have occurred in medical management for both cancer and CVD conditions in that period,[12] whereas the lack of cancer-specific predictors is relevant because each cancer type have a different prognosis. Hence, there is substantial heterogeneity in the underlying risk of the study population. Not only because the underlying CVD risk might not be the same for a cancer survivor in 2002 than in 2018, but because each type of cancer has a different underlying prognosis.[11]

It is of interest to clinicians to understand how well performs an implemented prediction model in their already heterogenous populations (e.g., to what extent the existing risk prediction models can broadly predict CVD risk in survivors from all type of cancer). It is of particular importance for NZ doctors because of the implications in clinical management. In order to provide less biased estimates and more accurate predicted probabilities, future research should focus on addressing the potential competing risk issue to yield less biased estimates (or alternatively, predict all-cause mortality), as well as on exploring cancer-specific predictors, such as the type of cancer, their stage, or their treatment, respectively.[11] Both actions would end up generating new risk assessment tools better predicting cardiovascular outcomes. Cancer survivors would fall more often in the adequate risk category, and this would be translated into an adequate clinical management.

I declare no competing interests.

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