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# Nexus of Cancer and Cardiovascular Disease for Australia's First Peoples

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Australia's First Peoples, Aboriginal and Torres Strait Islanders,<sup>1</sup> have a life expectancy at birth approximately 10 years less than that for nonindigenous Australians (females: 73.7 v 83.1 years; males: 69.1 v 79.7 years, respectively).<sup>1</sup> Globally, this gap represents one of the largest within-country health inequalities and is largely underpinned by indigenous Australians' elevated mortality from chronic disease.<sup>1</sup> Despite the many government policies and programs aimed at addressing this disparity, it has persisted within a wider sociopolitical and historical context of social disadvantage and marginalization, dispossession, forced separation of families, and systemic and interpersonal racism.<sup>1,2</sup> For statistical purposes, the Australian Institute of Health and Welfare define indigenous status as someone who identifies as an Aboriginal and/or Torres Strait Islander person. This may be self-reported (eg, hospital admissions data collected include self-reported indigenous status at point of contact) or informed by other means (eg, coroners may use information on indigenous identification from family, medical practitioners, or other sources to indicate indigenous status on a person's death certificate).

Cancer and cardiovascular disease are the leading causes of death for both indigenous and nonindigenous Australians; accounting for almost one third of the life-expectancy gap.<sup>1</sup> The disparities in the cancer burden have been well documented.<sup>1,3</sup> Advancements in the early detection and treatment of cancer have contributed to a gain in cancer survival for Australians in general; however, 5-year survival for indigenous Australians diagnosed with cancer is 15 percentage points lower than for their nonindigenous counterparts.<sup>4</sup> The cancer mortality gap is widening, with the mortality rate increasing by 21% in the past two decades for indigenous Australians, while decreasing by 16% for nonindigenous Australians.<sup>4</sup> These disparities are underpinned by a higher incidence of aggressive cancer types, more frequent diagnosis at advanced-stage disease, and lower rates of cancer treatment of indigenous patients.<sup>4</sup> In addition, greater exposure to risk factors, higher comorbidity levels, lower rates of cancer screening, and reduced access to health

services and optimal care also contribute to poorer cancer outcomes for indigenous Australians.<sup>5</sup>

Cardiovascular disease accounts for a quarter of all deaths among indigenous Australians.<sup>1</sup> There has been a reduction in cardiovascular mortality in Australia in recent decades<sup>1</sup>; during 1998 and 2012, mortality rates declined similarly for indigenous and nonindigenous Australians for ischemic heart disease (48% and 49%, respectively) and stroke (41% and 34%, respectively).<sup>6</sup> These improvements are thought to be largely due to public health programs targeting tobacco use coupled with advancements in our understanding and treatment of the disease.<sup>1</sup> Smoking rates declined between 2001 and 2011 to 2013 for both indigenous (49% and 42%, respectively) and nonindigenous (22% and 16%, respectively) people,<sup>1</sup> although indigenous Australians continue to have a higher rate.<sup>1,6</sup> In parallel, indigenous Australians continue to have a 50% higher risk of cardiovascular disease mortality compared with nonindigenous Australians,<sup>1,6</sup> 60% higher for ischemic heart disease and 40% higher for stroke.<sup>6</sup>

Despite the extensive research as separate conditions, little is known about the nexus between cancer and cardiovascular disease. Limited data suggest that cardiovascular disease is one of the most common comorbidities among indigenous patients with cancer. It is estimated that approximately one quarter of indigenous Australian adult patients with cancer have a preexisting cardiovascular condition at the time of their cancer diagnosis,<sup>7</sup> most commonly, hypertension (14%), angina (5%), congestive heart failure (5%), and cardiac arrhythmias (4%).<sup>8</sup> There is no published evidence of the proportion of indigenous Australians who at the onset of their cardiovascular disease have a preexisting cancer diagnosis. In the last decade, the recognition of the importance of the cancer–cardiovascular disease relationship has increased.<sup>9</sup> Given that cardiovascular disease is the leading noncancer cause of death among patients with cancer,<sup>10</sup> more detailed investigation on the nature, extent, and impact of the relationship between cancer and cardiovascular disease is warranted.

There are multiple plausible explanations for the coexistence of cancer and cardiovascular disease.

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## CONTEXT

### Key Objective

This commentary summarizes the state of cardio-oncology evidence and practice in Australia and calls for equity to be at the heart of the development of this new multidisciplinary field.

### Knowledge Generated

Cardiovascular disease is common among people diagnosed with cancer, largely due to shared risk factors and the cardiotoxic nature of some cancer therapies. Cardio-oncology aims to prevent, screen, treat, and monitor cardiovascular risk among people diagnosed with cancer. Although cardio-oncology guidelines have been developed for some countries, this field is still in its infancy in Australia, and fundamental research questions largely remain unanswered. Furthermore, to ensure equity in the development of this new field, an organized, multidisciplinary and indigenous-led approach is necessary.

### Relevance

Indigenous Australians experience a greater burden of cancer and cardiovascular disease than nonindigenous Australians. These two diseases account for one third of the persistent life-expectancy gap between indigenous and nonindigenous Australians.

Although unlikely, it could be a chance occurrence with no etiologic connection, what Sarfati and Gurney refer to as common conditions occurring commonly.<sup>11</sup> It is plausible that cancer could cause cardiovascular disease,<sup>9,11</sup> and it is also recognized, albeit more recently, that heart disease may lead to increased cancer diagnosis. Specifically, retrospective and registry data in multiple patient populations suggest that cancer is more common in patients with a prior diagnosis of heart failure.<sup>12,13</sup> More recently, a possible mechanistic link has been provided from murine experiments, suggesting that a number of potential circulating factors secreted by the failing heart may promote tumor growth.<sup>14</sup>

There is ample evidence that cancer therapies can lead to the development or worsening of various cardiovascular diseases. It has been extensively documented that most cancer therapies are associated with adverse cardiovascular events, ranging from accelerated hypertension, thromboembolic events, and arrhythmias, to myocardial infarctions and overt heart failure.<sup>15,16</sup> These adverse events were first recognized in 1967,<sup>17</sup> and, more recently, this discovery has led to the development and advancement of cardio-oncology, a specific subspecialty of cardiology.<sup>9</sup> However, although well described in international cohorts,<sup>18,19</sup> only limited Australian research has explored cardiovascular outcomes after cancer treatment. Significant cardiac dysfunction has been reported in more than 10% of patients treated with anthracycline chemotherapy.<sup>20</sup> Seven percent of patients with breast and hematologic cancer (6% of indigenous patients) treated with chemotherapy were hospitalized for heart failure during the 3.3-year median follow-up period, with lower survival rates for those who developed heart failure.<sup>21,22</sup> Survival of indigenous patients who did and did not develop heart failure was not explored.<sup>21</sup> In addition, treatment of cardiovascular disease may influence cancer risk. For

example, patients treated with statins for dyslipidemia were found to have improved survival in prostate cancer,<sup>23</sup> head and neck cancers,<sup>24</sup> and esophageal cancers.<sup>25</sup> Other findings suggest that antihypertensive treatment with renin-angiotensin-aldosterone system inhibitors may provide some protective effects in patients with prostate cancer.<sup>26</sup>

Preexisting comorbidity may also influence doctor-patient decisions related to treatment options, uptake, and completion. For example, patients with cancer with cardiovascular comorbidity are typically precluded from certain anticancer therapies, such as trastuzumab and anthracycline chemotherapy.<sup>27</sup> Likewise, heart failure therapy has been found to be underutilized among patients with cancer who experience significant cardiac dysfunction.<sup>20</sup>

Furthermore, cancer and cardiovascular disease may co-exist because of shared risk factors, such as smoking, poor diet, lack of physical activity, obesity, alcohol consumption, dental disease, and chronic infection.<sup>28</sup> These factors can induce inflammation, which underlies the development of both diseases.<sup>29</sup> Prevention is critical to reduce cardiovascular risk after a cancer diagnosis. There is some evidence that people with cancer who quit smoking at the time of their diagnosis have a similar median survival time to former smokers and nonsmokers, and significantly higher survival than those who continue to smoke after cancer diagnosis.<sup>30</sup> In addition, anti-inflammatory treatments, such as aspirin, may offer cardioprotection for patients with cancer during treatment.<sup>31</sup> Finally, cancer and cardiovascular disease could plausibly codevelop through the effects of a third disease. For example, diabetes, hypertension, and hyperlipidemia are each implicated in both cancer and cardiovascular risk, although it is unclear whether there is a critical sequence in which the diseases develop. In a previous study of indigenous Australian patients with cancer, diabetes was the most common comorbidity (30%), followed by cardiovascular disease (23%).<sup>7</sup>

There is robust evidence indicating the detrimental impact of such multimorbidity on the levels of disability, costs of care, adverse treatment-related events, and overall morbidity and mortality among cancer survivors.<sup>32,33</sup> Beyond deepening our understanding of the mechanisms underpinning the relationship between cancer and cardiovascular disease, the broader social context and implications of such a link need to be considered. Previous studies highlight the significant role of socioeconomic disparities in both the prevalence and impact of multimorbidity.<sup>34,35</sup> Among people with cancer, rates of depression, anxiety, coronary heart disease, chronic obstructive pulmonary disease, and diabetes have been shown to vary significantly according to socioeconomic status, with a rate that is close to double for the most socioeconomically disadvantaged compared with the least disadvantaged people.<sup>34</sup> Given the substantial economic, health, and social challenges experienced by many indigenous Australians, multimorbidity and indigenous people with cancer require close attention.

Addressing the determinants of multimorbidity and its impact on health outcomes necessitates important changes to existing models of health care provision.<sup>35</sup> To reduce disparities in chronic disease outcomes, such service and systems improvements must be equitable, as well as efficacious and of high quality.<sup>35</sup> Reducing the disparate burden of multimorbidity for indigenous Australians requires an understanding of the barriers to optimal and culturally safe health care, identifying unmet needs among this patient group, and building the capabilities of health care services to engage indigenous people. Moreover, strengthening the capabilities of all health professionals to recognize and respond to barriers and needs is a key element of any such strategy. Developments in this field have identified core curricula requirements and related competencies in indigenous health for medical and other health professionals.<sup>36</sup> Promoting tailored pathways into health professional education and training for indigenous people is an important element of promoting indigenous leadership of health care and indigenous health policy,<sup>37</sup> and is likely to result in more appropriate and effective health services.

From a health system perspective, understanding the current economic burden of multimorbidity among patients with cancer is imperative to ensure the efficient and equitable allocation of finite resources for prevention and treatment. There is a scarcity of Australian studies identifying the distribution of health system costs by treatment pathways or of the costs associated with the interactions between multiple chronic diseases. Cost is a known barrier to accessing care for both indigenous and nonindigenous Australians.<sup>38</sup> A recent report found that 8% of people 15 years of age and older delayed seeking care because of

cost in 2016 to 2017.<sup>39</sup> People with cancer may delay or skip treatment because of the cost,<sup>40</sup> and there is growing concern about financial toxicity for people diagnosed with cancer.<sup>41</sup> Recently, Callander et al<sup>42</sup> reported that indigenous people with cancer had lower out-of-pocket costs compared with their nonindigenous counterparts, but also accessed significantly fewer Medicare services. An increase in the number of multimorbidities and the associated complexity of care may increase the cost to the individual, which may be a barrier to accessing appropriate and timely care.

An important question that warrants attention is whether existing models of precision medicine in cancer care are adaptable to the challenges of multimorbidity and the populations most affected. As addressing multimorbidity becomes more widely recognized as a priority for cancer care, some studies have begun to explore these issues in a limited manner<sup>43</sup> and few with research among indigenous people. Other pressing clinical implications of multimorbidity for all Australians with cancer also warrant attention, but perhaps most pertinently for indigenous Australians. Such issues include better understanding of (1) the extent to which baseline risk assessments of cardiovascular and other comorbidities are performed for patients with cancer before cancer treatment and how the need and impact of this assessment are communicated to patients and their families, (2) patients' experiences of coping with multimorbidity alongside their cancer care, (3) the impact of multimorbidity on patient-clinician communication about treatment options and shared decision making, (4) what clinicians consider in terms of patients' social and health disparities and multimorbidity when making clinical decisions regarding cancer care and treatment, and (5) how clinicians across disciplines (eg, oncologists, cardiologists, primary care providers) communicate important patient information among themselves and what impact this has on patient experiences and outcomes. Because patients with multimorbidity are typically excluded from clinical trials of cancer treatments and models of care, there is a need to identify and use appropriate and robust epidemiologic methods to generate such information for patients with multimorbidity.

Cardio-oncology is an emerging field that addresses the two leading causes of death in Australians and has the potential to reduce the persistent gap in life expectancy between indigenous and nonindigenous Australians. Critically, reducing such inequities will require policy and service delivery improvements that address underlying determinants and shared risk factors of multimorbidity. The development of models of care to successfully achieve this will require an organized, multidisciplinary, and indigenous-led approach and, given the rise in multimorbidity, the time for action is now.

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