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Physical activity and dietary considerations for prostate cancer patients: future research directions

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This review considers current evidence on physical activity and dietary behaviours in the context of prostate cancer prevention and survivorship outcomes. Prostate cancer is the second most common cancer amongst men, with over 1.4 million newly diagnosed cases globally each year. Due to earlier detection via screening and advances in treatments, survival rates are amongst the highest of all cancer populations. However, hormone treatments (i.e. androgen deprivation therapy) can lead to undesirable body composition changes, increased fatigue and reduced health-related quality of life, which can impair the overall wellbeing of men living with and beyond prostate cancer. Existing research has only provided limited evidence that physical activity and nutrition can impact a man’s risk of prostate cancer but cohort studies suggest they can influence survival outcomes after diagnosis. Additionally, data from observational and intervention studies suggest that habitual physical activity (or structured exercise) and healthy diets can help to ameliorate hormone-related treatment side-effects. Current physical activity guidelines state that prostate cancer patients should complete at least three sessions of moderate-intensity aerobic exercise per week, along with two resistance exercise sessions, but dietary guidelines for prostate cancer patients are less well defined. In conclusion, regular physical activity and nutritional interventions may improve survival outcomes and attenuate some adverse side-effects of hormone treatments in men with prostate cancer. However, further research is required to improve our understanding of the health impacts of physical activity (including structured exercise) and nutrition in relation to prostate cancer prevention and survivorship.

Prostate cancer: Physical activity: Diet: Nutrition

Introduction

Globally, prostate cancer is the second most common cancer in men, with approximately 1.4 million cases and 375 000 deaths per annum⁽¹⁾. This is consistent with UK data reported by Cancer Research UK, which shows that the prostate is the most common cancer site in men⁽²⁾. Incidence rates have increased over the last

15 years, and are predicted to continue, mainly being linked to an increase in life expectancy and an increase in detection rate via screening⁽³⁾. Prostate cancer survival rates have also increased, due to advances in treatment and earlier detection due to screening⁽⁴⁾. The age-standardised 1-year survival rate in England is 96.6%, and with a corresponding 10-year survival rate of 77.6 %⁽⁵⁾. Because of the high incidence of prostate

Abbreviations: ADT, androgen deprivation therapy; HR-QoL, health-related quality of life.

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cancer, and side-effects associated with the long-term treatment plans of men living with and beyond locally advanced and metastatic disease, it is important to consider the role of physical activity (including structured exercise) and nutrition in strategies for prostate cancer prevention and survivorship.

Over the last 20 years, a large number of observational and intervention studies have investigated the effects of physical activity, structured exercise and dietary behaviours on prostate cancer risk and survivorship outcomes. The aim of this review was to summarise key physical activity and nutrition research in this context and to identify areas where further research is required.

Physical activity and dietary considerations for prostate cancer risk

The 2018 Physical Activity Guidelines Advisory Committee Scientific Report chapter on cancer⁽⁶⁾ was informed by a systematic review, which synthesised current evidence on exercise and risk of the common cancers⁽⁷⁾. Although there is evidence that habitual physical activity is associated with a 12–25% reduced risk of seven cancer types, there is no convincing evidence of an inverse association between a physically active lifestyle and risk of developing prostate cancer. A systematic review and meta-analysis of forty-eight cohort studies and twenty-four case-control studies also reported no clear association between habitual physical activity and prostate cancer risk, with point estimates for individual studies indicating risk reductions and increased risk⁽⁸⁾. However, supplementary data from this meta-analysis showed that long-term (>10 years), occupational physical activity significantly reduced total prostate cancer incidence by 17% and long-term recreational physical activity significantly reduced the risk of advanced prostate cancer by 25%⁽⁸⁾. As these results were based on a relatively low number of studies, more research is needed to consolidate these findings.

Regarding dietary influences on risk, the World Cancer Research Fund and American Institute for Cancer Research Continuous Update Project focuses on associations between exercise, diet and cancer risk. Although their previous report⁽⁹⁾ suggested that diets high in calcium increased prostate cancer risk, in their most recent update, the Expert Panel concluded there was no strong evidence linking any individual food group to the risk of prostate cancer⁽¹⁰⁾. However, the report did state there was limited, but suggestive evidence that dairy products, diets high in calcium and low plasma alpha-tocopherol or selenium concentrations may increase risk, but with further research on these dietary constituents being required. The report also found a significant link between prostate cancer risk and BMI, which has dietary implications, with each additional 5 kg/m² BMI increment increasing the risk of advanced prostate cancer by 8% and prostate cancer mortality by 11%. The World Cancer Research Fund and American Institute for Cancer Research dietary recommendations⁽¹⁰⁾ are therefore mainly focused on helping

individuals maintain a healthy weight, as a result of consuming a diet high in wholegrains, vegetables, fruits and beans, reducing the consumption of sugar-sweetened drinks, and avoiding processed foods high in fat or sugar.

Overall, while current evidence suggests that exercise and dietary habits may not directly lower an individual's risk of prostate cancer, an active lifestyle and healthy eating behaviours increase the likelihood of maintaining a healthy weight and, therefore, could indirectly reduce the risk of advanced prostate cancer, and potentially have important implications for prostate cancer survival.

Physical activity and dietary considerations for prostate cancer survival

Previous research^(7,11,12) has suggested there may be a link between physical activity and survival outcomes for prostate cancer patients. A prospective study of 1455 prostate cancer patients found patients who completed brisk walking for >3 h per week had a 57% lower rate of disease progression than patients who walked at an easy pace for <3 h per week⁽¹¹⁾. Other research has reported similar findings, with prostate cancer patients in the highest quartile of postdiagnosis physical activity having a 42% reduced risk of all-cause mortality compared with the lowest quartile⁽¹²⁾. Furthermore, a review found a 38% reduction in risk of prostate cancer mortality for men in the highest physical activity category compared with the lowest⁽⁷⁾. One limitation of cohort studies which investigate links between physical activity and survival is the possibility of reverse causation. This is where patients with a higher disease burden who have a lower expected survival time are unable to engage in physical activity due to the more severe symptoms they are experiencing. To reduce the risk of reverse causation, it has been recommended to use disease progression rather than mortality as an outcome measure⁽¹¹⁾.

The importance of regular physical activity for prostate cancer patients is highlighted in current recommendations for cancer patients published by the American College of Sports Medicine⁽¹³⁾. Their review of previously published evidence concluded that participation in structured exercise was safe for prostate cancer patients, and details the amount and type of exercise that should be completed to improve specific health outcomes. Their overall recommendation is that cancer patients should complete moderate-intensity aerobic activity for ≥30 min at least three times per week, along with at least two resistance exercise sessions per week, using at least two sets of 8–15 repetitions at 60% of one repetition maximum or above, for at least 8–12 weeks. This recommendation is for all cancer patients, although it recognises that potential adaptations may be required for specific subgroups. For example, patients with bone metastases will require modifications to their exercise programmes to reduce fracture risk. Despite these recommendations, and the link between a physically active lifestyle and survival, a survey of prostate cancer patients found that 47.5% were completing no

moderate or vigorous physical activity⁽¹⁴⁾. This highlights the need for interventions that promote and provide support for long-term physical activity behaviour change.

Studies investigating the relationship between dietary behaviours and prostate cancer survival have also reported some interesting associations. For example, prostate cancer patients in the highest quintile of vegetable fat consumption had a 29% lower risk of lethal prostate cancer and a 26% reduced risk of all-cause mortality, while adherence to a Mediterranean diet after diagnosis reduced overall mortality risk by 22%⁽¹⁵⁾. Moreover, a review suggested several dietary factors, including coffee, cruciferous vegetables and vegetable fats, may reduce the risk of prostate cancer progression by up to 59%⁽¹⁶⁾. However, further research is required to corroborate these findings and determine the optimal diet for improving prostate cancer survival outcomes.

As for primary prevention, a potential mediator of reported associations between habitual physical activity, diet and prostate cancer survival is the effect of exercise and healthy dietary behaviours on body weight. A recent review found that a postdiagnosis weight gain of >5% body weight was associated with a 65% increased risk of prostate cancer mortality, and 27% increased risk of all-cause mortality, when compared with stable weight patients postdiagnosis (<3% increase)⁽¹⁷⁾. Therefore, physical activity and dietary behaviours, which help to promote a healthy body weight (i.e. reduce the amount of excess body fat), after diagnosis may be important for improving patient survival outcomes.

Physical activity and dietary considerations for the quality of prostate cancer survivorship

Due to the high survival rates for prostate cancer, it is important to consider long-term health and wellbeing. One of the most common treatments is androgen deprivation therapy (ADT), which is given to 38.4% of non-metastatic prostate cancer patients globally, but with the UK rate at 54.6%⁽¹⁸⁾. The aim of ADT is to inhibit the effect of hormones such as testosterone on prostate cancer cell growth⁽¹⁹⁾. Current guidelines published by the National Institute for Health and Care Excellence recommend that ADT may be used as an individual treatment to control prostate cancer growth, or in combination with other treatments such as radiotherapy with a curative intent⁽²⁰⁾.

While ADT is an important treatment for controlling prostate cancer progression, it has side-effects which may reduce a patient's lifespan and health-related quality of life (HR-QoL). There is evidence of elevated cardiovascular risk for men receiving ADT, with a review of over 22 000 ADT patients finding a 20% higher risk of cardiovascular morbidity than prostate cancer patients who did not receive ADT⁽²¹⁾. However, this elevated risk has not been found in all studies⁽²²⁾ and may depend on the type of ADT received⁽²³⁾ or confounding influences, including lifestyle behaviours. Men receiving ADT also frequently report increased feelings of fatigue unrelated to recent activity levels and hot flashes^(24,25).

An elevated risk of sexual dysfunction, diabetes, bone fractures and dementia have also been reported *v.* men who receive active surveillance, with the risk of sexual dysfunction increasing further when ADT is combined with radiotherapy and surgery⁽²⁶⁾.

Another important side-effect of ADT is the adverse impact it has on body composition, including an increase in body weight associated with accumulation of body fat, often accompanied by a reduction in lean body mass (i.e. bone mineral density and skeletal muscle mass)⁽²⁷⁾. A loss of lean body mass in older men may increase their risk of falls and fractures, impairing their ability to perform daily activities and resulting in a loss of functional independence⁽²⁸⁾. Furthermore, older age might augment the effect of ADT on skeletal muscle mass. A longitudinal study showed that men on ADT aged >70 years lost 2.8% of their lean body mass over a 3-year period, compared with a 0.9% loss for men <70 years of age⁽²⁹⁾. Importantly, men who were within their first 6 months of ADT at the start of the study also lost significantly more lean body mass than men who had already been on ADT for longer than 6 months (3.7 *v.* 2.0%, respectively). These data suggest that men over 70 years, who are starting ADT could be particularly vulnerable to losing lean body mass. Strategies aimed at preserving lean mass in newly diagnosed men >70 years starting on ADT could therefore be particularly important for preserving functional independence and HR-QoL.

Studies have found that exercise programmes (aerobic, resistance, combined) can attenuate the effects of ADT on body composition in prostate cancer patients when compared with usual care^(30,31). A meta-analysis of 11 randomised control trials found that participating in an exercise training programme increased whole-body lean mass by a mean difference of 0.7 kg, reduced whole-body fat mass by 0.67% and improved aerobic fitness compared with usual care⁽³²⁾. Similar results have been reported by other systematic reviews^(33,34) along with reductions in fatigue^(34,35), and improvements in HR-QoL^(33,35). Collectively, these data highlight the potential benefits of exercise programmes for prostate cancer patients on ADT, in terms of attenuating the adverse effects of treatment on body composition and improvements in HR-QoL. It is important to note that patients are recommended to complete both aerobic and resistance exercise as these may have separate complementary benefits, as well as a combined effect⁽¹³⁾.

One particularly effective strategy for helping to preserve lean body mass is resistance exercise, which promotes muscle protein synthesis⁽³⁶⁾. However, this effect may be blunted in older men⁽³⁷⁾ and this may explain why previous studies investigating lean body mass using dual-energy x-ray absorptiometry, found no significant benefit of resistance exercise on lean body mass^(38,39). For this reason, nutritional strategies such as concurrent protein supplementation alongside exercise may provide an additional anabolic stimulus to enhance muscle synthesis in older individuals⁽⁴⁰⁾. Of relevance to prostate cancer patients, a study which investigated the effect of resistance exercise and daily protein supplementation using milk protein concentrate in healthy older



men found that this combination led to a 1.6 kg improvement in lean mass compared with resistance training alone⁽⁴¹⁾. Similarly, in prostate cancer patients, an intervention combining resistance and impact exercise with protein supplementation improved total lean body mass by 1.0 kg compared with usual care, although only in participants with high adherence to the intervention⁽⁴²⁾. A recent review concluded that protein supplementation is likely to be beneficial for men with prostate cancer, but highlighted the need for future studies to investigate the combination of resistance exercise with protein supplementation⁽⁴³⁾. While future research is required, the use of protein supplementation alongside exercise provides an example of how exercise and nutrition may be used concurrently as a strategy for reducing the adverse side-effects of ADT, and subsequently preserving a patient's musculoskeletal health, HR-QoL and independence.

An alternative dietary supplement of interest is *n*-3 fatty acids. It has been proposed that dietary *n*-3 fatty acids could help to reduce sarcopenia due to their anti-inflammatory effects and their anabolic effects via the mammalian target of rapamycin pathway⁽⁴⁴⁾. A meta-analysis investigating *n*-3 fatty acid supplementation in older adults found that it led to skeletal muscle mass gain and improved physical function⁽⁴⁵⁾. However, these results have not yet been replicated in prostate cancer patients, with previous research only focusing on the effect of *n*-3 fatty acids on disease progression⁽⁴⁶⁾. Importantly, previous research has concluded that daily *n*-3 fatty acid supplementation of 1 g EPA and 1.84 g DHA was well-tolerated and safe, with all adverse events considered minor⁽⁴⁷⁾. Further research aimed at investigating whether the combination of *n*-3 fatty acid supplementation and exercise could provide a viable strategy for lean mass preservation in prostate cancer patients on ADT is warranted.

It is important to consider several factors when interpreting current evidence. For example, as previously highlighted, the impact of ADT on lean body mass outcomes is dependent on age and the duration of ADT⁽²⁹⁾. It seems that studies aimed at investigating the effect of physical activity and dietary interventions in older men starting on ADT are warranted, as the impact of ADT side-effects could be more pronounced than those reported for younger men, and men of all ages who have been receiving ADT for some time. However, most existing research has not targeted older men, and very few studies have been focused on newly diagnosed patients starting on ADT. Additionally, although supervised exercise interventions have been shown to be effective in terms of wide-ranging health outcomes, there is also a need for effective home-based, remotely supervised interventions, which may reduce the cost of intervention delivery, and allow access to patients who are unable to attend supervised sessions for logistical reasons^(48,49). Future research should investigate ways to safely reduce the amount of exercise supervision via the provision of cost-effective support for long-term behaviour change (maintenance).

In contrast to recently published exercise guidelines for prostate cancer patients⁽¹³⁾, there are no equivalent

dietary guidelines. In a review of potential evidence for dietary guidelines relevant for prostate cancer patients on ADT, it was found that of the sixteen included papers only four examined the effect of a dietary intervention alone, with the other twelve also including elements of exercise, medication or counselling⁽⁵⁰⁾. This combination of diet with other elements is a common research design, which makes it difficult to isolate the effects of dietary changes. Nevertheless, some small-scale studies have suggested health benefits resulting from specific dietary interventions. For example, a pilot study randomised twenty-three prostate cancer patients to either their usual diet or a Mediterranean diet (low saturated fat, 2 fruit + 5 veg/d, no red meat, 3 weekly fish portions, daily portion of nuts/seeds)⁽⁵¹⁾. Patients on the Mediterranean diet had improved fatigue, quality of life, lean body mass and total body mass compared with the control group. Similarly, a study which recruited fifty-nine patients found that high-dose vitamin D supplementation (50 000 IU per week above the RDA) improved the bioelectrical impedance 'phase angle' of prostate cancer patients, which is a non-invasive technique used to assess functionality and frailty, and with lower phase angle values signalling the onset of functional decline⁽⁵²⁾. However, due to the small sample sizes, further research is required before recommending these dietary changes to prostate cancer patients. Indeed, this is a major limitation of existing nutritional intervention studies, consistent with systematic review evidence, that the majority of studies are either underpowered, at high or unknown risk of bias or too short in duration⁽⁵³⁾.

Physical activity considerations for metastatic prostate cancer patients

Metastatic prostate cancer (advanced prostate cancer) is where the cancer has spread to other sites around the body. Metastatic prostate cancer is considered incurable, and the aim of treatment is to delay disease progression and maintain/improve the patient's HR-QoL⁽²⁰⁾. The median survival time for metastatic prostate cancer patients was estimated to be 71 months from diagnosis⁽⁵⁴⁾.

Exercise guidelines from the American College of Sports Medicine recommend the same quantity of exercise for metastatic prostate cancer patients as non-metastatic patients, although recognising the need to modify exercise based on a patient's condition⁽¹³⁾. For example, the location of bone metastases could restrict which areas of the body can safely be 'loaded' during exercise, limiting the exercise modalities (particularly resistance exercises) that can be undertaken. It is therefore important that metastatic prostate cancer patients receive an individualised exercise prescription from a qualified exercise professional, in consultation with the patient's medical health care team⁽⁵⁵⁾.

Traditionally, patients with metastatic prostate cancer were excluded from research involving exercise due to safety concerns. Early studies with small sample sizes showed that exercise could be conducted safely by

advanced prostate cancer patients, and had benefits such as a 5% improvement in 400 m walk time, and a 11% increase in muscle strength^(56–58). These studies used supervised exercise interventions, but with the range of exercises available for each patient being restricted on the basis of their metastatic profile (including bone metastases). However, despite the benefits of exercise, a survey of advanced prostate cancer patients found that only 29% were meeting aerobic exercise guidelines⁽⁵⁹⁾.

An increasing number of studies are now focusing on metastatic prostate cancer patients^(60–62). For example, the INTERVAL-GAP4 study is investigating the effect of a supervised 2-year high-intensity aerobic and resistance exercise intervention on survival outcomes in advanced prostate cancer patients⁽⁶⁰⁾. However, high-intensity exercise may not be practical for a large proportion of metastatic prostate cancer patients, and so research investigating more pragmatic, accessible and adoptable exercise interventions is also required. Similarly, factors such as the timing of intervention onset, and balance of face-to-face and remote supervision given to patients, require further research to elucidate the optimal exercise conditions for advanced prostate cancer patients.

Dietary considerations for metastatic prostate cancer patients

A limited number of studies have investigated the effect of dietary interventions on health outcomes in metastatic prostate cancer patients. A feasibility/internal pilot study involving fifty patients with non-localised prostate cancer (26% metastatic patients) showed that a lifestyle intervention (exercise and dietary advice) including small-group healthy eating seminars led to significant reductions in total energy intake, saturated fat, total fat and monounsaturated fat intake⁽⁶³⁾. Although the changes in fat intake were also found in the larger randomised controlled trial (N 100; 20% metastatic patients)⁽⁶⁴⁾, the combination of exercise with a dietary intervention makes it difficult to identify whether other changes such as the improvement in HR-QoL are a result of the dietary intervention or exercise. Future research should examine interventions containing only dietary elements to isolate the health benefits of nutritional strategies for metastatic prostate cancer patients. For example, it has been proposed that the Mediterranean diet may have specific properties which could bring health benefits for this patient group⁽⁶⁵⁾.

Conclusions

Limited evidence suggests that regular physical activity and dietary behaviours can impact prostate cancer risk, though they could indirectly reduce risk by helping men to achieve and maintain a healthy body weight. Current research also suggests that a physically active lifestyle and healthy dietary behaviours can reduce the adverse effects of hormone treatment and improve survival outcomes for prostate cancer patients. However,

further studies are needed to inform the development of pragmatic interventions that can successfully enhance long-term adherence to existing guidelines and become part of standard medical care.

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Conflict of Interest

None.

Authorship

A. J. H. and J. M. S. drafted the manuscript. All authors critically reviewed and approved the final version of the manuscript.

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