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Review

Are we ready to predict late effects? A systematic review of clinically useful prediction models

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Abstract ***Background:*** After completing treatment for cancer, survivors may experience late effects: consequences of treatment that persist or arise after a latent period.
Purpose: To identify and describe all models that predict the risk of late effects and could be used in clinical practice.
Data sources: We searched Medline through April 2014.
Study selection: Studies describing models that (1) predicted the absolute risk of a late effect present at least 1 year post-treatment, and (2) could be used in a clinical setting.
Data extraction: Three authors independently extracted data pertaining to patient characteristics, late effects, the prediction model and model evaluation.
Data synthesis: Across 14 studies identified for review, nine late effects were predicted: erectile dysfunction and urinary incontinence after prostate cancer; arm lymphoedema, psychological morbidity, cardiomyopathy or heart failure and cardiac event after breast cancer; swallowing dysfunction after head and neck cancer; breast cancer after Hodgkin lymphoma and thyroid cancer after childhood cancer. Of these, four late effects are persistent effects of treatment and five appear after a latent period. Two studies were externally validated. Six studies were designed to inform decisions about treatment rather than survivorship care. Nomograms were the most common clinical output.

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Conclusion: Despite the call among survivorship experts for risk stratification, few published models are useful for risk-stratifying prevention, early detection or management of late effects. Few models address serious, modifiable late effects, limiting their utility. Cancer survivors would benefit from models focused on long-term, modifiable and serious late effects to inform the management of survivorship care.

1. Introduction

Due to improved screening, early detection and treatment, people with a diagnosis of cancer are living longer than ever before. Unfortunately, the consequences of the cancer and its treatment – late effects – threaten the health and quality of life of cancer survivors. Late effects include both persistent sequelae of treatment (long-term effects) and conditions that develop after a latent asymptomatic period (late-occurring effects). The prevention, early detection and management of late effects pose a significant challenge to survivors and their healthcare providers. In the United States, 13.7 million individuals have ever been diagnosed with cancer, 64% of whom were diagnosed at least 5 years ago [1,2]. This large and heterogeneous group of survivors will differ in their long-term needs, requiring different intensity of follow-up. For survivors who underwent chest radiation for Hodgkin lymphoma, it is not clear who would benefit most from routine breast cancer screening. Similarly, for patients who received anthracycline chemotherapy, it may be appropriate for oncologists to routinely monitor cardiac function for some patients to detect early signs of cardiovascular disease – but not all patients, given the harms of overdiagnosis, the costs and the resource intensity that can be associated with cardiac monitoring.

Because healthcare needs vary widely among cancer survivors, there has been a call for personalised care tailored to individual needs [3,4]. Survivorship experts have promoted risk stratification to determine the intensity and setting for post-treatment follow-up [5]. The Institute of Medicine recommends lifelong 'risk-based' health care for all childhood cancer survivors [6]. This entails a systematic plan for periodic screening, surveillance and prevention that is adapted to the risks arising from the cancer, its therapy, genetic predispositions, lifestyle behaviours and comorbid conditions [6,7]. Survivors at the highest risk for serious late effects may require frequent monitoring or management, while those at lower risk may not benefit from such intensive follow-up. Indeed, overutilisation of intensive follow-up for low risk survivors may be costly and lead to overdiagnosis. Similarly, depending on the late effect, survivors at highest risk may be most appropriately managed by their oncology team or specialised survivorship clinics, while lower risk survivors could safely transition their care to a well-informed primary care provider.

In order to risk-stratify cancer survivorship care, clinicians need tools to identify patients at high risk for serious late effects. Such tools include simple algorithms (such as referring all patients who receive chest radiation for cardiovascular screening) or models that incorporate multiple variables (risk prediction modelling). Risk prediction modelling is a general term to describe mathematical methods of estimating individualised risk among patients. Ideally such models are developed among one group of people and then externally validated among a different, independent group of people to measure the appropriateness of extrapolating findings. When external validation is not feasible, internal validation uses mathematical methods to correct for optimism, mitigating the dangers of overstating findings from a single study population. Clinical risk prediction models are intended to be useful in a medical setting, where a healthcare provider can use a patient's clinical data to calculate an absolute risk of an event occurring. The clinician can then use risk information to direct care, and cancer survivors can use their personalised risk to guide self-management. In order to have a feasible clinical risk prediction model, parsimony is critical. It is important that models include only the parameters that are accessible to the clinicians who are using the model to make decisions. Our goal was to identify and describe all existing models that predict the risk of late effects and could be used by clinicians to risk-stratify the care of cancer survivors. We conducted a systematic review of the literature to identify and summarise such models, focusing on characterising whether the model is ready for use in clinical practice.

2. Methods

2.1. Data sources and searches

We systematically searched MEDLINE from inception through April 2014 for studies meeting eligibility criteria. We required that studies include a statistical method that predicted the absolute risk of a late effect that was present at least 1 year post-treatment. We did not include studies that predicted recurrence, unless recurrence was combined with a late effect as the study outcome. We only included studies with models that clinicians who did not