

# ADVANCING PROSTATE CANCER SURVIVORSHIP RESEARCH IN AUSTRALIA

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## Abstract

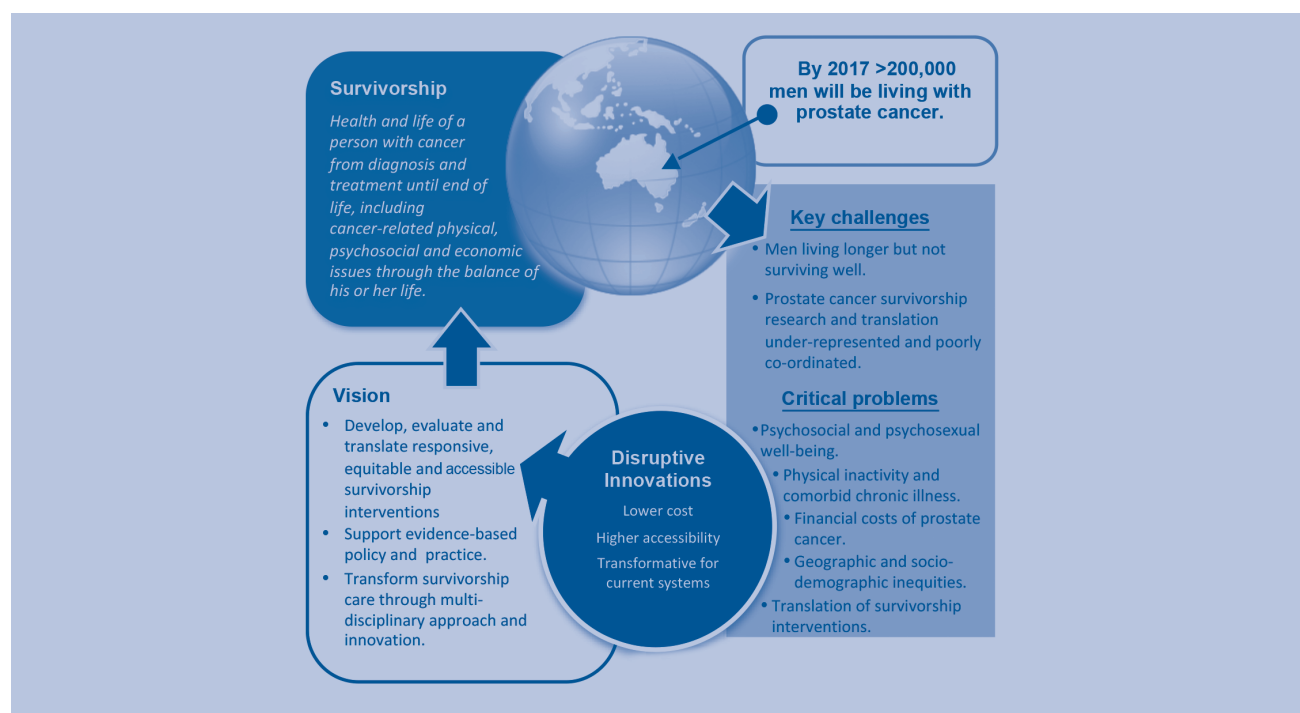
Prostate cancer is the most common cancer affecting Australian men, with 1 in 7 males diagnosed before the age of 75 years and most now surviving long-term in the absence of adequate and accessible supportive care for their wellbeing. A substantive proportion of men with prostate cancer experience heightened psychological distress and ongoing unmet needs for supportive care in the domains of sexuality and psychosocial care. This perspective focuses on: men's psychosocial and psychosexual needs; the role of exercise in survivorship care; health economics; and geographic and sociodemographic disparities in outcomes. It is proposed that prostate cancer survivorship research, translation and education needs to articulate with key factors that influence the acceptability and uptake of services. Stepped care approaches are also needed to meet the challenges of increasing prostate cancer prevalence taking into account constraints in health care resources and unique barriers to care such as geographic location, health literacy, and other aspects of social disadvantage. Finally, close linkage to community with the patient and family placed at the centre of the care model will be crucial.

Prostate cancer is the most common cancer affecting Australian men (excluding keratinocyte cancers), with 1 in 7 males diagnosed before the age of 75 years. The scale of the challenge is immense – five-year relative survival rates for prostate cancer in Australia have increased dramatically from 58% in 1982-87 to 92% in 2006-2010.<sup>1</sup> In 2008 and 2009, prostate cancer was the highest ranked male cancer in terms of health system expenditure in Australia, totalling \$347 million or 14% of the total male health system expenditure on cancer.<sup>2</sup> By 2017, there will be more than 200,000 men

living with prostate cancer in Australia and 80% of these men will be long-term survivors.<sup>3,4</sup>

Although many more men are surviving prostate cancer than ever before, they are not necessarily surviving well.<sup>6</sup> Survivorship encompasses the health and life of a person with cancer from diagnosis and treatment until end of life, including cancer-related physical, psychosocial and economic issues through the balance of his or her life, and within this the experience of his or her family, partners and caregivers.<sup>6</sup> Men are now

Figure 1: Prostate cancer survivorship



living longer with ongoing physical, psychosexual and practical burdens related to diagnosis and treatment of their prostate cancer, with these effects compounded by high rates of comorbid illness that relate to lifestyle factors such as inactivity and obesity.<sup>8</sup> Problematically, evidence demonstrates that men's supportive care, physical, practical and informational, emotional and psychological needs are not being met in any systematic way.<sup>9</sup> There are several challenges and barriers to obtaining the best possible survivorship outcomes for men with prostate cancer, and large gaps in knowledge that urgently need to be addressed. This perspective focuses on: psychosocial and psychosexual needs; the role of exercise in survivorship care; economics of new and existing interventions; and geographic and sociodemographic disparities in outcomes. A model proposing a way forward is presented (see figure 1).

### Psychosocial and psychosexual care

In Australia, between 10 and 23% of men diagnosed with prostate cancer report high levels of psychological distress.<sup>7</sup> Other studies have found a 17.5% prevalence of depression in men with localised prostate cancer,<sup>8</sup> and an eight-year longitudinal study found that 30–40% of men reported ongoing health-related distress, worry, feeling low and insomnia.<sup>9</sup> Men's risk of suicide is increased in the first six to 12 months after the diagnosis of prostate cancer,<sup>10–12</sup> and recent research has found that men with prostate cancer have an increased prevalence of suicide relative to population norms, with risk increasing with time from diagnosis.<sup>7</sup> Early high distress is a predictor of

ongoing high distress and hence detecting heightened distress early is a key priority.<sup>9–13</sup> However, men are typically low users of psychological support services for cancer and are less likely than women to discuss their psychosocial concerns with their health care providers.<sup>14</sup> This means their distress is often unnoticed and untreated. Effective (and cost effective) approaches to psychosocial care for these men will likely require screening for distress and tailored problem assessment to efficiently direct psychosocial care services to where they are needed most,<sup>15</sup> including a mechanism for stepping up the intensity of care when problems do not resolve.<sup>16</sup>

Sexual dysfunction is arguably the most highly prevalent long-term deleterious side-effect of prostate cancer treatment. Current treatments commonly result in erectile dysfunction, often accompanied by loss of desire and difficulty reaching orgasm.<sup>17</sup> All active treatments for prostate cancer have been found to be associated with long-term poorer sexual outcomes, with prevalence rates for erectile dysfunction ranging from 36% to 87%.<sup>18,19</sup> The mainstay of treatment for erectile dysfunction is medical management that if administered early in the course of recovery, may assist with smooth muscle preservation and improve erectile function through increased tissue oxygenation.<sup>20,21</sup> However, many men are reluctant to seek medical help for erectile dysfunction even when bothered by their poor erections, with satisfaction and adherence to treatments often poor.<sup>17,22</sup> Unmet sexuality needs are highly prevalent in these men.<sup>23,24</sup>

To date, interventions to address intimacy and sexual outcomes for men with prostate cancer have reported low recruitment (22%), high attrition (up to 50%), small sample sizes and equivocal or disappointing results.<sup>25-29</sup> Our group has undertaken the largest randomised trial to date delivering psychosexual support to couples after surgery for prostate cancer. While men in the two intervention arms used medical treatment for erectile dysfunction more frequently than men in usual care, no significant effects were found for sexual function, unmet sexuality needs, or sexual self-confidence. This study provides further evidence that current best practice approaches to psychosexual treatments for prostate cancer, based largely on expert opinion, may not translate into better sexual outcomes.<sup>30</sup> Theory building foundational research is needed in this area that applies masculinity and life course models and relevant behavioural frameworks to better understand men's response to prostate cancer related sexual dysfunction.<sup>31,32</sup> From this, a theory-based and improved model of psychosexual intervention could then be developed, tested and, if effective, translated into practice.

## Integrating exercise medicine into survivorship care

Research has consistently demonstrated that exercise improves physical and mental health in men with prostate cancer during and following completion of targeted exercise interventions.<sup>33-39</sup> More specifically, resistance and aerobic exercise have been shown to enhance the musculoskeletal system, improve cardiorespiratory capacity and prevent functional decline, as well as improve sexual health and overall quality of life in men with localised prostate cancer.<sup>37,40-42</sup> Few studies have examined the impact of exercise in men with advanced bone metastatic disease.<sup>43</sup> In the setting of active surveillance, preliminary studies involving basic exercise advice report decreased numbers of patients undergoing prostate cancer active treatment, as well as modulation of the biological processes involved in tumorigenesis.<sup>44,45</sup> Kenfield and colleagues demonstrated a 61% lowering risk of prostate cancer death in men who regularly engage in vigorous physical activity.<sup>46</sup> These findings have been recently confirmed in a large cohort study of 4623 men diagnosed with prostate cancer, where prostate-specific mortality was significantly lower in men walking/cycling 20 minutes or more/day or exercising for at least one hour/week,<sup>47</sup> adding to the growing body of evidence suggesting that exercise may extend survival for cancer patients.<sup>48,49</sup> Exercise may suppress tumour progression with a range of mechanisms proposed including improved immune function, reduced systemic inflammation, epigenetic modulation, beneficial myokine and adipokine profiles,<sup>50</sup> telomere alterations,<sup>51</sup> as well as exercise effects on endocrine function including the insulin/IGF axis.<sup>52</sup> Maintaining or increasing muscle mass, as well as regular high intensity activation of these tissues, has

potential to produce endogenous medicine, which suppresses tumour progression as well as reducing metabolic and cardiovascular disease.<sup>53</sup>

Novel approaches to ameliorating treatment toxicities of 'super-castrate' androgen deprivation therapy (ADT), as well as chemotherapy in prostate cancer, are also urgently needed. ADT has proven highly successful in slowing or even reversing the progression of certain prostate cancers and is a much used pharmaceutical approach in the management of men with both localised and metastatic disease. However, for some patients, prostate specific antigen (PSA) serum levels or PSA velocity starts to increase, indicating the cancer is proliferating and is now termed castrate resistant prostate cancer (CRPC).<sup>54</sup> There are several new drugs (e.g. abiraterone and enzalutamide) now available in Australia which are being prescribed for CRPC patients, however patients may experience treatment toxicities. In 2013, the team at The Institute of Cancer Research who developed abiraterone acetate, published a paper reporting the changes in body composition accompanying maximal androgen suppression with abiraterone acetate in men with CRPC.<sup>55</sup> Significant and clinically meaningful alterations in muscle and fat composition resulted from abiraterone acetate, with between 2.8 and 4.3% decline in muscle over a median of 7.5 months. This study highlights concerns about development of significant sarcopenia and increased visceral fat in patients on abiraterone acetate, which is in addition to the previously reported toxicities of this drug. Low muscle mass and high body fat termed 'sarcopenic obesity', is a particularly high risk condition for a range of chronic diseases, in particular metabolic syndrome, type II diabetes and cardiovascular disease. It is also a perfect storm driving functional decline, increased risk of falls and fractures, and ultimately lower quality of life and even death, although not directly attributable to the cancer. In addition, chemohormonal therapy (ADT + docetaxel) is being trialled over ADT alone in men with high volume newly metastatic prostate cancer.<sup>56</sup> These two developments are rapidly resulting in considerably changed practice in the management of men with advanced prostate cancer, including metastatic and CRPC. While exercise medicine has the potential to significantly ameliorate treatment toxicities of 'super-castrate' ADT treatments as well as chemotherapy, no study to date has been conducted to empirically evaluate this, or even if such an intervention is safe and feasible.

## Economic costs of prostate cancer

Healthcare costs are rapidly growing in Australia and driven by new technologies in the form of more expensive services and therapies, more services per patient, and an increasing population that is ageing.<sup>57</sup> Healthcare expenditure for prostate cancer is no exception and this means, compared with a decade ago, men diagnosed and treated with prostate cancer

today receive more tests, services and treatment combinations than ever before.<sup>57</sup> It is expected that this increased spending translates to better life expectancy, but also better quality of life for these men. Few studies have measured healthcare costs for men with prostate cancer - the best known in Australia is Gordon et al,<sup>58</sup> which measured Medicare Benefits Scheme/ Pharmaceutical Benefits Scheme and out-of-pocket costs only; hospital inpatient and outpatient costs were not reported. It is important to understand the full range of financial implications of existing and new treatments for prostate cancer. Currently, although several studies have estimated a limited proportion of costs,<sup>59-61</sup> the full costs to the health system, costs to the individual and to society are not fully understood.

Frequencies of use and costs of different treatments vary substantially across Australia and by age at diagnosis.<sup>58</sup> For example, the average cost to the Medicare Benefits Scheme and Pharmaceutical Benefits Scheme per man treated with ADT was \$18,622 in 2011; radical prostatectomy was \$7810 and external beam radiotherapy \$14,307.<sup>58</sup> Hospital costs of outpatient care, diagnostics and out-of-pocket expenses are additional costs. Moreover, the effects on recovery time, quality of life and survival vary by treatment modality. Identifying the interventions for different stages of disease that provide the best patient outcomes and are considered to be good value for money is fundamental. In order for Australia to have an efficient and more sustainable healthcare system, new technologies need to be assessed for their cost-effectiveness. Cost-effectiveness is the process by which the health expenditure required to implement an intervention is judged against the value of health and health gain it can produce, relative to the next best alternatives. Choices that are made by decision makers to eliminate products and services that are not cost-effective, free resources for existing healthcare provision and for new services. It is therefore crucial that emerging technologies and supportive care interventions for prostate cancer are based on sound cost-effectiveness to provide the best healthcare outcomes for Australian men. Emerging technologies for prostate cancer include several focal therapies, proton beam radiation, multi-parametric magnetic resonance imaging for diagnosis, robot-assisted surgery, and new drug therapies for advanced prostate cancer, among others.

## Geographic and socio-demographic inequalities

Critical geographic and socio-demographic differences in mortality rates and survival outcomes for men with prostate cancer are not well described or understood.<sup>62</sup> Our recent systematic review found strong evidence that, both in Australia and internationally, prostate cancer outcomes are associated with where men live and their ability to pay for health care.<sup>63</sup> Men living in urban or affluent areas had higher rates of PSA

testing, higher prostate cancer incidence, lower risk of advanced prostate cancer, better survival, greater access or use of medical services and lower mortality rates than men living in rural or disadvantaged areas respectively. If anything, despite increasing stakeholder and media attention, and the implementation of health policies and programs designed to reduce the urban-rural inequality,<sup>64</sup> these inequalities have increased over time.<sup>62,65-68</sup> Moreover, the magnitude of the urban-rural inequality is increasing over time.<sup>62,65-68</sup> In Australia, men diagnosed with prostate cancer while living outside the capital cities, were 24% more likely to die within five years of diagnosis,<sup>62</sup> with two studies in NSW showing that this poorer survival for men living in rural and remote areas remained after adjustment for stage at diagnosis.<sup>68,69</sup> Given the high prevalence of prostate cancer in Australia, these disparities are a cause for national concern.

We urgently need an understanding of why survival and other outcomes for Australian men diagnosed with prostate cancer depend on where they live. Unless we better understand the reasons for observed inequities, and the important issues faced by prostate cancer patients in rural, remote and disadvantaged areas, these inequities will remain and men will continue to have poorer outcomes as a result of where they live. To date, there have been no systematic investigations of small area patterns of prostate cancer incidence and survival at a national level, limiting the ability to obtain sufficient information to appropriately intervene. We propose two ways forward here, first to undertake complex spatial modelling and visualisation methods to quantify the extent of small area geographical differences in prostate cancer outcomes. Second, to apply a mix of ecological analyses on the small area estimates, combined with qualitative studies to identify those risk-modifying factors that are associated with prostate cancer outcomes, and how these factors vary by geographical area.

## Prostate cancer survivorship research and practice

Increased survivor numbers and disparities among those affected challenges society, the healthcare system and its workforce. However, survivorship research in prostate cancer is underrepresented nationally and internationally compared to basic and clinical research in prostate cancer, and relative to breast cancer survivorship research; in Australia and elsewhere the effort is poorly coordinated across disciplines and jurisdictions.<sup>7-72</sup> In an international scan of research and translation in prostate cancer survivorship, we concluded that there was currently no clearly evident systematic national or international approach to the transfer and dissemination of knowledge and skills for enhancing prostate cancer survivorship, a conclusion also supported by published comment in the recently released American Cancer Society survivorship guidelines.<sup>73</sup> In Australia and



elsewhere, evidence-based survivorship care for men with prostate cancer is the exception rather than the rule. The problem is exacerbated by already high and dramatically increasing prostate cancer prevalence – an ensuing high health care services load for these patients – and centralisation of specialist services resulting in geographic and socioeconomic barriers to access. Current research and practice in prostate cancer survivorship in Australia is disjointed and disconnected across community and acute settings, disciplines and state boundaries.

## Conclusion

In order to produce real outcomes for men and their families, prostate cancer survivorship research, translation and education needs to: articulate key factors that influence the acceptability and uptake of services;<sup>31,32</sup> apply stepped care approaches to meet the challenges of increasing prostate cancer prevalence, constraints in health care resources and unique barriers to care such as geographic location, health literacy and other aspects of social disadvantage;<sup>74,75</sup> link closely to community;<sup>76</sup> and place the patient and family at the centre of the care model.<sup>77</sup> We believe this approach, linkage and collaboration between all key groups is critical to make a meaningful difference in the lives of men with prostate cancer, not only in Australia but globally.

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